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Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients (Review)

Hodson EM, Ladhani M, Webster AC, Strippoli GFM, Craig JC

Hodson EM, Ladhani M, Webster AC, Strippoli GFM, Craig JC.
Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients.
Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD003774.
DOI: 10.1002/14651858.CD003774.pub4.

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[Intervention Review]

Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients

Elisabeth M Hodson[1,2], Maleeka Ladhani[1], Angela C Webster[2,3,4], Giovanni FM Strippoli[2,4,5,6,7], Jonathan C Craig[2,4]

[1]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [2]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [3]Centre for Transplant and Renal Research, Westmead Millennium Institute, The University of Sydney at Westmead, Westmead, Australia. [4]Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [5]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [6]Department of Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy. [7]Medical-Scientific Office, Diaverum, Lund, Sweden

Contact address: Elisabeth M Hodson, Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Australia. elisabeth.hodson@health.nsw.gov.au.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2013.

Citation: Hodson EM, Ladhani M, Webster AC, Strippoli GFM, Craig JC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD003774. DOI: 10.1002/14651858.CD003774.pub4.

ABSTRACT

Background

The risk of cytomegalovirus (CMV) infection in solid organ transplant recipients has resulted in the frequent use of prophylaxis with the aim of preventing the clinical syndrome associated with CMV infection. This is an update of a review first published in 2005 and updated in 2008.

Objectives

To determine the benefits and harms of antiviral medications to prevent CMV disease and all-cause mortality in solid organ transplant recipients.

Search methods

We searched MEDLINE, EMBASE and the Cochrane Central Registry of Controlled Trials (CENTRAL) in *The Cochrane Library* to February 2004 for the first version of this review. The Cochrane Renal Group's specialised register was searched to February 2007 and to July 2011 for the first and current updates of the review without language restriction.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs comparing antiviral medications with placebo or no treatment, comparing different antiviral medications and comparing different regimens of the same antiviral medications in recipients of any solid organ transplant. Studies examining pre-emptive therapy were excluded.

Data collection and analysis

Two authors independently assessed study eligibility, risk of bias and extracted data. Results were reported as risk ratios (RR) or risk differences (RD) with 95% confidence intervals (CI) for dichotomous outcomes and by mean difference (MD) with 95% CI for continuous outcomes. Statistical analyses were performed using the random-effects model. Subgroup analysis and univariate meta-regression were performed using restricted maximum-likelihood to estimate the between study variance. Multivariate meta-regression was performed to investigate whether the results were altered after allowing for differences in drugs used, organ transplanted, and recipient CMV serostatus at the time of transplantation.

Main results

We identified 37 studies (4342 participants). Risk of bias attributes were poorly performed or reported with low risk of bias reported for sequence generation, allocation concealment, blinding and selective outcome reporting in 25% or fewer studies.

Prophylaxis with aciclovir, ganciclovir or valaciclovir compared with placebo or no treatment significantly reduced the risk for CMV disease (19 studies; RR 0.42, 95% CI 0.34 to 0.52), CMV infection (17 studies; RR 0.61, 95% CI 0.48 to 0.77), and all-cause mortality (17 studies; RR 0.63, 95% CI 0.43 to 0.92) primarily due to reduced mortality from CMV disease (7 studies; RR 0.26, 95% CI 0.08 to 0.78). Prophylaxis reduced the risk of herpes simplex and herpes zoster disease, bacterial and protozoal infections but not fungal infection, acute rejection or graft loss.

Meta-regression showed no significant difference in the relative benefit of treatment (risk of CMV disease or all-cause mortality) by organ transplanted or CMV serostatus; no conclusions were possible for CMV negative recipients of negative organs.

Neurological dysfunction was more common with ganciclovir and valaciclovir compared with placebo/no treatment. In direct comparison studies, ganciclovir was more effective than aciclovir in preventing CMV disease (7 studies; RR 0.37, 95% CI 0.23 to 0.60) and leucopenia was more common with aciclovir. Valganciclovir and IV ganciclovir were as effective as oral ganciclovir. The efficacy and adverse effects of valganciclovir/ganciclovir did not differ from valaciclovir in three small studies. Extended duration prophylaxis significantly reduced the risk of CMV disease compared with three months therapy (2 studies; RR 0.20, 95% CI 0.12 to 0.35). Leucopenia was more common with extended duration prophylaxis but severe treatment associated adverse effects did not differ between extended and three month durations of treatment.

Authors' conclusions

Prophylaxis with antiviral medications reduces CMV disease and CMV-associated mortality in solid organ transplant recipients. These data suggest that antiviral prophylaxis should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants.

PLAIN LANGUAGE SUMMARY

Antiviral drugs used as protective and preventive therapy reduce CMV disease and CMV-associated deaths in solid organ transplant recipients

Cytomegalovirus (CMV; a herpes virus) is the most common type of virus detected in people who have received solid organ transplants (kidney, heart, liver, lung and pancreas). CMV disease is a major cause of illness and death during the first six to 12 months after transplantation. Two main strategies to prevent CMV disease have been adopted: protection and prevention (prophylaxis) of viral infections for all organ recipients using antiviral drugs, or 'pre-emptive therapy' of organ recipients, who develop evidence of CMV infection during routine screening.

We looked at the benefits and harms of antiviral prophylaxis to prevent CMV disease in people who are solid organ transplant recipients. The evidence we found shows that some antiviral drugs (ganciclovir, valaciclovir and aciclovir) reduced the risk of CMV disease, death due to CMV disease, clinical disease caused by herpes simplex and herpes zoster viruses, bacterial infections and protozoal infections.

For CMV disease and death, the relative benefits of aciclovir, ganciclovir and valaciclovir appear consistent across recipients of heart, kidney and liver transplants. These benefits occur in both CMV positive transplant recipients and CMV negative transplant recipients of CMV positive donor organs, with or without the inclusion of antilymphocyte antibody therapy, and the benefits were seen at all measured time points. We found that ganciclovir is more effective than aciclovir and as effective as valganciclovir, which is currently the most commonly used antiviral drug to prevent CMV disease in transplant recipients.

Extended duration of prophylaxis was found to be more effective than three months of therapy in kidney and lung transplant recipients. More studies are needed to determine the optimum duration and dosage of antiviral drugs for all solid organ transplant recipients.

Summary of findings for the main comparison. Antiviral prophylaxis versus placebo/no treatment compared with use for preventing cytomegalovirus disease in solid organ transplant recipients

Antiviral prophylaxis versus placebo/no treatment compared with use for preventing cytomegalovirus disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients
Settings: tertiary hospitals
Intervention: antiviral prophylaxis versus placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		Antiviral prophylaxis versus placebo/no treatment				
CMV disease and CMV infection in all treated patients: all symptomatic CMV disease	**Study population**		**RR 0.42** (0.34 to 0.52)	1981 (19 studies)	⊕⊕⊕⊕ **high**	
	299 per 1000	**126 per 1000** (102 to 156)				
	Moderate					
	357 per 1000	**150 per 1000** (121 to 186)				
CMV disease for different organ transplants: Kidney transplant recipients	**Study population**		**RR 0.42** (0.31 to 0.57)	1132 (11 studies)	⊕⊕⊕⊕ **high**	
	297 per 1000	**125 per 1000** (92 to 169)				
	Moderate					
	400 per 1000	**168 per 1000** (124 to 228)				
CMV disease for different organ transplants: Liver transplant recipients	**Study population**		**RR 0.49** (0.29 to 0.84)	616 (5 studies)	⊕⊕⊕⊖ **moderate**[e]	
	262 per 1000	**128 per 1000** (76 to 220)				

	Moderate				
	306 per 1000	**150 per 1000** (89 to 257)			
CMV disease for different organ transplants: Heart transplant recipients	**Study population**		**RR 0.39** (0.25 to 0.63)	232 (3 studies)	⊕⊕⊕⊖ **moderate**[e]
	412 per 1000	**161 per 1000** (103 to 260)			
	Moderate				
	425 per 1000	**166 per 1000** (106 to 268)			
Death associated with CMV disease	**Study population**		**RR 0.26** (0.08 to 0.78)	1300 (7 studies)	⊕⊕⊕⊖ **moderate**[2]
	23 per 1000	**6 per 1000** (2 to 18)			
	Moderate				
	39 per 1000	**10 per 1000** (3 to 30)			
All-cause mortality according to antiviral medication	**Study population**		**RR 0.63** (0.43 to 0.92)	1838 (17 studies)	⊕⊕⊕⊕ **high**
	71 per 1000	**45 per 1000** (30 to 65)			
	Moderate				
	45 per 1000	**28 per 1000** (19 to 41)			
Graft loss: all medications	**Study population**		**RR 0.74** (0.47 to 1.17)	825 (10 studies)	⊕⊕⊕⊖ **moderate**[2]
	93 per 1000	**69 per 1000** (44 to 109)			
	Moderate				
	117 per 1000	**87 per 1000**			

		(55 to 137)			
Acute rejection: all medications	**Study population**		**RR 0.9** (0.78 to 1.05)	1420 (13 studies)	⊕⊕⊕⊕ **high**
	468 per 1000	**421 per 1000** (365 to 491)			
	Moderate				
	500 per 1000	**450 per 1000** (390 to 525)			
Herpes simplex and Herpes zoster infection: all medications	**Study population**		**RR 0.27** (0.19 to 0.4)	1483 (9 studies)	⊕⊕⊕⊕ **high**
	281 per 1000	**76 per 1000** (53 to 113)			
	Moderate				
	260 per 1000	**70 per 1000** (49 to 104)			

*The 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)
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: 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
Very low quality: We are very uncertain about the estimate

[e]Only 7/19 studies reported on this outcome. Small numbers of events.
[2]Few studies and events.

Summary of findings 2. Ganciclovir versus aciclovir for preventing cytomegalovirus disease in solid organ transplant recipients

Ganciclovir versus aciclovir for preventing cytomegalovirus disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients
Settings: tertiary hospitals
Intervention: ganciclovir versus aciclovir

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ganciclovir versus aciclovir				
CMV disease and CMV infection in all treated patients: CMV disease in all patients	Study population		RR 0.37 (0.23 to 0.6)	1113 (7 studies)	⊕⊕⊕⊕ high	
	177 per 1000	66 per 1000 (41 to 106)				
	Moderate					
	226 per 1000	84 per 1000 (52 to 136)				
Death associated with CMV disease	Study population		RR 0.33 (0.07 to 1.58)	832 (6 studies)	⊕⊕⊕⊖ moderate[e]	
	10 per 1000	3 per 1000 (1 to 15)				
	Moderate					
	9 per 1000	3 per 1000 (1 to 14)				
All-cause mortality	Study population		RR 1.13 (0.82 to 1.58)	1138 (8 studies)	⊕⊕⊕⊖ moderate[e]	
	103 per 1000	117 per 1000 (85 to 163)				
	Moderate					
	109 per 1000	123 per 1000 (89 to 172)				
Acute rejection	Study population		RR 0.98 (0.87 to 1.1)	1009 (6 studies)	⊕⊕⊕⊕ high	
	491 per 1000	481 per 1000 (427 to 540)				
	Moderate					
	517 per 1000	507 per 1000				

		(450 to 569)			
Graft loss	**Study population**		**RR 0.55** (0.27 to 1.13)	268 (3 studies)	⊕⊕⊝⊝ **low**[e]
	148 per 1000	**81 per 1000** (40 to 167)			
	Moderate				
	167 per 1000	**92 per 1000** (45 to 189)			
Other viral infections	**Study population**		**RR 0.81** (0.32 to 2.01)	740 (4 studies)	⊕⊕⊕⊝ **moderate**[e]
	35 per 1000	**28 per 1000** (11 to 70)			
	Moderate				
	44 per 1000	**36 per 1000** (14 to 88)			
Invasive fungal infections	**Study population**		**RR 0.67** (0.4 to 1.1)	401 (3 studies)	⊕⊕⊝⊝ **low**[e]
	149 per 1000	**100 per 1000** (60 to 164)			
	Moderate				
	51 per 1000	**34 per 1000** (20 to 56)			

*The 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)
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: 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
Very low quality: We are very uncertain about the estimate

[e]Small number of events in limited number of studies.

Summary of findings 3. Valaciclovir versus ganciclovir or valganciclovir for preventing cytomegalovirus disease in solid organ transplant recipients

Valaciclovir versus ganciclovir or valganciclovir for preventing cytomegalovirus disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients
Settings: known or unknown
Intervention: valaciclovir versus ganciclovir or valganciclovir

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Valaciclovir versus ganciclovir or valganciclovir				
CMV disease and CMV infection in all treated patients: CMV disease	**Study population**		**RR 0.74** (0.15 to 3.75)	188 (3 studies)	⊕⊕⊖⊖ **low**[e]	
	32 per 1000	**24 per 1000** (5 to 120)				
	Moderate					
	25 per 1000	**19 per 1000** (4 to 94)				
All-cause mortality	**Study population**		**RR 1.03** (0.15 to 6.9)	154 (2 studies)	⊕⊕⊖⊖ **low**[e]	
	26 per 1000	**27 per 1000** (4 to 182)				
	Moderate					
	28 per 1000	**29 per 1000** (4 to 193)				
Acute rejection	**Study population**		**RR 0.91** (0.22 to 3.73)	188 (3 studies)	⊕⊕⊖⊖ **low**[e]	
	181 per 1000	**165 per 1000** (40 to 675)				
	Moderate					
	125 per 1000	**114 per 1000**				

		(27 to 466)			
Graft loss	**Study population**		**RR 1.34** (0.23 to 7.86)	107 (2 studies)	⊕⊕⊝⊝ **low**[e]
	73 per 1000	**97 per 1000** (17 to 572)			
	Moderate				
	56 per 1000	**75 per 1000** (13 to 440)			

*The 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)
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: 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
Very low quality: We are very uncertain about the estimate

[e]Small numbers of patients.

Summary of findings 4. Extended duration compared with 3 months of valganciclovir compared with use for preventing cytomegalovirus disease in solid organ transplant recipients

Extended duration compared with 3 months of valganciclovir compared with use for preventing cytomegalovirus disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients
Settings: known or unknown
Intervention: extended duration compared with three months of valganciclovir

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
		Extended duration compared with three months of valganciclovir				
CMV disease at end of treatment	**Study population**		**RR 0.2** (0.12 to 0.35)	454 (2 studies)	⊕⊕⊕⊕ **high**	
	314 per 1000	**63 per 1000**				

		(38 to 110)			
	Moderate				
	316 per 1000	**63 per 1000** (38 to 111)			
CMV syndrome	**Study population**		**RR 0.4** (0.27 to 0.6)	454 (2 studies)	⊕⊕⊕⊕ **high**
	310 per 1000	**124 per 1000** (84 to 186)			
	Moderate				
	272 per 1000	**109 per 1000** (73 to 163)			
CMV invasive disease: Number at 12 months	**Study population**		**RR 0.23** (0.01 to 3.5)	454 (2 studies)	⊕⊕⊖⊖ **low**[e]
	66 per 1000	**15 per 1000** (1 to 229)			
	Moderate				
	109 per 1000	**25 per 1000** (1 to 381)			
CMV infection at end of treatment	**Study population**		**RR 0.27** (0.1 to 0.71)	454 (2 studies)	⊕⊕⊕⊕ **high**
	502 per 1000	**136 per 1000** (50 to 357)			
	Moderate				
	542 per 1000	**146 per 1000** (54 to 385)			
Biopsy-proven acute rejection at 12 months	**Study population**		**RR 0.99** (0.42 to 2.37)	454 (2 studies)	⊕⊕⊖⊖ **low**[e]
	183 per 1000	**182 per 1000** (77 to 435)			
	Moderate				

	192 per 1000	**190 per 1000** (81 to 455)				
Opportunistic infections	**Study population**		**RR 0.71** (0.33 to 1.57)	456 (2 studies)	⊕⊕⊝⊝ **low**[e]	
	343 per 1000	**244 per 1000** (113 to 539)				
	Moderate					
	399 per 1000	**283 per 1000** (132 to 626)				
Total treatment related adverse effects	**Study population**		See comment	456 (2 studies)	⊕⊕⊕⊕ **high**	Risks were calculated from pooled risk differences
	426 per 1000	**503 per 1000** (418 to 588)				
	Moderate					
	353 per 1000	**417 per 1000** (346 to 487)				

*The 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).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: 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
Very low quality: We are very uncertain about the estimate

[e]Considerable heterogeneity between studies.

BACKGROUND

Description of the condition

Cytomegalovirus (CMV) is the most common virus pathogen in solid organ transplant recipients being a major cause of morbidity and mortality during the first six months post-transplant (Fishman 1998; Rubin 2000). The overall incidence of symptomatic CMV disease in the transplant population ranges from 30% to 50% with the incidence and severity being highest among lung recipients (Linden 2000). Approximately 50% of deaths following lung transplantation are attributed to infection (Michaels 2000). Like all herpes viruses, CMV has the propensity to establish lifelong latency infection in the host after the initial infection has resolved. Therefore, a solid organ recipient may be infected either by exogenous virus or by reactivation of latent virus if they were CMV positive pre-transplant. Those at highest risk of symptomatic CMV disease are CMV seronegative patients who receive organs from CMV seropositive donors, and CMV seropositive patients on heavily immunosuppressive regimens (Fishman 1998; Rubin 2000). CMV may manifest as a non-specific illness characterised by fever, mononucleosis, leucopenia and thrombocytopenia, or as a variety of clinical syndromes including pneumonitis, hepatitis, encephalitis and focal gastrointestinal disease. In addition, CMV infection causes morbidity in organ recipients through indirect effects on their immune response (Rubin 1989), and is associated with increased risk of allograft injury and rejection (Grattan 1989; Keenan 1991), opportunistic infections (Fishman 1995; Hadley 1995; Van den Berg 1996) and late onset malignancies such as Epstein-Barr virus lymphoproliferative disease (Basgoz 1995).

Description of the intervention

Two main strategies to prevent CMV disease have been adopted: universal prophylaxis of organ recipients with antiviral agents and/or immunoglobulins, or pre-emptive therapy of organ recipients, who develop evidence of asymptomatic CMV infection during screening (Rubin 1989). Antiviral medications may be given intravenously (ganciclovir, aciclovir, immunoglobulins) but are now more commonly administered once daily orally with the availability of the longer acting oral preparations valganciclovir and valaciclovir. Prophylaxis is usually administered for three to six months during the time that patients are most at risk of CMV infection and disease. Pre-emptive therapy relies upon monitoring for CMV infection by pp65 antigenaemia assay or for CMV DNA using quantitative polymerase chain reaction (PCR) with administration of antiviral therapy when CMV infection is diagnosed (Emery 2000).

How the intervention might work

This review examines the use of prophylaxis to prevent CMV infection and CMV disease. Prophylaxis is usually administered for the first three to six months after transplant when the recipient is at highest risk of CMV infection. Prevention of CMV disease should reduce the associated morbidity and mortality. In addition, prophylaxis may reduce the indirect effects of CMV infection including opportunistic infections, acute rejection and graft loss.

Why it is important to do this review

There remains a lack of consensus on the merits of the various CMV prophylaxis protocols available (Fishman 1998; Humar 2009). Universal prophylaxis exposes all solid organ transplant recipients to the adverse effects of medications, particularly haematological effects (leucopenia, neutropenia, increased risk of infection) with valganciclovir, and neurological effects with valaciclovir. However, based on epidemiological studies many recipients do not develop disease without prophylaxis (Humar 2009). Thus, prophylaxis among kidney transplant recipients has commonly been limited to CMV negative recipients of CMV positive kidneys and to recipients receiving antibodies to lymphocyte antigens. Prophylaxis may also be associated with an increased risk of late onset CMV disease occurring after discontinuation of prophylaxis and with the development of resistant organisms (Humar 2009). A systematic review was therefore required to assess the benefits and harms of antiviral prophylaxis in solid organ transplants.

A meta-analysis of prophylactic treatment versus placebo/no treatment was originally published in *The Cochrane Database of Systematic Reviews* (Couchoud 1998a). When this review was updated in 2008, more recent articles comparing prophylaxis with antiviral medications (including aciclovir, ganciclovir, valaciclovir, valganciclovir) were included. This review also included studies comparing one prophylactic antiviral medication with another. We have examined the effect of prophylaxis with antiviral agents in recipients of solid organ transplant recipients on CMV disease, all CMV infection, the incidence of acute rejection, graft loss, opportunistic infections and death. We have compared the treatment effect of each regimen among different solid organs and different risk groups. Finally, the review evaluated potential harms caused by antiviral medications, namely nephrotoxicity, bone marrow suppression, and emergence of resistant CMV strains. Other reviews have evaluated pre-emptive therapy on detection of CMV viraemia (Strippoli 2006a; Strippoli 2006b) and the use of other agents (immunoglobulins, vaccines, interferon) alone or in combination with antiviral medications (Hodson 2007). The review was originally published in 2005 and was updated in 2008. It is now updated in 2013.

The Cochrane review *Pre-emptive therapy for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients* (Owers 2013) has been updated concomitantly with this review. Pre-emptive therapy compared with placebo/no specific therapy reduced the risk of CMV disease by 70% (6 studies; 288 participants). While there was no significant difference in the prevention of CMV disease with pre-emptive therapy compared with prophylaxis (7 studies; 753 participants), there was some imprecision of results and significant heterogeneity among studies limiting the applicability of these data to patient management.

OBJECTIVES

This review aimed to assess the benefits and harms of antiviral medications for preventing symptomatic CMV disease in solid organ transplant recipients of all ages, irrespective of CMV serostatus prior to transplantation. The secondary aims were to evaluate the efficacy of antiviral medications in preventing all CMV infection (symptomatic and asymptomatic where CMV is detected only by laboratory investigation) and in decreasing the incidence of acute rejection, graft loss, death (all-cause mortality and mortality due to CMV disease), opportunistic infections and to evaluate the harms of each antiviral medication.

The review compared studies of antiviral medications with placebo/no treatment and explored comparisons between two or more antiviral agents and/or two different doses or durations of the same antiviral agent. Thirdly, it has compared the treatment effect

of each regimen between different solid organs and finally, among the different risk groups (i.e. pre-existent CMV serostatus and/or level of immunosuppression).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable method) were included.

Types of participants

Participants of all ages, irrespective of CMV serostatus prior to transplantation, who have undergone at least one solid organ transplant (kidney, liver, lung, heart, pancreas). Bone marrow and other cellular transplants were excluded.

Types of interventions

Interventions included antiviral medications (aciclovir, ganciclovir, valaciclovir, valganciclovir). Comparisons were made between antiviral medications and placebo/no treatment, two different antiviral medications, or two varying doses or durations of an antiviral medication.

Studies of pre-emptive treatment (i.e. treatment on detection of CMV viraemia), immunoglobulin alone or with antiviral medications, vaccines or interferon were excluded. Treatment regimens for symptomatic CMV disease were excluded as these are the subject of other reviews (Strippoli 2006a; Strippoli 2006b; Hodson 2007).

Types of outcome measures

Primary outcomes

The primary outcome measures were the incidence of CMV disease (documented CMV infection with clinical symptoms) and all-cause mortality. The definition of symptomatic CMV disease used was that defined by the study investigators. This was usually the diagnosis of CMV infection in association with one or more of the following: CMV syndrome (temperature of 38°C or more with no other documented source in association with one or more of atypical lymphocytosis, leucopenia or thrombocytopenia), pneumonitis, focal gastrointestinal disease, liver function abnormality, or encephalitis.

Secondary outcomes

Secondary outcomes included the incidence all CMV infection (symptomatic and asymptomatic); acute rejection; graft loss; death due to CMV disease; opportunistic infections; time to CMV disease; and harms (including nephrotoxicity, bone marrow suppression, emergence of resistant CMV strains, late onset of CMV disease). All outcomes were recorded as present/absent except time to the development of CMV disease.

The definition of CMV infection used was that defined by the study investigators. This was usually the isolation of CMV from a cultured specimen from any site, or positive histopathology or CMV antigen detection in a tissue specimen, or the presence of CMV pp65 antigenaemia, or an elevation in CMV viral load as detected by qualitative or quantitative PCR (as defined by the investigator).

Graft loss was defined as the need for dialysis for kidney transplantation or retransplantation for other organs during the follow-up period of the study. Acute rejection was defined as used by the individual authors. This was either biopsy proven or clinical, defined by rise in creatinine levels with respect to kidney transplants or response to rejection treatment.

Search methods for identification of studies

Initial search

A systematic and comprehensive literature search was carried out to identify eligible RCTs (Appendix 1). There was no language restriction. We searched:

- The Cochrane Renal Group's specialised register (February 2004).
- The Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library* Issue 1, 2004).
- MEDLINE (1966 to February 2004) using the optimally sensitive search strategy developed for identification of RCTs (Dickersin 1994).
- EMBASE (1980 to February 2004) using the optimally sensitive search strategy developed for identification of RCTs (Lefebvre 1996).

The Trials Search Coordinator ensured that all relevant studies had been identified. Additional studies were located through article reference lists and from abstracts from international meetings.

Review update 2008

For this update the Cochrane Renal Group's specialised register and CENTRAL was searched to February 2007. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2007). Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the complete list of nephrology conference proceedings searched.

Electronic searches

For the current update (2013) we searched the Cochrane Renal Group's specialised register to July 2011 through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's specialised register contains studies identified from the following sources.

- Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL.
- Weekly searches of MEDLINE OVID SP.
- Handsearching of renal-related journals and the proceedings of major renal conferences.
- Searching of the current year of EMBASE OVID SP.
- Weekly current awareness alerts for selected renal journals.
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the specialised register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the

scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the specialised register section of information about the Cochrane Renal Group.

Appendix 1 presents terms used in search strategies for this review.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

Two authors independently screened titles and abstracts retrieved from the searches and identified those studies that met the inclusion criteria. This process favoured over-selection in order to include all relevant studies. The full article was retrieved if uncertainty existed or when the abstract was not available. Any disagreement with article selection was resolved through discussion and consultation.

Data extraction and management

Two authors independently extracted data from eligible studies using standardised data extraction forms. Studies reported in foreign language journals were translated before data extraction. Participant characteristics (number, age, sex, comorbidities), interventions (type of treatment, dose, duration, co-interventions) and primary and secondary outcome measures were recorded. Authors were contacted to obtain missing information on allocation concealment. Any discrepancies in data extraction were resolved in discussion. Where results of a study were published more than once, the most complete data were extracted from all sources and used in the analysis only once.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011; Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes (CMV disease, all-cause mortality) were expressed as risk ratios (RR) with 95% confidence intervals (CI). Risk differences (RD) with 95% confidence intervals were calculated for adverse effects. Continuous outcomes were calculated as mean differences (MD) with 95% CI.

Unit of analysis issues

If available, data for the first period of cross-over studies were to be included in meta-analyses; otherwise, cross-over studies were reported in the text only.

Dealing with missing data

Study authors were contacted for information on sequence generation, allocation concealments and for missing data. Where missing data were few and not thought likely to influence results, the available data were analysed.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

The updated review included all studies identified in the Cochrane Renal Group's specialised register, which is updated regularly with published and unpublished reports identified in congress proceedings. This reduces the risk of publication bias. All reports of a single study were reviewed to ensure that all outcomes were reported to reduce the risk of selection bias.

Data synthesis

Data were pooled using a random-effects model to calculate a summary estimate of effect.

Subgroup analysis and investigation of heterogeneity

To explore clinical differences among studies that might be expected to influence the magnitude of the treatment effect for the primary outcomes of CMV disease and all-cause mortality, subgroup analysis and univariate meta-regression was performed using STATA software (StataCorp LP, Texas, USA) using restricted maximum-likelihood to estimate the between-study variance. The potential sources of variability defined a priori were organ transplanted, antiviral medication used, use of immunosuppressive regimen including antibody therapy, treatment duration, donor/recipient CMV status at transplant, the time from transplant that the outcomes were measured, and methodological quality. Multivariate meta-regression was performed to investigate whether the results were altered after allowing for the differences in drug used, organ transplanted and recipient CMV serostatus at the time of transplantation.

Sensitivity analysis

Where a study's results differed considerably from other studies in a meta-analysis, exclusion of the study was investigated to determine whether this altered the result of the meta-analysis.

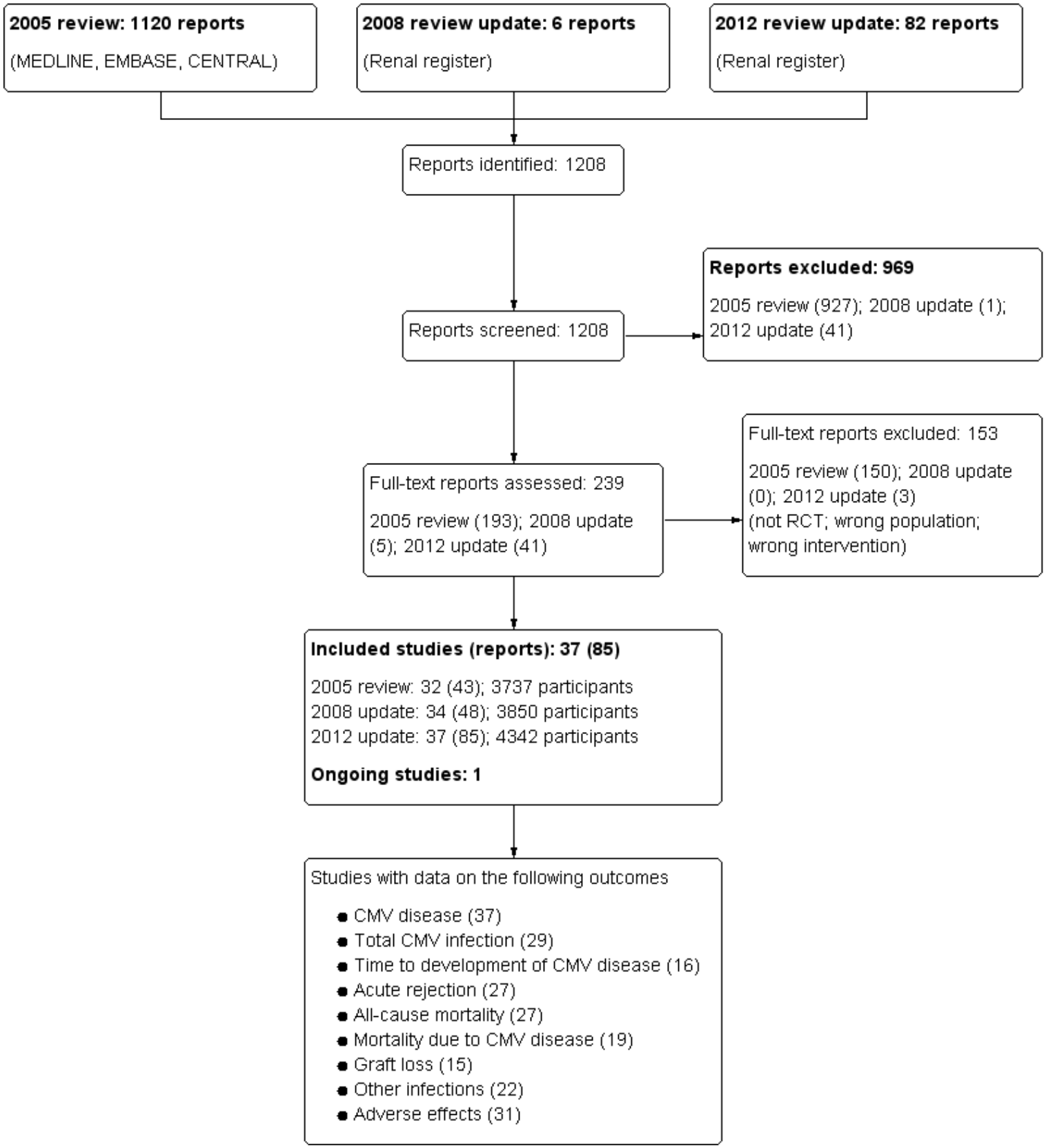
RESULTS

Description of studies

Results of the search

In the original search in February 2004, 1120 reports were initially identified from the literature search (Figure 1). The titles were screened and 927 articles were excluded. The remaining 193 abstracts or full text reports were screened and 32 studies were included.

Figure 1. Study flow diagram.



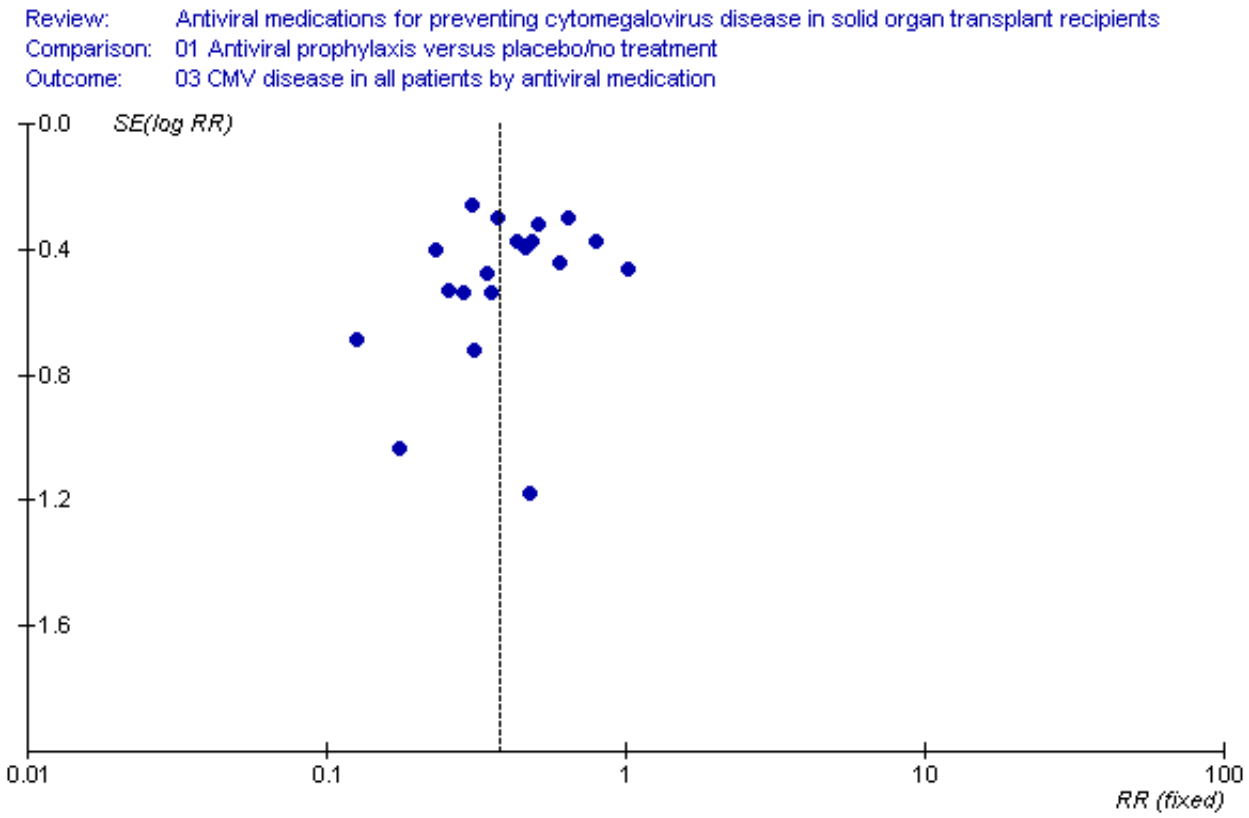
In the 2008 update, two new studies (two reports) were included, and three additional reports of already included studies were identified. One study was excluded because the intervention was ineligible for inclusion.

A further search in July 2011 identified six new potentially eligible studies (17 reports) and 18 new excluded studies (31 reports). There were also 29 additional reports of 13 already included studies and four additional reports of three studies, which had already been excluded. Of the six potentially eligible studies, three studies (14 reports) were included (2VAL Study 2010 Kidney; IMPACT 2010 Kidney; Palmer 2010 Lung), two were excluded after full text review (Said 2007; Pescovitz 2009) and one was an ongoing study (Villano 2010).

Included studies

In the original review published in 2005, 19 studies compared aciclovir (Balfour 1989 Kidney; Barkholt 1999 Liver; Gavalda 1997 Liver; Kletzmayr 1996 Kidney; Rostaing 1994 Kidney; Saliba 1993 Liver), ganciclovir (Ahsan 1997 Kidney; Brennan 1997 Kidney; Cohen 1993 Liver; Conti 1995 Kidney; Gane 1997 Liver; Hibberd 1995 Kidney; Leray 1995 Kidney; Macdonald 1995 Heart; Merigan 1992 Heart; Pouteil-Noble 1996 Kidney; Rondeau 1993 Kidney) or valaciclovir (Egan 2002 Heart; Lowance 1999 Kidney) with placebo or no treatment. Fifteen of these 19 studies excluded CMV negative recipients of CMV negative donors. Eleven studies compared different antiviral medications (Badley 1997 Liver, Duncan 1993 Lung, Flechner 1998 Kidney, Green 1997 Liver, Martin 1994 Liver; Nakazato 1993 Liver; Paya 2004 All; Reischig 2005 Kidney; Rubin 2002 All; Winston 2003 Liver; Winston 1995 Liver); and two studies (Hertz 1998 Heart/lung; Winston 2004 Liver) compared different regimens of ganciclovir administration. Recipients of transplants other than heart, kidney and liver were not included in studies comparing treatment with placebo or no treatment and were investigated in only three comparison studies. All identified studies were published in English language. Among studies comparing antiviral medications with placebo/no treatment, no significant publication bias could be demonstrated on funnel plot (Figure 2). There were too few studies comparing ganciclovir and aciclovir to subject the data to a funnel plot. The 2005 review included 32 studies (3737 participants) (Figure 1).

Figure 2. Funnel plot of 19 trials comparing antiviral medications with placebo or no treatment



In the 2008 update, five additional publications were included. These were an abstract of an included study (Ahsan 1997 Kidney); one publication reported the full results of an included study, and an additional publication assessed one outcome from that study (Reischig 2005 Kidney); and two new studies (Nafar 2005 Kidney; Pavlopoulou 2005 Kidney). Pavlopoulou 2005 Kidney compared valaciclovir with ganciclovir and Nafar 2005 Kidney compared oral with IV ganciclovir. The 2008 update included 34 studies (3850 participants).

In the 2013 update, three additional studies were included (2VAL Study 2010 Kidney; IMPACT 2010 Kidney; Palmer 2010 Lung). 2VAL Study 2010 Kidney compared valaciclovir with valganciclovir, but only preliminary results at four months were available; IMPACT

2010 Kidney compared 200 days of oral valganciclovir with 100 days in kidney transplant recipients; and Palmer 2010 Lung compared 12 months of oral valganciclovir with three months in lung transplant recipients. The 2012 update included 37 studies (4342 participants).

Green 1997 Liver specifically included children; the inclusion criteria for the Paya 2004 All and Rubin 2002 All studies indicated that children aged over 12 years could be included; however, the youngest participant in the Rubin 2002 All study was aged 20 years, and the average participant age in the Paya 2004 All study was 45 years.

Excluded studies

In the 2005 review, we excluded 47 studies after full text review: four were systematic reviews; 10 were narrative reviews; 12 involved ineligible interventions; and 21 were not RCTs.

In the 2008 update, one study was excluded because it compared pre-emptive therapy with prophylaxis (Khoury 2006).

In the 2013 update, 19 additional studies (34 reports) were excluded after reviewing abstracts: six were not RCTs and 13 studies involved an ineligible intervention. We excluded two studies after full text review: Pescovitz 2009 was a pharmacokinetic study and Said 2007 was a sequential study. We also identified four additional reports of three studies that had previously been excluded.

Risk of bias in included studies

Allocation

The risk of bias was low for sequence generation in 12 studies (2VAL Study 2010 Kidney; Ahsan 1997 Kidney; Badley 1997 Liver; Balfour 1989 Kidney; Cohen 1993 Liver; Egan 2002 Heart; Flechner 1998 Kidney; Macdonald 1995 Heart; Martin 1994 Liver; Palmer 2010 Lung; Paya 2004 All; Reischig 2005 Kidney); high in one study (Brennan 1997 Kidney); and unclear in the remaining studies.

Of 19 studies comparing prophylaxis with placebo or no treatment, the risk of bias was low for allocation concealment in four (21%) studies (Cohen 1993 Liver; Egan 2002 Heart;; Pouteil-Noble 1996 Kidney; Saliba 1993 Liver); high in one study (Brennan 1997 Kidney); and the information was unclear in 14 studies. Of 13 studies comparing different medications, allocation concealment bias was low in six studies (2VAL Study 2010 Kidney; Badley 1997 Liver; Flechner 1998 Kidney; Paya 2004 All; Reischig 2005 Kidney; Rubin 2002 All); and information was not available for seven studies. Of the remaining studies, allocation concealment bias was low in two studies (IMPACT 2010 Kidney; Palmer 2010 Lung) but Information on allocation concealment was not available for three (Hertz 1998 Heart/lung; Nafar 2005 Kidney; Winston 2004 Liver).

Blinding

Performance bias was assessed as low risk in 10 studies (27%), including seven that compared prophylaxis with placebo (Balfour 1989 Kidney; Barkholt 1999 Liver; Gane 1997 Liver; Lowance 1999 Kidney; Macdonald 1995 Heart; Merigan 1992 Heart; Pouteil-Noble 1996 Kidney); one study comparing different antiviral agents (Paya 2004 All); and two studies comparing different durations of the same medication (IMPACT 2010 Kidney; Palmer 2010 Lung). The risk of bias was unclear for blinding of participants and investigators in one study (Egan 2002 Heart); and the remaining studies were assessed as being at high risk of performance bias.

The risk of detection bias was low in nine studies (24%) (Balfour 1989 Kidney; Barkholt 1999 Liver; Gane 1997 Liver; IMPACT 2010 Kidney; Lowance 1999 Kidney; Macdonald 1995 Heart; Merigan 1992 Heart; Palmer 2010 Lung; Paya 2004 All; Pouteil-Noble 1996 Kidney); unclear in one study (Egan 2002 Heart); and the remaining studies were judged to be at high risk of detection bias.

Incomplete outcome data

We identified 34 studies (92%) that were considered to be at low risk of attrition bias. Of these, 19 studies compared prophylaxis with placebo/no treatment (Ahsan 1997 Kidney; Balfour 1989 Kidney; Barkholt 1999 Liver; Brennan 1997 Kidney; Cohen 1993 Liver; Conti 1995 Kidney; Egan 2002 Heart; Gane 1997 Liver; Gavalda 1997 Liver; Hibberd 1995 Kidney; Kletzmayr 1996 Kidney; Lowance 1999 Kidney; Macdonald 1995 Heart; Merigan 1992 Heart; Pouteil-Noble 1996 Kidney; Rondeau 1993 Kidney; Rostaing 1994 Kidney; Saliba 1993 Liver; Winston 1995 Liver); 10 compared different antiviral medications (Badley 1997 Liver; Duncan 1993 Lung; Flechner 1998 Kidney; Green 1997 Liver; Martin 1994 Liver; Nakazato 1993 Liver; Pavlopoulou 2005 Kidney; Paya 2004 All; Rubin 2002 All; Winston 2003 Liver); and five compared different regimens of ganciclovir (Hertz 1998 Heart/lung; Nafar 2005 Kidney; Winston 2004 Liver) or of valganciclovir (IMPACT 2010 Kidney; Palmer 2010 Lung). In two studies, it was unclear whether attrition bias existed (2VAL Study 2010 Kidney; Leray 1995 Kidney). The remaining study was considered to be at high risk of attrition bias (Nafar 2005 Kidney).

Selective reporting

No protocols were available. Studies were considered to be at low risk of bias if they reported all the expected outcomes (CMV disease, CMV infection, acute rejection, graft loss, death, opportunistic infections, adverse effects). Seven studies were considered to be at low risk of bias (Balfour 1989 Kidney; Barkholt 1999 Liver; Egan 2002 Heart; Gane 1997 Liver; IMPACT 2010 Kidney; Paya 2004 All; Winston 1995 Liver). Four studies were considered to be at unclear risk of bias (2VAL Study 2010 Kidney; Leray 1995 Kidney; Pouteil-Noble 1996 Kidney; Saliba 1993 Liver). The remaining 26 studies were considered to be at high risk of bias because they failed to report adequately on one or more outcomes.

Other potential sources of bias

Five studies were considered at low risk of bias as they reported funding from government or university sources (2VAL Study 2010 Kidney; Badley 1997 Liver; Balfour 1989 Kidney; Reischig 2005 Kidney; Rondeau 1993 Kidney). Thirteen studies were considered to be at high risk of bias because they reported pharmaceutical sponsorship (Barkholt 1999 Liver; Brennan 1997 Kidney; Egan 2002 Heart; Gane 1997 Liver; Hibberd 1995 Kidney; IMPACT 2010 Kidney; Lowance 1999 Kidney; Merigan 1992 Heart; Nakazato 1993 Liver; Palmer 2010 Lung; Paya 2004 All; Rubin 2002 All; Winston 2003 Liver; Winston 1995 Liver). In the remaining 19 studies it was unclear whether pharmaceutical sponsorship existed or what impact it had on the conduct of the study.

Effects of interventions

See: **Summary of findings for the main comparison** Antiviral prophylaxis versus placebo/no treatment compared with use for preventing cytomegalovirus disease in solid organ transplant recipients; **Summary of findings 2** Ganciclovir versus aciclovir for preventing cytomegalovirus disease in solid organ transplant

recipients; **Summary of findings 3** Valaciclovir versus ganciclovir or valganciclovir for preventing cytomegalovirus disease in solid organ transplant recipients; **Summary of findings 4** Extended duration compared with 3 months of valganciclovir compared with use for preventing cytomegalovirus disease in solid organ transplant recipients

Antiviral medication versus placebo/no treatment

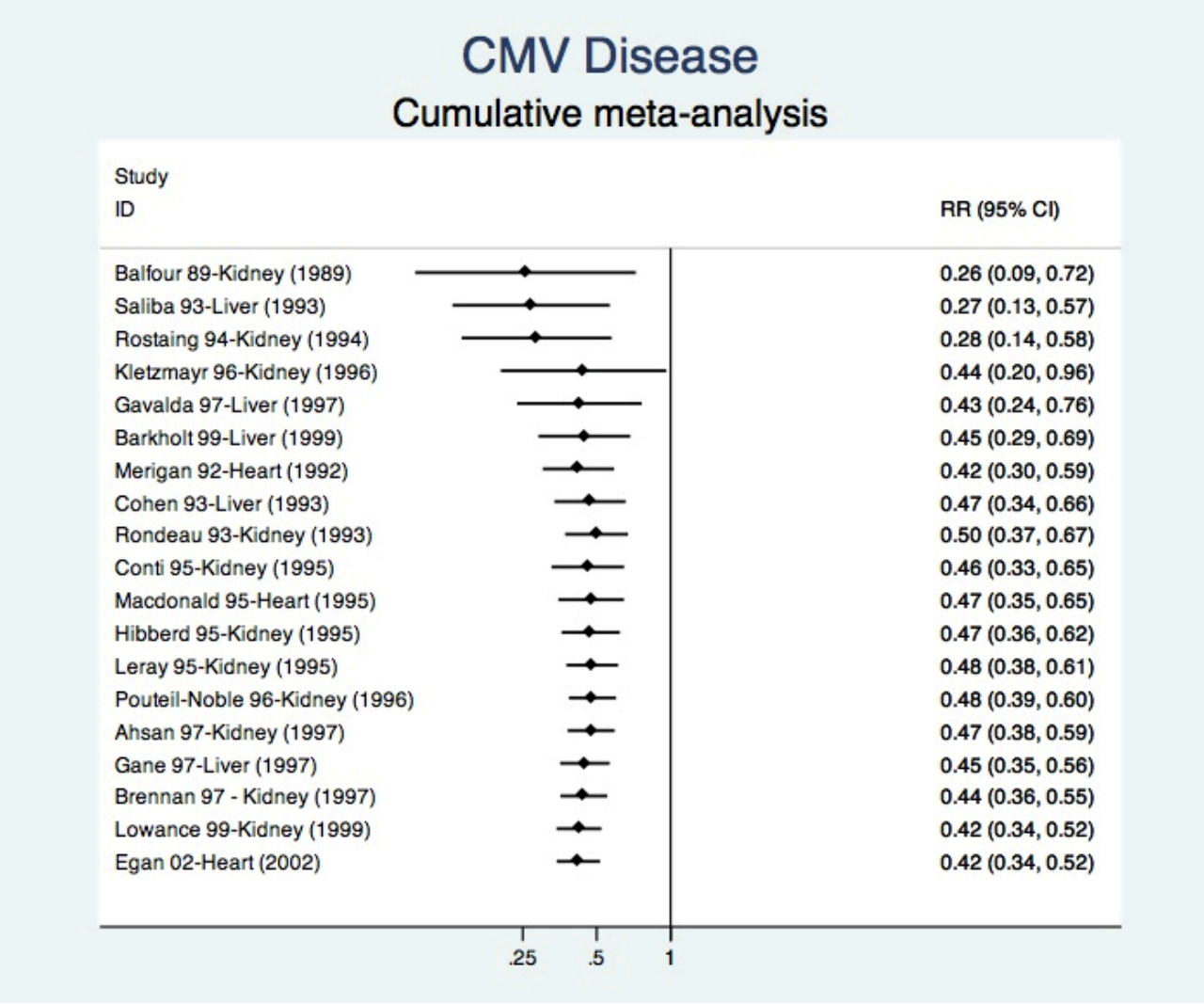
We identified 19 studies (1981 patients) that compared antiviral medications with placebo or no treatment. Six studies administered aciclovir (Balfour 1989 Kidney; Barkholt 1999 Liver; Gavalda 1997 Liver; Kletzmayr 1996 Kidney; Rostaing 1994 Kidney; Saliba 1993 Liver); 11 studies administered ganciclovir (Ahsan 1997 Kidney; Brennan 1997 Kidney; Cohen 1993 Liver; Conti 1995 Kidney; Gane 1997 Liver; Hibberd 1995 Kidney; Leray 1995 Kidney; Macdonald 1995 Heart; Merigan 1992 Heart; Pouteil-Noble 1996 Kidney; Rondeau 1993 Kidney); and two studies administered valaciclovir (Egan 2002 Heart; Lowance 1999 Kidney).

CMV disease and CMV infection

The average risk of CMV disease was 30% (range 11% to 72%). Prophylaxis with all agents significantly reduced the risk for CMV disease overall (Analysis 1.1.1 (19 studies, 1981 participants): RR 0.42, 95% CI 0.34 to 0.52; I^2 = 13%), CMV syndrome (Analysis 1.1.2 (11 studies, 1570 participants): RR 0.41, 95% CI 0.29 to 0.57; I^2 = 0%) and CMV invasive organ disease (Analysis 1.1.3 (12 studies, 1628 participants): RR 0.34, 95% CI 0.21 to 0.55; I^2 = 35%) compared with placebo or no treatment. No significant heterogeneity between studies was detected in the effect of prophylaxis on CMV disease, syndrome and invasive organ disease.

Figure 3 shows the cumulative meta-analysis demonstrating changes over time for CMV disease. There was a consistent reduction in CMV disease with antiviral prophylaxis from the first study in 1989 with the relative risk remaining stable from 1996 but with a progressive narrowing in confidence intervals.

Figure 3. CMV disease: cumulative meta-analysis showing change over time



Time to onset of CMV disease was reported in 11 studies. Prophylaxis significantly increased the time from transplant to the onset of CMV disease in nine studies. Different methods of reporting prevented these data being combined in a meta-analysis.

The average risk of CMV infection in the placebo/no treatment arms of all studies was 49% (range 36% to 100%). Prophylaxis significantly reduced CMV infection (Analysis 1.1.4 (17 studies, 1786 participants): RR 0.61, 95% CI 0.48 to 0.77; I^2 = 76%). Considerable heterogeneity existed between studies for CMV infection with no explanation apparent, but the summary estimates for individual studies favoured prophylaxis in 15/17 studies.

Subgroup analyses for CMV disease

Subgroup analyses according to antibody status, antiviral medications, organ transplanted, treatment duration, use of antilymphocyte therapy, time to outcome assessment, study quality and other aspects of study design did not demonstrate any differences in treatment effects. Multivariate meta-regression showed no significant difference in CMV disease after allowing for potential confounding or effect-modification by prophylactic drug used, organ transplanted or recipient serostatus in CMV positive recipients and CMV negative recipients of CMV positive donors. (See Table 1).

CMV disease in patients stratified by antibody status

Subgroup analysis revealed that treatment efficacy in CMV disease did not vary significantly according to recipient serostatus. Medication significantly reduced the risk of CMV disease (Analysis 1.2.1 (13 studies, 1348 participants): RR 0.34, 95% CI 0.24 to 0.50; I^2 = 24%) in CMV positive recipients (donor positive or negative). Medication significantly reduced the risk of CMV disease (Analysis 1.2.2 (10 studies, 423 participants): RR 0.52, 95% CI 0.37 to 0.73; I^2 = 27%) in CMV negative recipients of CMV positive organs.

Subgroup analysis showed that treatment efficacy did not vary in CMV positive recipients if they received a CMV positive organ (Analysis 1.2.4 (5 studies, 276 participants): RR 0.19, 95% CI 0.09 to 0.37; I^2 = 0%) or CMV negative organ (Analysis 1.2.5 (5 studies, 160 participants): RR 0.32, 95% CI 0.11 to 0.95; I^2 = 0%).

Insufficient data (Analysis 1.2.3; 4 studies, 38 participants, 2 events) were available to determine the efficacy of prophylaxis on CMV disease in CMV negative recipients of CMV negative donors.

CMV disease in all patients stratified by antiviral medication

The treatment efficacy did not vary according to antiviral medication used on subgroup analysis. When analysed separately aciclovir (Analysis 1.3.1 (6 studies, 421 participants): RR 0.45, 95% CI 0.29 to 0.69; I^2 = 8%), ganciclovir (Analysis 1.3.2 (11 studies, 917 participants): RR 0.44, 95% CI 0.34 to 0.58; I^2 = 23%) and valaciclovir (Analysis 1.3.3 (2 studies, 643 participants): RR 0.30, 95% CI 0.19 to 0.49; I^2 = 0%) significantly reduced the risk for CMV disease compared with placebo or no treatment.

CMV disease in all patients stratified by transplanted organ

The treatment efficacy on CMV disease did not vary according to organ transplanted. Prophylaxis was effective in reducing the risk of CMV disease in kidney (Analysis 1.4.1 (11 studies, 1132 participants): RR 0.42, 95% CI 0.31 to 0.57; I^2 = 27%), liver (Analysis 1.4.2 (5 studies, 616 participants): RR 0.49, 95% CI 0.29 to 0.84; I^2 = 57%) and heart transplant recipients (Analysis 1.4.3 (3 studies, 232 participants): RR 0.39, 95% CI 0.25 to 0.63; I^2 = 0%).

CMV disease in ganciclovir treated patients stratified by treatment duration

In ganciclovir studies, duration of treatment was arbitrarily divided into fewer than six weeks and six weeks or more. There was no difference in treatment efficacy (Analysis 1.5). Effect of duration could not be assessed for other medications, which were generally administered for three months.

CMV disease in patients stratified for the use of antilymphocyte antibody

Subgroup analysis showed no difference in treatment efficacy against CMV disease if the immunosuppressive regimen did (Analysis 1.6.1 (11 studies, 666 participants): RR 0.43, 95% CI 0.33 to 0.55; I^2 = 0%) or did not (Analysis 1.7.1 (6 studies, 649 participants): RR 0.47, 95% CI 0.29 to 0.76; I^2 = 47%) include an antilymphocyte antibody given during prophylaxis for induction or rejection.

CMV-related death or other causes

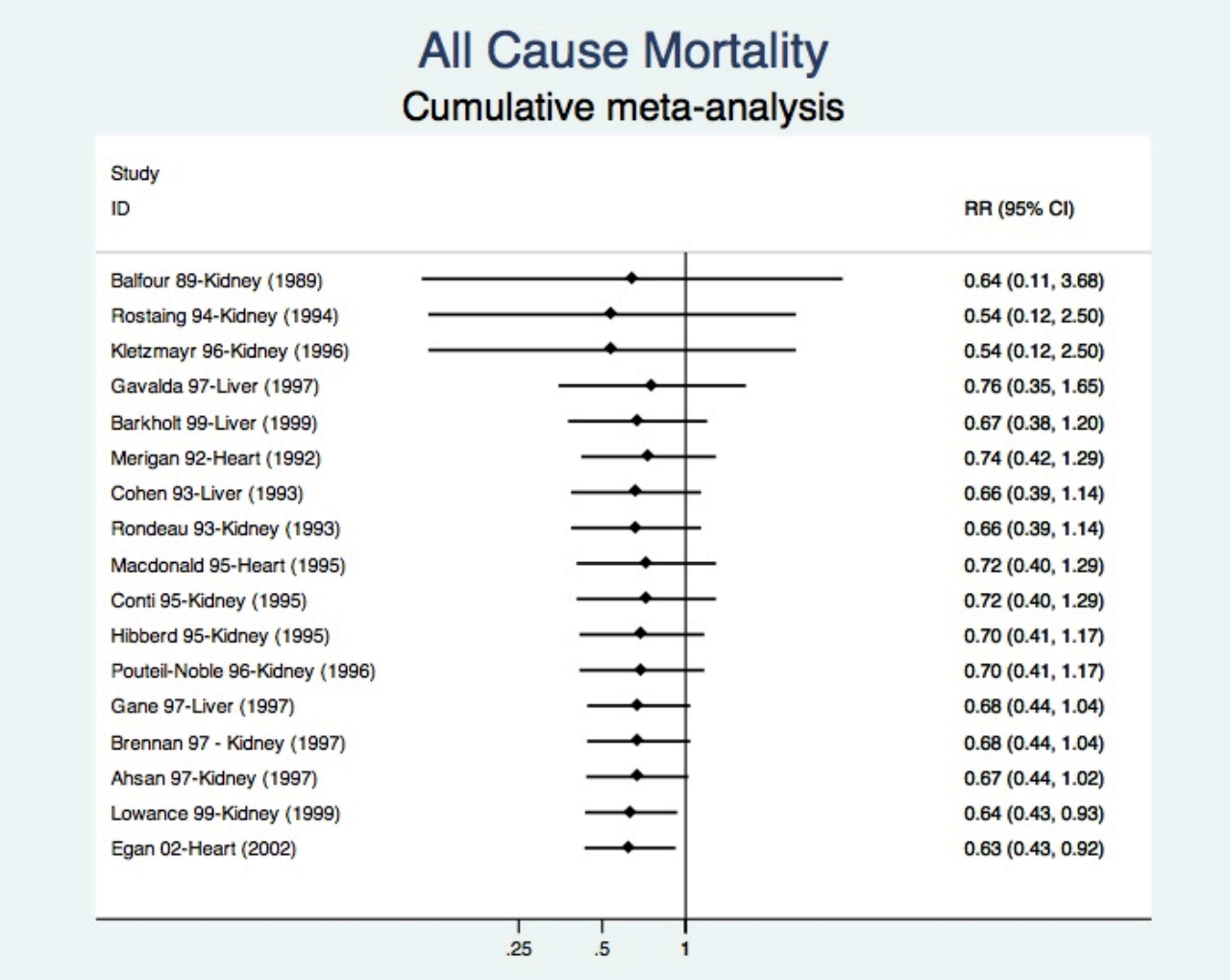
In seven studies that reported the number of deaths due to CMV disease, the average mortality rates in the placebo/no treatment arms due to CMV disease and to non-CMV causes were 2.3% (range 0.3% to 7.4%) and 5.7% (0% to 15.6%) respectively. Prophylaxis significantly reduced the risk of death due to CMV disease (Analysis 1.8.1 (7 studies, 1300 patients): RR 0.26, 95% CI 0.08 to 0.78; I^2 = 0%) but not the risk from non-CMV causes (Analysis 1.8.2 (7 studies, 1300 patients): RR 0.71, 95% CI 0.44 to 1.17; I^2 = 0%).

All-cause mortality

The average all-cause mortality rate reported at one year or less post-transplant in the placebo/no treatment arms of all studies was 7.1% (range 0% to 37%). Prophylaxis significantly reduced all-cause mortality (Analysis 1.9 (17 studies, 1838 participants): RR 0.63, 95% CI 0.43 to 0.92; I^2 = 0%).

Figure 4 shows the cumulative meta-analyses demonstrating change over time for all-cause mortality. While the relative risk remained stable, the confidence intervals narrowed progressively with evidence for a significant reduction in all-cause mortality becoming evident with the addition of the Lowance 1999 Kidney study.

Figure 4. All-cause mortality cumulative meta-analysis showing change over time



Subgroup analyses for all-cause mortality

Subgroup analyses according to CMV status, antiviral medications, organ transplanted, treatment duration, use of antilymphocyte therapy, time to outcome assessment, study quality and other aspects of study design did not demonstrate any differences in all-cause mortality. Multivariate meta-regression showed no significant difference in all-cause mortality after allowing for potential confounding or effect-modification by prophylactic drug used, organ transplanted or recipient serostatus in CMV positive recipients and CMV negative recipients of CMV positive donors. (See Table 1).

All-cause mortality stratified by CMV status

No differences in all-cause mortality were seen with CMV positive recipients (Analysis 1.10.1 (7 studies, 738 participants): RR 0.59, 95% CI 0.30 to 1.18; I^2 = 2%) or CMV negative recipients of CMV positive organs (Analysis 1.10.2 (4 studies, 288 participants): RR 1.42 95% CI 0.44 to 4.66; I^2 = 0%) on subgroup analysis. Data were not available to determine if the effects of antiviral medications on all-cause mortality differed between CMV positive recipients of CMV negative and CMV positive recipients of CMV positive organs.

All-cause mortality stratified by transplanted organ

All-cause mortality was reduced (Analysis 1.11 (17 studies, 1838 participants): RR 0.63, 95% CI 0.43 to 0.92; I^2 = 0%). However, the reduction could not be demonstrated for individual organs because of the small numbers of events and patients for individual organs.

All-cause mortality in ganciclovir treated patients stratified by treatment duration

There was no difference in all-cause mortality among studies evaluating ganciclovir for six weeks or less or more than six weeks (Analysis 1.12).

All-cause mortality in studies stratified according to use of antilymphocyte therapy

There was no difference in all-cause mortality whether or not antibody therapy was administered (Analysis 1.6.2; Analysis 1.7.2).

Additional outcomes

For graft loss, acute rejection, invasive fungal infection and post-transplant lymphoproliferative disease (PTLD) there was no significant difference between antiviral prophylaxis and placebo or no treatment (Analysis 1.7.1; Analysis 1.13.2; Analysis 1.13.4;

Analysis 1.13.6). The risk of acute rejection did not differ on subgroup analysis between studies using biopsy diagnosis (Analysis 1.14.1 (5 studies, 827 participants): RR 0.97, 95% CI 0.71 to 1.32; I^2 = 62%) and those using clinical criteria (Analysis 1.14.2 (8 studies, 599 participants): RR 0.91, 95% CI 0.76 to 1.08; I^2 = 14%). In one study using valaciclovir with subgroups pre-specified according to CMV serostatus, prophylaxis significantly reduced the risk of acute rejection in CMV negative recipients of CMV positive kidneys (Lowance 1999 Kidney) (Analysis 1.15.1 (208 participants): RR 0.51, 95% CI 0.35 to 0.74) compared with CMV positive recipients (Analysis 1.15.2 (408 participants): RR 0.84, 95% CI 0.63 to 1.10) (test of interaction χ^2 = 4.33; P = 0.04). This difference is responsible for the heterogeneity demonstrated between valaciclovir studies for acute rejection (Analysis 1.15.3 (2 studies, 643 participants): RR 0.81, 95% CI 0.55 to 1.19; I^2 = 85%).

Prophylaxis with aciclovir, ganciclovir or valaciclovir reduced the risk for clinical disease caused by herpes simplex and herpes zoster (Analysis 1.13.3 (9 studies, 1483 participants): RR 0.27, 95% CI 0.19 to 0.40; I^2 = 27%). Combining the studies of different medications showed that bacterial (Analysis 1.13.5 (3 studies, 175 participants): RR 0.65, 95% CI 0.44 to 0.96; I^2 = 0%) and protozoal infections (Analysis 1.13.7 (2 studies, 114 participants): RR 0.31, 95% CI 0.10 to 0.99; I^2 = 0%) were significantly reduced by prophylaxis.

There were 16 studies that reported data on adverse effects of medications. Except for six placebo-controlled studies, we could not determine baseline adjusted effects of medications on leucopenia, kidney function and neurological dysfunction as the numbers of patients with these abnormalities were not reported for the no treatment groups. In placebo-controlled studies, valaciclovir significantly increased the risk for hallucinations (8.5% compared with 0.97%) (Analysis 1.16.9 (1 study, 616 participants): RR 8.78, 95% CI 2.69 to 28.71). There was no significant difference in neurological dysfunction with aciclovir (Analysis 1.16.3). No significant differences were identified for leucopenia (Analysis 1.16.1; Analysis 1.16.4; Analysis 1.16.7) or reduced kidney function (Analysis 1.16.2; Analysis 1.16.5; Analysis 1.16.8) with any medication (See Table 2).

Subgroup analyses by methodological quality for CMV disease and all-cause mortality

Subgroup analysis, stratifying studies by methodological quality and aspects of study design, specified a priori, showed that treatment efficacy to reduce CMV disease and all-cause mortality did not vary significantly among studies.

- Study publication date: Studies were arbitrarily divided into those published before 1997 and those published in or after 1997. There was no difference in treatment efficacy.
- Study quality: Studies were divided according to quality assessment (adequate allocation concealment or other, blinding or no blinding, intention to treat analysis carried out or not). On subgroup analysis, no differences in treatment efficacy for CMV disease or all-cause mortality were detected for allocation concealment (Analysis 2.1; Analysis 3.1) blinding (Analysis 2.2; Analysis 3.2) or intention-to-treat analysis (Analysis 2.3; Analysis 3.3).
- Time of outcome assessment: There was no difference in treatment efficacy for CMV disease and all-cause mortality if outcome was assessed at three to six months or nine to 12 months (Analysis 2.4; Analysis 3.4).

Ganciclovir versus aciclovir

Eight studies compared ganciclovir with aciclovir (Badley 1997 Liver; Duncan 1993 Lung; Flechner 1998 Kidney; Martin 1994 Liver; Nakazato 1993 Liver; Rubin 2002 All; Winston 1995 Liver; Winston 2003 Liver).

CMV disease and CMV infection

In head-to-head studies, ganciclovir was more effective than aciclovir in preventing CMV disease in all recipients (Analysis 4.1.1 (7 studies, 1113 participants): RR 0.37, 95% CI 0.23 to 0.60; I^2 = 33%), in CMV positive recipients (Analysis 4.2.1 (5 studies, 722 participants): RR 0.27, 95% CI 0.13 to 0.55; I^2 = 7%) and in CMV negative recipients of CMV positive organs (Analysis 4.3.1 (5 studies, 246 participants): RR 0.64, 95% CI 0.41 to 0.99; I^2 = 0%). There were insufficient data in CMV negative recipients of CMV negative donors to determine if a difference in efficacy exists (Analysis 4.4).

On subgroup analysis, no differences in efficacy could be demonstrated between studies in which the participants received ganciclovir for three months (Analysis 4.1.5 (4 studies, 703 participants): RR 0.28, 95% CI 0.09 to 0.82; I^2 = 62%) and those in which the participants received ganciclovir followed by aciclovir (Analysis 4.1.6 (3 studies, 410 participants): RR 0.38, 95% CI 0.22 to 0.64; I^2 = 0%). Subgroup analysis demonstrated the efficacy of antiviral medication was not dependent on the organ transplanted for either CMV disease (Analysis 4.5.1; Analysis 4.5.2; Analysis 4.5.3) or CMV infection (Analysis 4.5.4; Analysis 4.5.5; Analysis 4.5.6).

Ganciclovir was more effective than aciclovir in reducing CMV infection (Analysis 4.1.4 (6 studies, 815 participants): RR 0.44; 95% CI 0.28 to 0.67; I^2 = 73%) in all recipients and in CMV positive recipients (Analysis 4.2.2 (5 studies, 522 participants): RR 0.30, 95% CI 0.16 to 0.58; I^2 = 70%) but not in CMV negative recipients of CMV positive organs (Analysis 4.3.4 (4 studies, 228 participants): RR 0.63, 95% CI 0.36 to 1.09; I^2 = 58%) but there was significant heterogeneity among the studies.

All-cause mortality

There were no significant differences in the risk of death due to CMV disease (Analysis 4.6.1 (6 studies, 832 participants): RR 0.33, 95% CI 0.07 to 1.58; I^2 = 0%) or all-cause mortality (Analysis 4.6.2 (8 studies, 1138 participants): RR 1.13, 95% CI 0.82 to 1.58; I^2 = 0%).

Additional outcomes

No significant differences were reported for acute rejection (Analysis 4.7.1); graft loss (Analysis 4.7.2); other viral infections (Analysis 4.7.3); fungal infections (Analysis 4.7.4); bacterial infections (Analysis 4.7.5); protozoal infections (Analysis 4.7.6); or obliterative bronchiolitis in lung transplant recipients (Analysis 4.7.7). Three studies or fewer provided outcomes for graft loss, obliterative bronchiolitis and for opportunistic infections other than other viral infections.

Leucopenia was significantly more common with ganciclovir compared with aciclovir (Analysis 4.7.8 (6 studies, 955 participants): RR 3.28, 95% CI 1.48 to 7.25; I^2 = 0%) but no significant differences were demonstrated for kidney (Analysis 4.7.9) or neurological dysfunction (Analysis 4.7.10).

Ganciclovir/aciclovir versus ganciclovir

One study (Green 1997 Liver) compared ganciclovir given for 14 days followed by aciclovir to one year with ganciclovir for 14 days in 48 children, who had received liver transplants. No significant differences in efficacy were demonstrated for CMV disease (Analysis 5.1.1), CMV infection (Analysis 5.1.2), all-cause mortality (Analysis 5.2.1) or Epstein-Barr virus infections (Analysis 5.3.1).

Valganciclovir versus ganciclovir

One study (Paya 2004 All) compared valganciclovir with ganciclovir in CMV negative recipients of CMV positive organs and included patients receiving kidney, liver, heart and combined kidney-pancreas transplants.

CMV disease and CMV infection

Valganciclovir and ganciclovir were not significantly different in the prevention of CMV disease at six months (Analysis 6.1.1) or one year post-transplant (Analysis 6.1.2). Similarly there were no significant differences at six months and one year in the prevention of CMV syndrome (Analysis 6.1.3; Analysis 6.1.4*)* and CMV invasive organ disease (Analysis 6.1.5; Analysis 6.1.6). Subgroup analysis showed that, at six months, valganciclovir was significantly more effective than ganciclovir in kidney transplant recipients (Analysis 6.1.8 (120 participants): RR 0.27, 95% CI 0.01 to 0.75) compared with liver, heart or kidney-pancreas transplant recipients (Analysis 6.1.7; Analysis 6.1.9; Analysis 6.1.10) (test of interaction Chi^2 = 6.34; P = 0.01).

There were no significant differences at six months (Analysis 6.1.11) and one year (Analysis 6.1.12) in the prevention of CMV infection.

All-cause mortality

No significant differences were detected between medications in death due to CMV disease (Analysis 6.2.1) or all-cause mortality (Analysis 6.2.2).

Additional outcomes

No significant differences were detected in acute rejection, graft loss and opportunistic infections (Analysis 6.3.1; Analysis 6.3.2; Analysis 6.3.3). Neutrophil counts below 1000/mm^3 occurred in 13% of patients treated with valganciclovir compared with 8% treated with ganciclovir but the difference was not significant (Analysis 6.3.7). No differences were detected in cessation of medications due to neutropenia, anaemia, thrombocytopenia or tremor (Analysis 6.3.4; Analysis 6.3.5; Analysis 6.3.6; Analysis 6.3.7; Analysis 6.3.8).

Valaciclovir versus ganciclovir/valganciclovir

Three studies compared valaciclovir with ganciclovir (Pavlopoulou 2005 Kidney; Reischig 2005 Kidney) or with valganciclovir (2VAL Study 2010 Kidney) in kidney transplant recipients.

CMV disease and CMV infection

The risk of CMV disease (Analysis 7.1.1) and CMV infection (Analysis 7.1.2) did not differ significantly with valaciclovir compared with ganciclovir or valganciclovir prophylaxis. There was no significant difference in the risk of CMV disease (Analysis 7.1.3) and CMV infection (Analysis 7.1.4) in CMV positive recipients of CMV positive or negative transplants or of the risk of CMV disease (Analysis 7.1.5) and CMV infection (Analysis 7.1.6) in CMV negative recipients of CMV positive organs.

All-cause mortality

No significant differences were detected in all-cause mortality (Analysis 7.2.1).

Additional outcomes

The risk of acute rejection did not differ significantly with valaciclovir compared with ganciclovir (Analysis 7.3.1 (3 studies, 188 participants): RR 0.91; 95% CI 0.22 to 3.73; I^2 = 64%). However, there was significant heterogeneity among the three studies with Reischig 2005 Kidney reporting a significantly reduced risk for acute rejection with valaciclovir (seen in participants with delayed graft function), while 2VAL Study 2010 Kidney showed a trend towards a higher risk of rejection with valaciclovir. No difference in the risk of graft loss was detected (Analysis 7.3.3).

No differences were detected in the risk of leucopenia, thrombocytopenia, anaemia, neurological dysfunction or need to reduce or cease study medications (Analysis 7.3.3; Analysis 7.3.4; Analysis 7.3.5; Analysis 7.3.6; Analysis 7.3.7). No differences were detected in the risk for other herpes infections (Analysis 7.3.8). Non-viral infections were increased in patients treated with valaciclovir in one study (Analysis 7.3.9 (83 participants): RR 0.59, 95% CI 0.44 to 0.80) due to the increase in urinary tract infections in that group.

Kidney function

Kidney function at the end of the study did not differ significantly with valaciclovir compared with ganciclovir or valganciclovir (Analysis 7.4.1; Analysis 7.4.2).

Prophylaxis with different regimens of ganciclovir

Hertz 1998 Heart/lung compared daily with thrice weekly IV ganciclovir in heart-lung transplant recipients. Winston 2004 Liver and Nafar 2005 Kidney compared oral with IV ganciclovir.

Daily versus thrice weekly ganciclovir

No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection (Analysis 8.1.1; Analysis 8.1.2; Analysis 8.1.3; Analysis 8.1.4). In addition, no differences in all-cause mortality and death due to CMV disease (Analysis 8.1.5; Analysis 8.1.6) or in bacteraemia, bronchiolitis obliterans or leucopenia (Analysis 8.1.7; Analysis 8.1.8; Analysis 8.1.9) were detected.

Oral versus IV ganciclovir

No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection (Analysis 8.2.1; Analysis 8.2.2; Analysis 8.2.3; Analysis 8.2.4). In addition, no differences in all-cause mortality, acute rejection or graft loss (Analysis 8.2.5; Analysis 8.2.6; Analysis 8.2.7) or in leucopenia and the need to cease medications due to leucopenia (Analysis 8.2.8; Analysis 8.2.9) were detected.

Prophylaxis with extended durations of valganciclovir

Two studies compared extended durations of valganciclovir. One study compared 200 days with 100 days in kidney transplant recipients (IMPACT 2010 Kidney) and the other study compared one year with three months in lung transplant recipients (Palmer 2010

Lung). Data included in meta-analyses from Palmer 2010 Lung were taken from percentages reported in the study as the authors were not able to provide the original data.

CMV disease and CMV infection

The risk of CMV disease was significantly reduced at the end of treatment (Analysis 9.1.1 (2 studies, 454 participants): RR 0.20, 95% CI 0.12 to 0.35; I^2 = 0%), at 9 months (Analysis 9.1.2 (1 study, 318 participants): RR 0.39, 95% CI 0.25 to 0.60), 12 months (Analysis 9.1.3 (1 study, 318 participants): RR 0.44, 95% CI 0.29 to 0.66) and 24 months (Analysis 9.1.4 (1 study, 318 participants): RR 0.55, 95% CI 0.38 to 0.79). The number of patients with CMV syndrome (Analysis 9.2 (2 studies, 454 participants): RR 0.27, 95% CI 0.10 to 0.71/; I^2 = 12%) was also significantly reduced. The risk for CMV invasive disease was higher in lung transplant recipients compared with kidney transplant recipients at 12 months so there was considerable heterogeneity in the analysis (Analysis 9.3.1 (2 studies, 454 participants): RR 0.17, 95% CI 0.03 to 1.34; I^2 = 44%). There were few episodes of CMV invasive disease in kidney transplant recipients and the numbers did not differ at 24 months (Analysis 9.3.2).

The risk of CMV infection was significantly reduced at the end of treatment (Analysis 9.4.1 (2 studies, 454 participants): RR 0.27, 95% CI 0.10 to 0.71; I^2 = 82%), at 9 months (Analysis 9.4.2 (1 study, 318 participants): RR 0.27, 95% CI 0.10 to 0.71) and at 12 months (Analysis 9.4.3 (1 study, 318 participants): RR 0.73, 95% CI 0.57 to 0.95).

Other outcomes

There were no significant differences in all-cause mortality at 12 (Analysis 9.5.1) and 24 months (Analysis 9.5.2), in graft loss at 12 (Analysis 9.6.1) and 24 months (Analysis 9.6.2), in biopsy proven acute rejection at < 100 days (Analysis 9.7.1), 12 months (Analysis 9.7.2) and 24 months (Analysis 9.7.3) and in post-transplant diabetes mellitus (Analysis 9.8.2). There was considerable heterogeneity (I^2 = 87%) in the analysis of opportunistic infections (Analysis 9.8.1 (2 studies, 454 participants): RR 0.71, 95% CI 0.33 to 1.57) since IMPACT 2010 Kidney reported that opportunistic infections were significantly less common among patients treated with extended duration valganciclovir while Palmer 2010 Lung found no difference (Analysis 9.8.1 (318 participants): RR 0.48, 95% CI 0.30 to 0.77).

Adverse effects

Total treatment related adverse effects (Analysis 9.9.1) and serious treatment related adverse effects (Analysis 9.9.2) did not differ significantly between treatment groups. Leucopenia was significantly more common (Analysis 9.9.3 (1 study, 320 participants): RD 0.12, 95% CI 0.01 to 0.22) and significantly more likely to result in treatment termination (Analysis 9.9.4 (1 study, 320 participants): RD 0.04, 95% CI 0.00 to 0.07) in patients treated for 200 days compared with those treated for 100 days in the IMPACT 2010 Kidney. Termination for any treatment-related adverse effect did not differ significantly in the Palmer 2010 Lung study (Analysis 9.9.5). While the number of hospitalisations did not differ overall or for all adverse effects (Analysis 9.9.7) among treatment groups, there were significantly fewer hospitalisations for CMV disease in patients treated for 200 days (Analysis 9.9.6 (1 study, 418 total hospitalisations): RD -0.10, 95% CI -0.17 to -0.04) in the IMPACT 2010 Kidney. There was no significant increase in CMV mutants, which confer ganciclovir resistance, in participants with positive viral load who were treated for an extended duration compared with those treated for 100 days or three months (Analysis 9.9.8).

DISCUSSION

Summary of main results

Antiviral agents compared with placebo/no specific treatment

This systematic review found that the antiviral agents, ganciclovir, valaciclovir and aciclovir, improve outcomes for solid organ transplant recipients far beyond the primary indication for use. In addition to reducing the risk of CMV disease by 60%, these agents reduced all-cause mortality by 40%, predominantly due to reduced mortality from CMV disease, as well as reducing clinical disease caused by herpes simplex and herpes zoster (70%), bacterial infections (35%), and protozoal infections (70%). The relative benefits of aciclovir, ganciclovir and valaciclovir in relation to CMV disease and mortality appeared to be consistent among recipients of heart, kidney and liver transplants. These benefits occurred in both CMV positive recipients and CMV negative recipients of CMV positive organs, irrespective of whether immunosuppression included antilymphocyte antibody therapy, and were not dependent on the time of outcome assessment. Although there were no placebo-controlled RCTs of valganciclovir, a study (Paya 2004 All) comparing valganciclovir (the prodrug of ganciclovir) and ganciclovir demonstrated no significant differences in the risk for CMV disease, all-cause mortality and other outcomes, indicating that outcomes demonstrated in this systematic review in placebo/no treatment studies can be extrapolated to valganciclovir.

There was no clear reduction in graft loss or acute rejection, although a small but clinically important benefit has not been excluded. The summary relative risk for both outcomes favours antiviral agents but the 95% confidence intervals were relatively wide and consistent with there being no effect. The exception was in a predefined subgroup in a single study (Lowance 1999 Kidney) in which CMV prophylaxis reduced the risk for biopsy-proven acute rejection in CMV negative recipients of CMV positive kidney transplants by 50%.

Based on data from a single large study (Lowance 1999 Kidney) valaciclovir significantly increased the risk for hallucinations. There was no significant increase in adverse effects with aciclovir or ganciclovir, although the 95% CIs were wide. Very few studies adequately reported harms so that significant differences in adverse effects between medication and placebo could be excluded. It is possible that other differences in side effect profiles exist between agents but have not been demonstrated.

Relative efficacy of antiviral medications

Having demonstrated that antiviral agents as a drug class reduce all-cause mortality and CMV disease, we then sought to determine which antiviral regimen was the most beneficial. Indirect comparisons demonstrated no difference between antiviral agents administered. In head-to-head studies ganciclovir was significantly more effective than aciclovir in preventing CMV disease, demonstrating the importance of assessing the comparative effects of drugs in direct comparison studies. This difference may be explained by differences in duration of therapy in the indirect studies. Aciclovir was administered for 84 days or more but

ganciclovir was given for shorter durations (9 to 42 days) in seven of the 11 included ganciclovir studies. Hence, agent and duration was evaluated rather than agent alone, as in direct comparison studies.

One large study (Paya 2004 All) demonstrated no significant difference in efficacy between ganciclovir and its prodrug, valganciclovir. Although three small studies demonstrated no difference in efficacy to prevent CMV disease among ganciclovir or valganciclovir and valaciclovir (2VAL Study 2010 Kidney; Pavlopoulou 2005 Kidney; Reischig 2005 Kidney), the wide confidence intervals of the summary estimate (RR 0.74, 95% CI 0.15 to 3.75) indicate that a significant difference in efficacy cannot be excluded. Based on existing study data, aciclovir is inferior to ganciclovir, and no clear superiority has been demonstrated between ganciclovir and valganciclovir or between valaciclovir and ganciclovir/valganciclovir.

Prophylaxis with extended durations of valganciclovir

Extended prophylaxis with valganciclovir resulted in significant reductions in the risks of CMV disease, CMV infection and opportunistic infections but no significant differences in other outcomes (acute rejection, all-cause mortality, graft loss). Leucopenia was more common with extended duration of prophylaxis, but hospitalisations due to CMV disease were reduced.

Overall completeness and applicability of evidence

Antiviral agents compared with placebo/no specific treatment

Our major findings, that CMV antiviral prophylaxis prevents CMV disease and all-cause mortality, irrespective of organ transplanted and CMV serostatus, are strengthened by two features of the data; the consistency of these findings across all studies and the finding that almost all eligible studies reported both major outcomes of interest (lack of outcome reporting bias). We identified 19 eligible studies and the summary estimate favours antiviral medication for the outcome 'prevention of CMV disease' in 18 studies. Similarly, 17 studies contributed data to the all-cause mortality outcome. With fewer events, the play of chance would be expected to be greater, but only two studies (Macdonald 1995 Heart; Merigan 1992 Heart) had point estimates suggesting increased mortality from CMV prophylaxis. Unlike the outcome of CMV disease, no individual study demonstrated a significant reduction in all-cause mortality with antiviral medication. This was evident only from the meta-analytic estimate. The overall I^2 was 12.6% for CMV disease and 0% for all-cause mortality demonstrating very low heterogeneity beyond chance, despite the clear differences in patient groups (Characteristics of included studies). Supporting this contention, as shown in Table 1, no pre-defined potential source of variability for the effects of antiviral medication was significant, including standard quality items for study conduct and reporting such as allocation concealment, blinding and intention-to-treat. We cannot exclude a difference in the magnitude of the effect of antiviral medication in solid organ transplant recipients. However, any difference is likely to be clinically unimportant since data from 19 studies and about 2000 patients were insufficient to demonstrate any difference. In addition, the remarkable consistency in results across all studies suggests any undetected difference would be in magnitude, and not direction of effect.

The data were relatively sparse in four areas, and further research is still needed. For the outcome of all-cause mortality in heart transplant recipients, there are few relevant studies (2), patients (205) and events (4) making the effects of antiviral medications on heart transplant recipients very uncertain. Both studies had higher death rates in the active arms but the 95% confidence intervals were very wide, results are consistent with other patient groups (liver and kidney), and the likely pathway for benefit - reduction in CMV disease - is evident in this patient group.

Second, there were very scant data in the seronegative donor to seronegative recipient group, even though this group is frequently given antiviral agents to prevent CMV disease (Baliga 2004). These patients are almost exclusively not enrolled in studies, because of low event rates. However, there are no studies examining the efficacy of antiviral agents to prevent de novo CMV disease in such CMV seronegative patients.

Third, our conclusions on the other benefits of antiviral medications and the adverse effects of these drugs (Table 2) must be considered more cautiously for reasons of imprecision of summary estimates and that many eligible studies did not report these outcomes. Therefore, these results may be biased. The direction of bias cannot be determined without obtaining additional data from the authors regarding these outcomes.

Fourth, only one study specifically addressed children (Green 1997 Liver). This is despite that children commonly receive prophylaxis with antiviral agents since they are at a high risk of CMV disease because many are CMV seronegative and receive organs from CMV seropositive donors. Information on the efficacy of prophylaxis with antiviral agents from RCTs of adult transplant recipients has been extrapolated to children. Non randomised studies suggest valganciclovir is effective and tolerated in children (Camacho-Gonzalez 2011).

Relative efficacy of antiviral medications

The data clearly demonstrated that ganciclovir was superior to aciclovir in preventing CMV disease, and aciclovir is no longer used for prophylaxis. A single large study indicated no significant differences between oral ganciclovir and oral valganciclovir. Clinical practice data from this study have been extrapolated to indicate that oral valganciclovir can substitute for oral ganciclovir and valganciclovir is now generally the preferred agent for prophylaxis. Oral ganciclovir is no longer marketed.

Limited data (3 studies, 188 patients) meant that it remains unclear whether there are any differences in efficacy between valganciclovir/ganciclovir and valaciclovir in preventing CMV disease. The full results of all included patients are awaited for the 2VAL Study 2010 Kidney to determine whether any differences in efficacy exist between valganciclovir and valaciclovir. The available studies comparing valganciclovir/ganciclovir with valaciclovir have only enrolled kidney transplant recipients and it is unclear whether the data can be extrapolated to other transplanted organs.

Prophylaxis with extended durations of valganciclovir

Two studies in kidney (318 recipient CMV positive, donor CMV negative participants) and lung transplant recipients (136 donor CMV positive/recipient CMV negative; and donor CMV positive or negative/recipient CMV positive participants) have demonstrated that extended durations of prophylaxis with valganciclovir resulted in a lower risk of CMV disease and infection. Neither study identified an increase in CMV mutations resistant to therapy, but study numbers were likely to be too small to demonstrate any difference.

Both studies reported few cases of CMV disease occurring after the end of the extended period of prophylaxis. Further data are required to demonstrate whether the benefits of extended prophylaxis in other organ transplants justify the increased costs and adverse effects.

Quality of the evidence

This review now contains 37 studies. Most studies, including those recently published, did not provide sufficient information to determine whether sequence generation and allocation concealment were at a low risk of bias (Figure 5; Figure 6). It is a matter of concern that there was no blinding of participants, investigators and outcome assessors in almost 75% of studies. The primary outcome of CMV syndrome is a clinical diagnosis supported by laboratory diagnosis of CMV infection and other information. Therefore, it is possible that CMV syndrome was misdiagnosed in some participants. Studies that lack adequate allocation concealment and blinding may overestimate treatment effects (Moher 1998; Schultz 1995).

Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

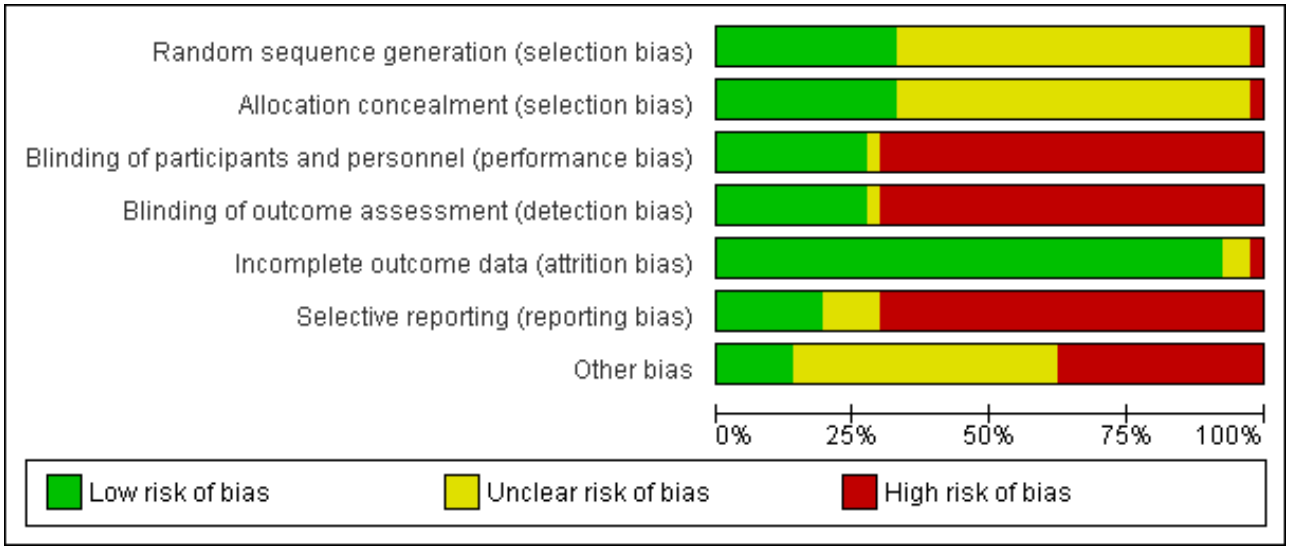


Figure 6. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

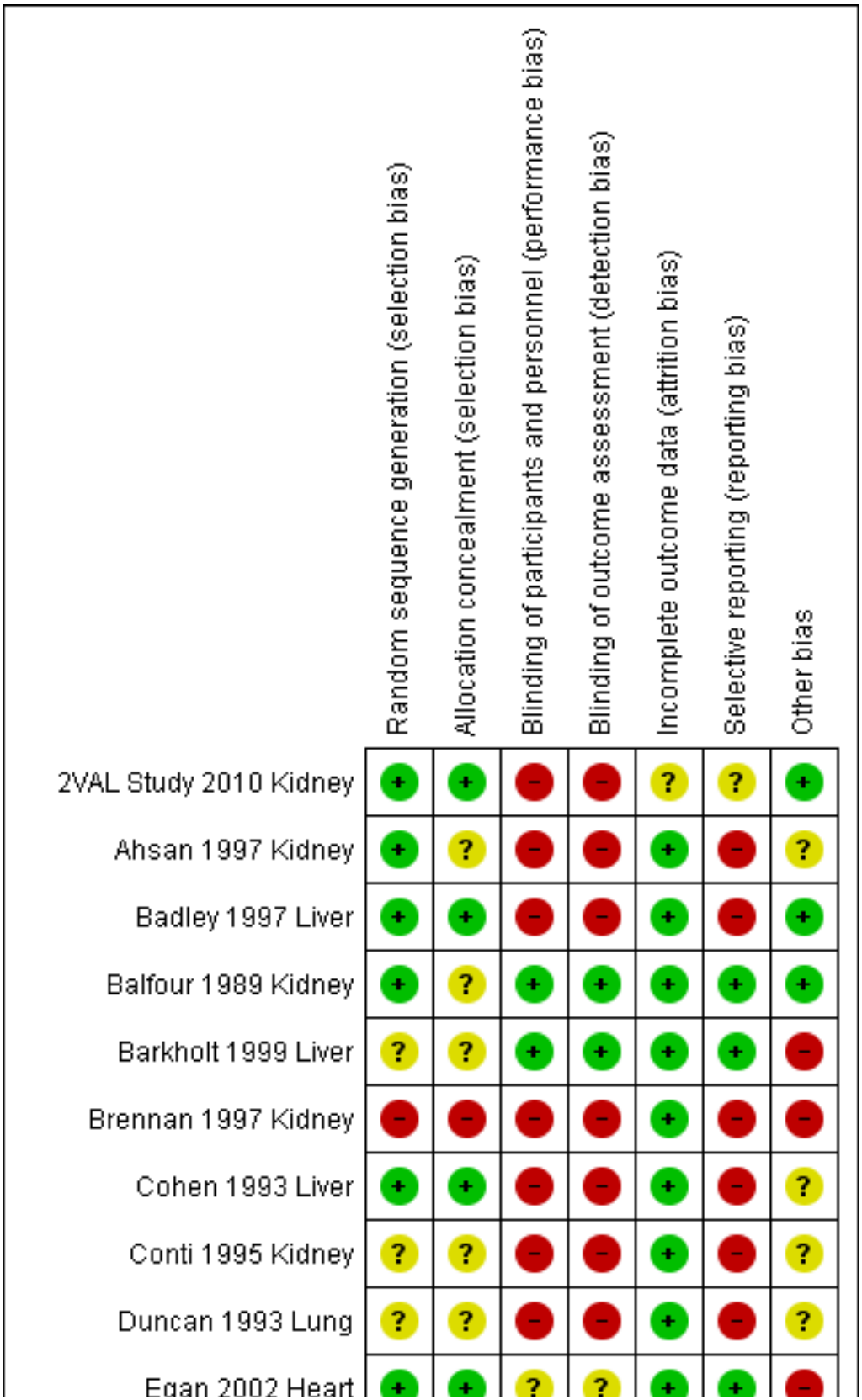


Figure 6. (Continued)

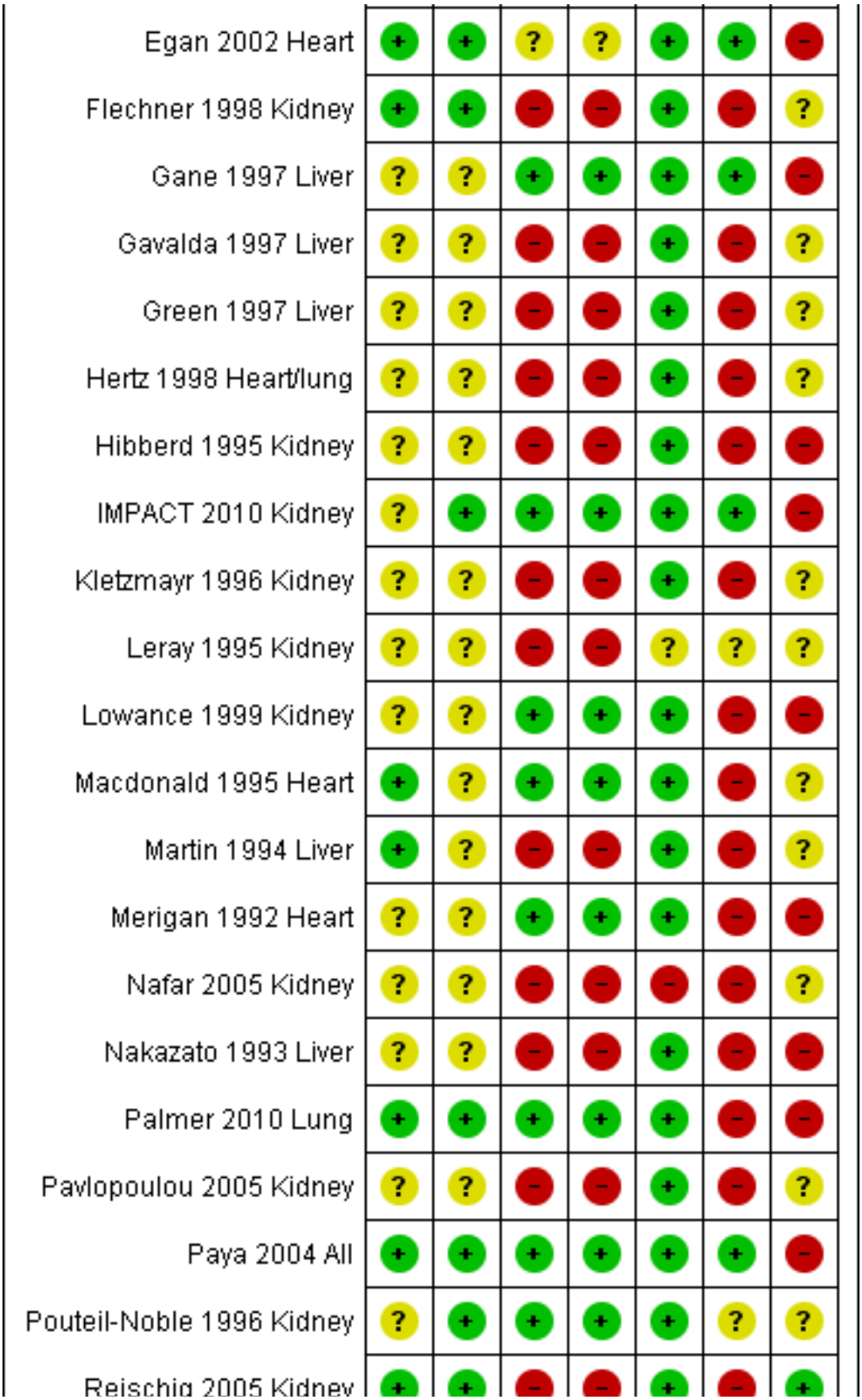
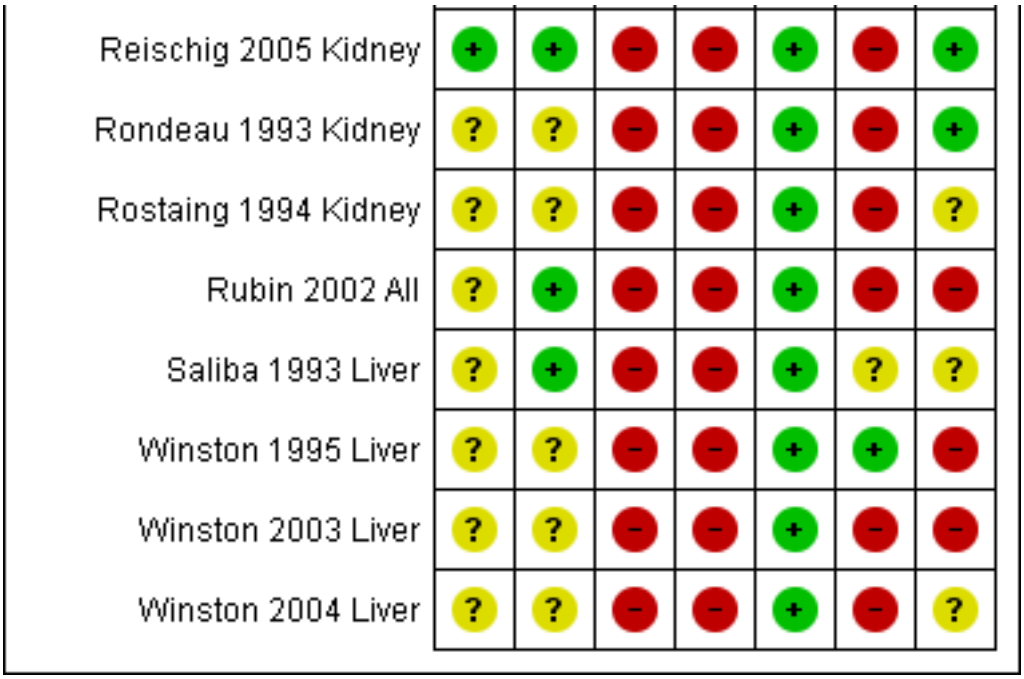


Figure 6. (Continued)



The overall quality of the evidence for studies comparing antiviral medications with placebo or no specific treatment was considered high for some outcomes (CMV disease, all-cause mortality, acute rejection, CMV disease in kidney transplant recipients). It was considered moderate for mortality due to CMV disease, CMV disease in liver or heart transplants and graft loss because of limited numbers of studies reporting these outcomes (Summary of findings for the main comparison).

The overall quality of the evidence for studies comparing ganciclovir and aciclovir was considered high for CMV disease in all patients and for acute rejection. It was considered moderate for all-cause mortality, mortality due to CMV disease and other viral infections, and low for other fungal infections and graft loss because of the limited number of events in the studies in which these outcomes were reported (Summary of findings 2).

The overall quality of the evidence for studies comparing ganciclovir/valganciclovir with aciclovir/valaciclovir was considered low because of the small number of studies with few participants (Summary of findings 3).

The overall quality of the evidence for studies comparing extended duration with three months of therapy was considered high for CMV disease, CMV syndrome, CMV infection and total adverse reactions. It was considered low for invasive CMV disease, acute rejection and opportunistic infections because of the heterogeneity between studies (Summary of findings 4).

Potential biases in the review process

The literature search was updated to July 2011. Although 29 additional reports of 13 studies, which had been included in previous versions of the review, were identified, these reports did not provide additional data for the review. It is possible that further reports of studies have been added to the Cochrane Renal Group's Specialised Register since the last search. Preliminary data from one study (2VAL Study 2010 Kidney) have been included in meta-analyses. It is possible that when full recruitment and follow-up are available, different results may be obtained.

About half the studies did not report all important outcomes so there is a risk of selection bias. In particular, there were limited data on death due to CMV disease, on graft loss and on other infections.

Agreements and disagreements with other studies or reviews

The results of this review confirm and expand the findings of three previous systematic reviews (Couchoud 1998b; Couchoud 1998a; Fiddian 2002; Gourishankar 2001), which included 12, 10 and 9 studies respectively comparing antiviral medications with placebo or no treatment for prevention of CMV disease. All found that prophylaxis reduced the risk for CMV disease in solid organ transplant recipients. One review (Couchoud 1998b; Couchoud 1998a) found no effect on mortality (10 studies; RR 0.69, 95% CI 0.41 to 1.18) and a second (Fiddian 2002), which included two studies using immunoglobulin and antiviral agents, found that prophylaxis with aciclovir or valaciclovir significantly reduced all-cause mortality (1321 patients; OR 0.60, 95% CI 0.40 to 0.90). Similarly, a more recent systematic review (Kalil 2005) including 11 studies, found that prophylaxis with antiviral medications compared with placebo or no specific treatment significantly reduced CMV disease, all-cause mortality and opportunistic infections with similar degrees of benefit to those found in our review, although inclusion criteria differed in the two reviews. Eight studies of prophylaxis included in our review were excluded from the analyses of universal prophylaxis in the review by Kalil 2005. The two reviews differed in that our review showed no significant reduction of acute rejection with antiviral prophylaxis but Kalil 2005 identified a significant reduction in acute rejection with treatment (OR 0.72, 95% CI 0.57 to 0.91) using a fixed-effect model for the analysis. However, there was some heterogeneity in

the analyses of acute rejection in both reviews. Further analyses using a random-effects model identified that both reviews found no significant differences in the risk of acute rejection between antiviral therapy and placebo/no specific treatment. Both reviews found a significant reduction in acute rejection using a fixed-effect model.

Our systematic review differs from previous reviews in that comparisons of different antiviral medications were included so that conclusions on the comparative effects of agents can be made. In addition, our review included a detailed exploration of potential heterogeneity. The finding of a reduction in all-cause mortality is largely explained by a reduced mortality due to CMV disease, although a reduction in mortality due to other causes cannot be totally excluded. The latter is biologically plausible because CMV disease leads to an increase in other opportunistic infections in heart and liver transplant recipients (George 1997; Valentine 1999). This is suggestive of a mechanism whereby the prevention of CMV disease may prevent other infective complications that contribute to overall mortality.

Both prophylaxis and pre-emptive therapy significantly reduce CMV disease compared with placebo or no specific therapy in solid organ transplant recipients. However, the available evidence base for prevention of CMV disease with prophylaxis compared with placebo/no specific therapy (19 studies, 1981 participants) is large and of high quality (GRADE) compared with the low quality data (6 studies, 288 participants) supporting pre-emptive therapy (Owers 2013). Further studies are required to determine the relative efficacies, adverse effects and costs of pre-emptive therapy and prophylaxis because currently available data (7 studies, 753 participants), while showing no significant differences in efficacy though a lower risk of leucopenia with pre-emptive therapy, demonstrated considerable heterogeneity among studies thus limiting the applicability of these data to patient management.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has shown that prophylaxis of CMV positive recipients and CMV negative recipients of CMV positive organs with antiviral medications given for three months post solid organ transplantation reduces the risk of CMV disease and all-cause mortality and may well reduce the risk of other opportunistic infections. What are the implications of this study to clinical practice? Previous treatment guidelines (Jassal 1998; Van der Bij 2001) recommended CMV prophylaxis for all recipients of solid organ transplants who received immunosuppression with antilymphocyte antibody products and for CMV negative recipients of CMV positive organs. In liver and heart transplant recipients, prophylaxis was also recommended for all CMV positive recipients of solid organ transplants because of the higher risk for CMV disease. Prophylaxis was not generally recommended for CMV positive kidney transplant recipients or for donor negative/recipient negative recipients (Jassal 1998) based on the low incidence of CMV disease in these groups. Our data suggested that these recommendations for use were too narrow because the benefits for patient survival and the constant relative benefits for CMV disease, irrespective of CMV serostatus, had not been recognised previously.

Recent guidelines recommend that all kidney transplant recipients except donor negative/recipient negative recipients should receive antiviral prophylaxis for at least three months post-transplant (KDIGO 2009). Similarly, guidelines from the AST Infectious Diseases Community of Practice (Humar 2009) recommend antiviral prophylaxis for both CMV seropositive recipients and for CMV seronegative recipients of CMV seropositive donors of any solid organ transplant. Consensus guidelines from the Infectious Disease Section of the Transplantation Society (Kotton 2010) recommended antiviral prophylaxis for CMV seronegative recipients of CMV positive donor organs. These guidelines considered that either prophylaxis or pre-emptive therapies could be used in CMV positive recipients but noted the lack of data on pre-emptive therapy in subpopulations including lung and small bowel transplants.

The absolute effects of antiviral medications on the prevention of CMV disease and all-cause mortality are shown quantitatively in groups of patients at different baseline risk for these outcomes (Table 3). The primary determinants for CMV disease are organ transplanted and serostatus whereas organ transplanted is the most important determinant for all-cause mortality. Table 3 shows that benefit exceeds harm for all but the lowest risk groups assuming equal importance of the outcomes. However, given that the clinical importance of all-cause mortality and CMV disease are significantly greater than the adverse effects of medications, most patients and clinicians, when provided with this information, are likely to use CMV prophylaxis with antiviral medications across all risk categories, except in the seronegative donor and recipient groups for whom there are few data.

Two RCTs (IMPACT 2010 Kidney; Palmer 2010 Lung) have now demonstrated that extended duration prophylaxis with valganciclovir in CMV seropositive donor/CMV negative recipients of kidney and lung transplants and seropositive recipients of lung transplants reduces the risk of CMV disease compared with three months of therapy suggesting that extended duration prophylaxis should be considered in patients at higher risk of CMV disease (Humar 2009).

Implications for research

There are no data from RCTs on the efficacy of prophylaxis compared with placebo in lung transplants and few data in heart transplants. However, such studies are no longer ethical based on the demonstration of efficacy in other organ transplants. Future studies may be required in the seronegative donor-recipient group depending on the prevalence of CMV disease in this group with newer and more potent immunosuppressive regimens. Further studies are required to determine optimum duration and dosage of medications in different organ transplants. Currently valganciclovir is most commonly used for prophylaxis. It remains possible that smaller doses than currently recommended may be effective for prophylaxis as demonstrated for IV ganciclovir (Hertz 1998 Heart/lung).

Further studies are required to evaluate the comparative effects, including harms, of antiviral medications in clinical use at present or in the future. More information is required on the efficacy of prophylaxis with different regimens of immunosuppressive regimens used for prevention and treatment of rejection in different organ transplants.

Overall, prophylaxis did not significantly reduce the risk for acute rejection or graft loss. Further information is required to determine whether prophylaxis can reduce the risk for rejection in particular groups of patients, whether it affects the number or severity of rejection episodes, and whether it reduces graft loss at time periods beyond one year.

Adequately powered and well-designed RCTs are required to determine the relative efficacies, adverse effects and costs of universal prophylaxis in comparison with pre-emptive therapies particularly in transplant populations at lower risk of CMV disease.

ACKNOWLEDGEMENTS

- Mr Peter Barclay, Dr Cheryl Jones, Ms Kathy Kable and Ms Dushanythi Vimalachandra who contributed to the original iteration of this review (Hodson 2005b). They contributed to the design, quality assessment, data collection, entry, analysis and interpretation, and writing of the review.
- This review has also been published in the *Lancet* (Hodson 2005c).
- The authors would like to thank all authors who responded to our enquiries about their studies.
- The authors wish to thank Ms Narelle Willis, Managing Editor of the Cochrane Renal Group, and Ms Ruth Mitchell and Ms Gail Higgins, Trials Search Co-ordinators of the Cochrane Renal Group, for their help with this study.
- The authors wish to thank Dr Cécile Couchoud, who wrote the initial systematic review *Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation* (Couchoud 1998a).

REFERENCES

References to studies included in this review

2VAL Study 2010 Kidney *{published data only}*

Randomized trial comparing valacyclovir versus valganciclovir prophylaxis of cytomegalovirus in renal transplant recipients. Australian and New Zealand Clinical Trials Registry ACTRN 12610000016033 Registered 26/9/2007.

Reischig T, Prucha M, Sedlackova L, Jindra P, Bouda M, Matejovic M. Lymphocyte function during valacyclovir and valganciclovir cytomegalovirus prophylaxis in renal transplant recipients [abstract]. *American Journal of Transplantation* 2010;**10**(Suppl 4):143.

* Reischig T, Prucha M, Sedlackova L, Lysak D, Bouda M, Matejovic M. Valganciclovir prophylaxis against cytomegalovirus impairs lymphocyte proliferation and activation in renal transplant recipients. *Antiviral Therapy* 2011;**16**(8):1227-35. [MEDLINE: 22155904]

Ahsan 1997 Kidney *{published data only}*

Ahsan N, Holman MJ, Dhilon S, Ream L, Yang HC. Oral ganciclovir (CytoveneR) effectively prevents cytomegalovirus (CMV) infection in renal transplant patients [abstract]. *Journal of the American Society of Nephrology* 1996;**7**(9):1929.

* Ahsan N, Holman MJ, Yang HC. Efficacy of oral ganciclovir in prevention of cytomegalovirus infection in post-kidney transplant patients. *Clinical Transplantation* 1997;**11**(6):633-9. [MEDLINE: 9408699]

Ahsan N, Holman MJ, Yang HC. Oral ganciclovir is effective in preventing CMV infection in renal transplant recipients [abstract]. *Nephrology* 1997;**3**(Suppl 1):S70.

Badley 1997 Liver *{published data only}*

* Badley AD, Seaberg EC, Porayko MK, Wiesner RH, Keating MR, Wilhelm MP, et al. Prophylaxis of cytomegalovirus infection in liver transplantation: A randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. *Transplantation* 1997;**64**(1):66-73. [MEDLINE: 9233703]

Paya CV, Marin E, Keating M, Dickson R, Porayko M, Wiesner R. Solid organ transplantation: results and implications of acyclovir use in liver transplants. *Journal of Medical Virology* 1993;**Suppl 1**:123-7. [MEDLINE: 8245877]

Balfour 1989 Kidney *{published data only}*

Balfour HH. Prevention of cytomegalovirus disease in renal allograft recipients. *Scandinavian Journal of Infectious Diseases - Supplement* 1991;**80**:88-93. [MEDLINE: 1725064]

* Balfour HH Jr, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *New England Journal of Medicine* 1989;**320**(21):1381-7. [MEDLINE: 2541335]

Balfour HH, Bean B, Mitchell CD, Sachs GW, Boen JR, Edelman CK. Acyclovir in immunocompromised patients with cytomegalovirus disease. A controlled trial at one institution. *American Journal of Medicine* 1982;**73**(1A):241-8. [MEDLINE: 6285715]

Balfour HH, Fletcher CV, Dunn D. Prevention of cytomegalovirus disease with oral acyclovir. *Transplantation Proceedings* 1991;**23**(2 Suppl 1):17-9. [MEDLINE: 1647558]

Fletcher CV, Englund JA, Edelman CK, Gross CR, Dunn DL, Balfour HH. Pharmacologic basis for high-dose oral acyclovir prophylaxis of cytomegalovirus disease in renal allograft recipients. *Antimicrobial Agents & Chemotherapy* 1991;**35**(5):938-43. [MEDLINE: 1649575]

Barkholt 1999 Liver *{published data only}*

Barkholt L, Lewensohn-Fuchs I, Ericzon BG, Tyden G, Andersson J. High-dose acyclovir prophylaxis reduces cytomegalovirus disease in liver transplant patients. *Transplant Infectious Disease* 1999;**1**(2):89-97. [MEDLINE: 11428976]

Brennan 1997 Kidney *{published data only}*

* Brennan DC, Garlock KA, Singer GG, Schnitzler MA, Lippmann BJ, Buller RS, et al. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. *Transplantation* 1997;**64**(12):1843-6. [MEDLINE: 9422429]

Brennan DC, Garlock KA, Singer GG, Schnizler MA, Lippmann BJ, Buller RS, et al. Prophylactic oral ganciclovir prevents cytomegalovirus infection and disease in renal transplant recipients [abstract]. 16th Annual Meeting. American Society of Transplant Physicians (ASTP); 1997 May 10-14; Chicago (ILL). 1997:87.

Brennan DC, Singer GG, Garlock KA, Schnitzler MA, Storch GA. Prophylactic oral ganciclovir prevents cytomegalovirus disease in renal transplant recipients [abstract]. *Nephrology* 1997;**3**(Suppl 1):S197.

Brennan DC, Storch GA, Singer GG, Lee L, Rueda J, Schnitzler MA. The prevalence of human herpesvirus-7 in renal transplant recipients is unaffected by oral or intravenous ganciclovir. *Journal of Infectious Diseases* 2000;**181**(5):1557-61. [MEDLINE: 10823753]

Singer GG, Storch GA, Burton KG, Lippmann BJ, Buller RS, Gaudreault-Keener M, et al. Prophylactic oral ganciclovir prevents cytomegalovirus disease in high-risk renal transplant recipients. [abstract]. *Journal of the American Society of Nephrology* 1996;**7**(9):1941.

Cohen 1993 Liver *{published data only}*

Cohen AT, O'Grady JG, Sutherland S, Sallie R, Tan KC, Williams R. Controlled trial of prophylactic versus therapeutic use of ganciclovir after liver transplantation in adults. *Journal of Medical Virology* 1993;**40**(1):5-9. [MEDLINE: 8390559]

Conti 1995 Kidney *{published data only}*

Conti DJ, Freed BM, Singh TP, Gallichio M, Gruber SA, Lempert N, et al. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplants recipients. *Archives of Surgery* 1995;**130**(11):1217-22. [MEDLINE: 7487465]

Duncan 1993 Lung *{published data only}*

Duncan SR, Grgurich WF, Iacono AT, Burckart GJ, Yousem SA, Paradis IL, et al. A comparison of ganciclovir and acyclovir to prevent cytomegalovirus after lung transplantation. *American Journal of Respiratory & Critical Care Medicine* 1994;**150**(1):146-52. [MEDLINE: 8025741]

Egan 2002 Heart *{published data only}*

Egan JJ, Carroll KB, Yonan N, Woodcock A, Crisp A. Valacyclovir prevention of cytomegalovirus reactivation after heart transplantation: a randomized trial. *Journal of Heart & Lung Transplantation* 2002;**21**(4):460-6. [MEDLINE: 11927223]

Flechner 1998 Kidney *{published data only}*

* Flechner SM, Avery RK, Fisher R, Mastroianni BA, Papajcik DA, O'Malley KJ, et al. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998;**66**(12):1682-8. [MEDLINE: 9884259]

Flechner SM, O'Malley K, Fisher R, Mastroianni B, Papajcik D, Avery R, et al. A randomized prospective trial of oral acyclovir vs oral ganciclovir for CMV prophylaxis in high risk kidney transplant recipients [abstract]. *Transplantation* 1998;**65**(12):S187.

Gane 1997 Liver *{published data only}*

* Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group. *Lancet* 1997;**350**(9093):1729-33. [MEDLINE: 9413463]

Saliba F, Bismuth H, Gane E, Valdecasas G, O'Grady J, Behrend M, et al. A randomized double blind versus placebo multicenter study of efficacy and tolerance of oral ganciclovir in the prevention of cytomegalovirus disease in hepatic transplanted patients. *Gastroenterologie Clinique et Biologique* 1997;**21**(2 bis):A157. [CENTRAL: CN-00583127]

Gavalda 1997 Liver *{published data only}*

Gavalda J, De Otero J, Murio E, Vargas V, Rossello J, Calico I, et al. Two grams daily of oral acyclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive liver transplant recipients. *Transplant International* 1997;**10**(6):462-5. [MEDLINE: 9428121]

Green 1997 Liver *{published data only}*

* Green M, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein- Barr virus disease after liver transplantation in children. *Clinical Infectious Diseases* 1997;**25**(6):1344-9. [MEDLINE: 9431375]

Green M, Reyes J, Nour B, Beatty D, Kaufman M, Wilson J, et al. Randomized trial of ganciclovir followed by high-dose oral acyclovir vs ganciclovir alone in the prevention of cytomegalovirus disease in pediatric liver transplant recipients: preliminary analysis. *Transplantation Proceedings* 1994;**26**(1):173-4. [MEDLINE: 8108926]

Hertz 1998 Heart/lung *{published data only}*

Hertz MI, Jordan C, Savik SK, Fox JMK, Park S, Bolman II RM, et al. Randomized trial of daily versus three-times-weekly prophylactic ganciclovir after lung and heart-lung transplantation. *Journal of Heart & Lung Transplantation* 1998;**17**(9):913-20. [MEDLINE: 9773865]

Hibberd 1995 Kidney *{published data only}*

Hibberd PL, Tolkoff-Rubin NE, Conti D, Stuart F, Thistlethwaite JR, Neylan JF, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease, in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Annals of Internal Medicine* 1995;**123**(1):18-26. [MEDLINE: 7762909]

IMPACT 2010 Kidney *{published data only}*

Blumberg E, Hauser I, Gahlemann CG, Berenson KL, Jardine A, Humar A. Cost-effectiveness model to evaluate 200-day vs 100-day valganciclovir (Valcyte®) prophylaxis to reduce CMV disease incidence post-transplant [abstract]. *American Journal of Transplantation* 2010;**10**(Suppl 4):126.

Chou S, Marousek G, Boivin G, Goyette N, Farhan M, Ives JA, et al. Recombinant phenotyping of cytomegalovirus sequence variants detected after 200 or 100 days of valganciclovir prophylaxis. *Transplantation* 2010;**90**(12):1409-13. [MEDLINE: 21030903]

Elston R, Bovin G, Goyette N, Voulgari A, Ives J, Farhan M. The IMPACT Study: genotypic analysis of cytomegalovirus UL54 and UL97 genes derived from patients receiving 100 or 200 days of valganciclovir (Valcyte®) prophylaxis [abstract]. *American Journal of Transplantation* 2010;**10**(Suppl 4):208.

Humar A, IMPACT ISC, Peeters P, Abramowicz D, Humar A, Lebranchu Y, et al. Response to questions regarding the design and results of the IMPACT trial. *American Journal of Transplantation* 2011;**11**(1):177-8. [MEDLINE: 21199360]

Humar A, Lebranchu Y, Vincenti F, Blumberg E, Punch J, Limaye A, et al. Long term results of the IMPACT study: 200 vs 100 days of valganciclovir prophylaxis in kidney transplant recipients [abstract]. *American Journal of Transplantation* 2010;**10**(Suppl S4):143.

* Humar A, Lebranchu Y, Vincenti F, Blumberg EA, Punch JD, Limaye AP, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *American Journal of Transplantation* 2010;**10**(5):1228-37. [MEDLINE: 20353469]

Humar A, Lebranchu Y, Vincenti F, Punch J, Abramowicz D, Blumberg E, et al. The Impact Study: Valganciclovir prophylaxis for until 200 days post-transplant in high risk kidney recipients substantially reduces the incidence of CMV disease [abstract]. *American Journal of Transplantation* 2009;**9**(Suppl 2):248.

Humar A, Limaye AP, Blumberg EA, Hauser IA, Vincenti F, Jardine AG, et al. Extended valganciclovir prophylaxis in D/R kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT Study. *Transplantation* 2010;**90**(12):1427-31. [MEDLINE: 21197713]

Kalil AC, Sun J, Florescu DF. IMPACT trial results should not change current standard of care of 100 days for cytomegalovirus prophylaxis. *American Journal of Transplantation* 2011;**11**(1):18-21. [MEDLINE: 21199346]

Welker H, Farhan M, Humar A, Washington C. Ganciclovir pharmacokinetic parameters do not change when extending valganciclovir cytomegalovirus prophylaxis from 100 to 200 days. *Transplantation* 2010;**90**(12):1414-9. [MEDLINE: 21076372]

Kletzmayr 1996 Kidney *{published data only}*

* Kletzmayr J, Kotzmann H, Popow-Kraupp T, Kovarik J, Klauser R. Impact of high-dose oral acyclovir prophylaxis on cytomegalovirus (CMV) disease in CMV high-risk renal transplant recipients. *Journal of the American Society of Nephrology* 1996;**7**(2):325-30. [MEDLINE: 8785404]

Kletzmayr J, Kotzmann H, Popow-Kraupp T, Kovarik J, Klauser R. Oral acyclovir in prevention of CMV disease in high-risk renal transplant recipients. [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:375.

Leray 1995 Kidney *{published data only}*

Leray H, Mourad G, Chong G, Segondy M, Mion C. Prophylactic treatment of cytomegalovirus primary infection with ganciclovir in renal transplant recipients. *Transplantation Proceedings* 1995;**27**(4):2448. [MEDLINE: 7652875]

Lowance 1999 Kidney *{published data only}*

Legendre CM, Norman DJ, Keating MR, Maclaine GD, Grant DM. Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation. *Transplantation* 2000;**70**(10):1463-8. [MEDLINE: 11118091]

Lowance D, Legendre C, Neumayer H, Norman D, Coggon G, Lee I, et al. Valaciclovir reduces the incidence of cytomegalovirus disease and acute graft rejection in CMV-seronegative recipients of a seropositive cadaveric renal allograft [abstract]. *Transplantation* 1998;**65**(12):S18.

* Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *New England Journal of Medicine* 1998;**340**(19):1462-70. [MEDLINE: 10320384]

Squifflet J, Mendez R. Valaciclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive renal allograft recipients [abstract]. 16th Annual Meeting. American Society of Transplant Physicians (ASTP); 1997 May 10-14; Chicago (ILL). 1997:87.

Macdonald 1995 Heart *{published data only}*

Macdonald PS, Keogh AM, Marshman D, Richens D, Harvison A, Kaan AM, et al. A double-blind placebo-controlled trial of low-dose ganciclovir to prevent cytomegalovirus disease after heart transplantation. *Journal of Heart & Lung Transplantation* 1995;**14**(1):32-8. [MEDLINE: 7727473]

Martin 1994 Liver *{published data only}*

Martin M, Manez R, Linden P, Estores D, Torre-Cisneros J, Kusne S, et al. A prospective randomized trial comparing sequential ganciclovir-high dose acyclovir to high dose acyclovir for prevention of cytomegalovirus disease in adult liver transplant recipients. *Transplantation* 1994;**58**(7):779-85. [MEDLINE: 7940710]

Merigan 1992 Heart *{published data only}*

* Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *New England Journal of Medicine* 1992;**326**(18):1182-6. [MEDLINE: 1313549]

Valantine HA, Gao SZ, Menon SG, Renlund DG, Hunt SA, Oyer P, et al. Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis: a post hoc analysis of a randomized, placebo-controlled study. *Circulation* 1999;**100**(1):61-6. [MEDLINE: 10393682]

Wagner JA, Ross H, Hunt S, Gamberg P, Valantine H, Merigan TC, Stinson EB. Prophylactic ganciclovir treatment reduces cytomegalovirus and fungal infections in orthotopic heart transplant recipients. ASTP 1995 Annual Meeting. 1995.

Wagner JA, Ross H, Hunt S, Gamberg P, Valantine H, Merigan TC, et al. Prophylactic ganciclovir treatment reduces fungal as well as cytomegalovirus infections after heart transplantation. *Transplantation* 1995;**60**(12):1473-7. [MEDLINE: 8545877]

Nafar 2005 Kidney *{published data only}*

Nafar M, Pezeshki ML, Farrokhi F, Einollahi B, Pour-Reza-Gholi F, Firouzan A, et al. A randomized prospective trial of oral versus intravenous ganciclovir for prophylaxis of cytomegalovirus infection and disease in high-risk kidney recipients. *Transplantation Proceedings* 2005;**37**(7):3053-5. [MEDLINE: 16213302]

Nakazato 1993 Liver *{published data only}*

Nakazato PZ, Burns W, Moore P, Garcia-Kennedy R, Cox K, Esquivel C. Viral prophylaxis in hepatic transplantation: Preliminary report of a randomized trial of acyclovir and gancyclovir. *Transplantation Proceedings* 1993;**25**(2):1935-7. [MEDLINE: 7682357]

Palmer 2010 Lung *{published data only}*

Finlen Copeland CA, Davis WA, Snyder LD, Banks M, Avery R, Palmer SM. Reduced lifetime incidence of cytomegalovirus with extended prophylaxis: Long-term follow up from a randomized controlled trial [abstract]. *Journal of Heart & Lung Transplantation* 2011;**30**(4 Suppl 1):S42. [EMBASE: 70383484]

* Palmer SM, Limaye AP, Banks M, Gallup D, Chapman J, Lawrence EC, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. *Annals of Internal Medicine* 2010;**152**(12):761-9. [MEDLINE: 20547904]

Pavlopoulou 2005 Kidney *{published data only}*

Pavlopoulou ID, Syriopoulou VP, Chelioti H, Daikos GL, Stamatiades D, Kostakis A, et al. A comparative randomised

study of valacyclovir vs. oral ganciclovir for cytomegalovirus prophylaxis in renal transplant recipients. *Clinical Microbiology & Infection* 2005;**11**(9):736-43. [MEDLINE: 16104989]

Paya 2004 All *{published data only}*

Boivin G, Goyette N, Gilbert C, Roberts N, Macey K, Paya C, et al. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. *Journal of Infectious Diseases* 2004;**189**(9):1615-8. [MEDLINE: 15116297]

Freeman RB, Macey K, Paya C, Pescovitz MD, Humar A, Dominquez E, et al. Risk factors for cytomegalovirus (CMV) disease: results from a multicenter randomized trial of valganciclovir (VGC) [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):391.

Humar A, Mazzulli T, Moussa G, Razonable RR, Paya CV, Pescovitz MD, et al. Clinical utility of cytomegalovirus (CMV) serology testing in high-risk CMV D+/R- transplant recipients. *American Journal of Transplantation* 2005;**5**(5):1065-70. [MEDLINE: 15816887]

* Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *American Journal of Transplantation* 2004;**4**(4):611-20. [MEDLINE: 15023154]

Pescovitz M, Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, et al. Valganciclovir for prevention of CMV disease: 12 month follow up of a randomized trial of 364 D +/R- transplant recipients [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):299.

Wiltshire H, Hirankarn S, Farrell C, Paya C, Pescovitz MD, Humar A, et al. Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clinical Pharmacokinetics* 2005;**44**(5):495-507. [MEDLINE: 15871635]

Wiltshire H, Paya CV, Pescovitz MD, Humar A, Dominguez E, Washburn K, et al. Pharmacodynamics of oral ganciclovir and valganciclovir in solid organ transplant recipients. *Transplantation* 2005;**79**(11):1477-83. [MEDLINE: 15940035]

Pouteil-Noble 1996 Kidney *{published data only}*

* Pouteil-Noble C, Megas F, Chapuis F, Bosshard S, Colin C, Hadj-Aissa A, et al. Cytomegalovirus prophylaxis by ganciclovir followed by high-dose acyclovir in renal transplantation: A randomized, controlled trial. *Transplantation Proceedings* 1996;**28**(5):2811. [MEDLINE: 8908072]

Pouteil-Noble C, Megas F, Chapuis F, Colul C, Bosshard S, Hadj-Aissa A, et al. Is CMV prophylaxis by ganciclovir-high dose acyclovir worthwhile in renal transplantation? A randomized, controlled, clinical and economical trial. [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:343.

Reischig 2005 Kidney *{published and unpublished data}*

Reischig T, Bouda M, Opatrny KJ, Treska V, Jindra P, Svecova M. Oral ganciclovir versus valacyclovir for prophylaxis of cytomegalovirus disease in renal transplant recipients [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002.

Reischig T, Jindra P, Mares J, Cechura M, Svecova M, Opatrny KJ, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection: a randomized comparison with oral ganciclovir and deferred therapy. [abstract]. *Transplantation* 2004;**78**(2 Suppl):483.

* Reischig T, Jindra P, Mares J, Opatrny K, Cechura M, Svecova M, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection. *Transplantation* 2005;**79**(3):317-24. [MEDLINE: 15699762]

Reischig T, Jindra P, Mares J, Opatrny K, Jr, Treska V, Cechura M, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection: a randomized comparison of oral ganciclovir and valacyclovir [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):493.

Reischig T, Jindra P, Svecova M, Kormunda S, Opatrny K, Treska V. The impact of cytomegalovirus disease and asymptomatic infection on acute renal allograft rejection. *Journal of Clinical Virology* 2006;**36**(2):146-51. [MEDLINE: 16531113]

Reischig T, Jindra P, Svecova M, Opatrny K, Treska V. The impact of cytomegalovirus disease and asymptomatic infection on acute renal allograft infection [abstract]. *American Journal of Transplantation* 2005;**5**(Suppl 11):382.

Reischig T, Opatrny JK, Treska V, Mares J, Jindra P, Svecova M. Prospective comparison of valacyclovir and oral ganciclovir for prevention of cytomegalovirus disease in high-risk renal transplant recipients. *Kidney & Blood Pressure Research* 2005;**28**(4):218-25. [MEDLINE: 16043964]

Reischig T, Opatrny K, Jr, Bouda M, Treska V, Jindra P, Svecova MT, et al. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation. *Transplant International* 2002;**15**(12):615-22. [MEDLINE: 12478408]

Rondeau 1993 Kidney *{published data only}*

* Rondeau E, Bourgeon B, Peraldi MN, Lang P, Buisson C, Schulte KM, et al. Effect of prophylactic ganciclovir on cytomegalovirus infection in renal transplant recipients. *Nephrology Dialysis Transplantation* 1993;**8**(9):858-62. [MEDLINE: 8255520]

Rondeau E, Bourgeon B, Peraldi MN, Lang P, Buisson C, Schulte KM, et al. Prophylaxis of CMV disease by ganciclovir (DHPG) in seronegative recipients of renal allograft from seropositive donors. *Transplant International* 1992;**5**(Suppl 1):S30-1.

Rostaing 1994 Kidney *{published data only}*

Rostaing L, Crespin A, Icart J, Lloveras JJ, Durand D, Martinet O, et al. Cytomegalovirus (CMV) prophylaxis by acyclovir in pre-transplant CMV-positive renal transplant recipients. *Transplant International* 1994;**7 Suppl 1**:331-5. [MEDLINE: 11271244]

Rubin 2002 All *{published data only}*

Rubin RH, Kemmerly SA, Conti D, Doran M, Murray BM, Neylan JF, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transplant Infectious Disease* 2000;**2**(3):112-7. [MEDLINE: 11429021]

Saliba 1993 Liver *{published data only}*

Saliba F, Eyraud D, Samuel D, David MF, Arulnaden JL, Dussaix E, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. *Transplantation Proceedings* 1993;**25**(1 Pt 2):1444-5. [MEDLINE: 8382876]

Winston 1995 Liver *{published data only}*

Winston DJ, Wirin D, Shaked A, Busuttil RW. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995;**346**(8967):69-74. [MEDLINE: 7603215]

Winston 2003 Liver *{published data only}*

Winston DJ, Busuttil RW. Randomized controlled trial of oral ganciclovir versus oral acyclovir after induction with intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in cytomegalovirus-seropositive liver transplant recipients. *Transplantation* 2003;**75**(2):229-33. [MEDLINE: 12548129]

Winston 2004 Liver *{published data only}*

Winston DJ, Busuttil RW. Randomized controlled trial of sequential intravenous and oral ganciclovir versus prolonged intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in high-risk cytomegalovirus-seronegative liver transplant recipients with cytomegalovirus-seropositive donors. *Transplantation* 2004;**77**(2):305-8. [MEDLINE: 14742998]

References to studies excluded from this review

Ahsan 1998 *{published data only}*

Ahsan N, Holman MJ, Sonderbye L, Langhoff E, Yang HC. Oral ganciclovir in the prevention of cytomegalovirus infection in postkidney transplant 'CMV at risk' recipients: A controlled, comparative study of two regimens (750 mg Bid and 500 mg Bid). *Transplantation Proceedings* 1998;**30**(4):1383-5. [MEDLINE: 9636560]

Arbo 2000 *{published data only}*

Arbo MD, Snydman DR, Wong JB, Goldberg HS, Schmid CH, Pauker SG. Cytomegalovirus immune globulin after liver transplantation: a cost-effectiveness analysis. *Clinical Transplantation* 2000;**14**(1):19-27. [MEDLINE: 10693631]

Brennan 1997 *{published data only}*

Brennan DC, Garlock KA, Lippmann BA, Buller RS, Gaudreault-Keener M, Lowell JA, et al. Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive or deferred therapy. *Journal of the American Society of Nephrology* 1997;**8**(1):118-25. [MEDLINE: 9013456]

Brennan DC, Garlock KA, Lippmann BJ, Buller RS, Gaudreault-Keener M, Lowell JA, et al. Polymerase chain reaction-triggered preemptive or deferred therapy to control cytomegalovirus-associated morbidity and costs in renal transplant patients. *Transplantation Proceedings* 1997;**29**(1-2):809-11. [MEDLINE: 9123536]

Brennan DC, Storch GA, Singer GG, Lee L, Rueda J, Schnitzler MA. The prevalence of human herpesvirus-7 in renal transplant recipients is unaffected by oral or intravenous ganciclovir. *Journal of Infectious Diseases* 2000;**181**(5):1557-61. [MEDLINE: 10823753]

Brennan 2001 *{published data only}*

Brennan DC. Cytomegalovirus in renal transplantation. *Journal of the American Society of Nephrology* 2001;**12**(4):848-55. [MEDLINE: 11274248]

Devolder 2010 *{published data only}*

Devolder I. The influence of intensive education and coaching on compliance for oral ganciclovir in the prophylaxis of CMV: an open randomised trial. clinicaltrials.gov/ct2/show/NCT00566072 (accessed 21 December 2012).

Dickinson 1996 *{published data only}*

Dickinson BI, Gora-Harper ML, McCraney SA, Gosland M. Studies evaluating high-dose acyclovir, intravenous immune globulin, and cytomegalovirus hyperimmunoglobulin for prophylaxis against cytomegalovirus in kidney transplant recipients. *Annals of Pharmacotherapy* 1996;**30**(12):1452-64. [MEDLINE: 8968459]

Falagas 1997 *{published data only}*

Falagas ME, Snydman DR, Ruthazer R, Griffith J, Werner BG, Freeman R, et al. Cytomegalovirus immune globulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. The Boston Center for Liver Transplantation CMVIG Study Group. *Clinical Transplantation* 1997;**11**(5 Pt 1):432-7. [MEDLINE: 9361936]

Fehir 1989 *{published data only}*

Fehir KM, Decker WA, Samo T, Young JB, Lederer E, Lawrence EC. Immune globulin (GAMMAGARD) prophylaxis of CMV infections in patients undergoing organ transplantation and allogeneic bone marrow transplantation. *Transplantation Proceedings* 1989;**21**(1 Pt 3):3107-9. [MEDLINE: 2539691]

Ferreira 2004 *{published data only}*

Ferreira A, Felipe CR, Motegi SA, Hosaka BA, Tamura MK, Kamura LA, et al. Relationship between immunosuppression and subsequent development of CMV disease [abstract]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego, (CA). 2004.

Fishman 2000 *{published data only}*

Fishman JA, Doran MT, Volpicelli SA, Cosimi AB, Flood JG, Rubin RH. Dosing of intravenous ganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplant recipients. *Transplantation* 2000;**69**(3):389-94. [MEDLINE: 10706048]

Gerna 2003 *{published data only}*

Gerna G, Baldanti F, Lilleri D, Parea M, Torsellini M, Castiglioni B, et al. Human cytomegalovirus pp67 mRNAemia versus pp65 antigenemia for guiding preemptive therapy in heart and lung transplant recipients: a prospective, randomized, controlled, open-label trial. *Transplantation* 2003;**75**(7):1012-9. [MEDLINE: 12698090]

Gerna 2008 *{published data only}*

Gerna G, Lilleri D, Callegaro A, Goglio A, Cortese S, Stroppa P, et al. Prophylaxis followed by preemptive therapy versus preemptive therapy for prevention of human cytomegalovirus disease in pediatric patients undergoing liver transplantation. *Transplantation* 2008;**86**(1):163-6. [MEDLINE: 18622294]

Greger 1988 *{published data only}*

Greger B, Schareck WD, Busing M, Mellert J, Muller GH, Hopt UT, et al. Are the risk of viral infections increased in kidney transplant patients receiving triple-drug therapy?. *Transplantation Proceedings* 1988;**20**(1 Suppl 1):466-8. [EMBASE: 1988111944]

Griffiths 1997 *{published data only}*

Griffiths PD. Prophylaxis against CMV infection in transplant patients. *Journal of Antimicrobial Chemotherapy* 1997;**39**(3):299-301. [MEDLINE: 9096177]

Griffiths 2010 *{published data only}*

Griffiths PD. Determining a viral load threshold for pre-emptive therapy for cytomegalovirus infection in transplant patients using real time PCR monitoring. clinicaltrials.gov/ct2/show/NCT00947141 (accessed 21 December 2012).

Grundmann 1986 *{published data only}*

Grundmann R, Wienand P, Runde A. The value of a prophylactic CMV-IgG-treatment in renal transplant recipients [abstract]. *Nephrology Dialysis Transplantation* 1986;**1**(2):144.

Hecht 1988 *{published data only}*

Hecht DW, Snydman DR, Crumpacker CS, Werner BG, Heinze-Lacey B. Ganciclovir for treatment of renal transplant-associated primary cytomegalovirus pneumonia. *Journal of Infectious Diseases* 1988;**157**(1):187-90. [MEDLINE: 2826608]

Huurman 2006 *{published data only}*

Huurman VA, Kalpoe JS, van de LP, Vaessen N, Ringers J, Kroes AC, et al. Choice of antibody immunotherapy influences cytomegalovirus viremia in simultaneous pancreas-kidney transplant recipients. *Diabetes Care* 2006;**29**(4):842-7. [MEDLINE: 16567825]

Jung 2001 *{published data only}*

Jung C, Engelmann E, Borner K, Offermann G. Preemptive oral ganciclovir therapy versus prophylaxis to prevent symptomatic cytomegalovirus infection after kidney transplantation. *Transplantation Proceedings* 2001;**33**(8):3621-3. [MEDLINE: 11750538]

Offermann G, Jung C. Preemptive oral ganciclovir therapy versus prophylaxis to prevent symptomatic cytomegalovirus infection after kidney transplantation [abstract no: 1094]. A Transplant Odyssey; 2001 Aug 20-23; Istanbul (Turkey). 2001.

Jurim 1996 *{published data only}*

Jurim O, Martin P, Winston DJ, Shackleton C, Holt C, Feller J, et al. Failure of ganciclovir prophylaxis to prevent allograft reinfection following orthotopic liver transplantation for chronic hepatitis B infection. *Liver Transplantation & Surgery* 1996;**2**(5):370-4. [MEDLINE: 9346678]

Khoury 2006 *{published data only}*

Brennan DC, Hardinger KL, Bohl DL, Lockwood M, Torrence S, Schuessler R, et al. Preemptive vs prophylactic valganciclovir for CMV in renal transplantation: early results from a randomized, prospective trial [abstract no: SA-FC009]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):23A.

Khoury JA, Storch GA, Bohl DL, Schuessler RM, Torrence SM, Lockwood M, et al. Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *American Journal of Transplantation* 2006;**6**(9):2134-43. [MEDLINE: 16780548]

Spinner ML, Saab G, Casabar E, Bowman LJ, Storch GA, Brennan DC. Impact of prophylactic versus preemptive valganciclovir on long-term renal allograft outcomes. *Transplantation* 2010;**90**(4):412-8. [MEDLINE: 20555305]

Kim 2000 *{published data only}*

Kim WR, Badley AD, Wiesner RH, Porayko MK, Seaberg EC, Keating MR, et al. The economic impact of cytomegalovirus infection after liver transplantation. *Transplantation* 2000;**69**(3):357-61. [MEDLINE: 10706042]

Kletzmayr 2000 *{published data only}*

Kletzmayr J, Kreuzwieser E, Watkins-Riedel T, Berlakovich G, Kovarik J, Klauser R. Long-term oral ganciclovir prophylaxis for prevention of cytomegalovirus infection and disease in cytomegalovirus high-risk renal transplant recipients. *Transplantation* 2000;**70**(8):1174-80. [MEDLINE: 11063336]

Kliem 2008 *{published data only}*

Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. *American Journal of Transplantation* 2008;**8**(5):975-83. [MEDLINE: 18261177]

Radermacher J, Fricke L, Burg M, Mischak H, Rohde F, Kliem V. Influence of prophylactic compared with early ganciclovir treatment on graft survival in renal allograft recipients [abstract]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):111A.

Koetz 2001 *{published data only}*

Koetz AC, Delbruch R, Furtwangler A, Hufert FT, Neumann-Haefelin D, Kirste G, et al. Cytomegalovirus pp65 antigen-guided preemptive therapy with ganciclovir in solid organ transplant recipients: a prospective double-blind, placebo-controlled study. *Transplantation* 2001;**72**(7):1325-7. [MEDLINE: 11602864]

Kuypers 1999 *{published data only}*

Kuypers DR, Vanrenterghem YF. Prophylaxis of cytomegalovirus infection in renal transplantation: new data for an old problem. *Nephrology Dialysis Transplantation* 1999;**14**(10):2304-8. [MEDLINE: 10528649]

Laske 1991 *{published data only}*

Laske A, Gallino A, Mohacsi P, Bauer EP, Carrel T, Von Segesser LK, et al. Prophylactic treatment with ganciclovir for cytomegalovirus infection in heart transplantation. *Transplantation Proceedings* 1991;**23**(1 Pt 2):1170-3. [MEDLINE: 1846456]

Laske 1992 *{published data only}*

Laske A, Carrel T, Niederhauser U, Bauer E, Pasic M, Von Segesser LK, et al. The prevention of cytomegalus infection after heart transplantation. *Helvetica Chirurgica Acta* 1992;**58**(4):527-32. [EMBASE: 1992114614]

Luan 2009 *{published data only}*

Luan FL, Stucky L, Park JM, Ojo A. Economic analysis of extended cytomegalovirus prophylaxis in high risk kidney transplant patients [abstract]. *American Journal of Transplantation* 2009;**9**(Suppl 2):250.

Lumbreras 1993 *{published data only}*

Lumbreras C, Otero JR, Herrero JA, Gomez R, Lizasoain M, Aguado JM, et al. Ganciclovir prophylaxis decreases frequency and severity of cytomegalovirus disease in seropositive liver transplant recipients treated with OKT3 monoclonal antibodies. *Antimicrobial Agents & Chemotherapy* 1993;**37**(11):2490-2. [MEDLINE: 8285641]

MacDonald 1991 *{published data only}*

MacDonald AS, Belitsky P, Cohen A, Lee S. Cytomegalovirus disease prophylaxis in seronegative recipients of kidneys from seropositive donors by combination of cytomegalovirus-hyperimmune globulin and low-dose acyclovir. *Transplantation Proceedings* 1991;**23**(1 Pt 2):1355-6. [MEDLINE: 1846463]

Marker 1980 *{published data only}*

Marker SC, Howard RJ, Groth KE, Mastri AR, Simmons RL, Balfour HH. A trial of vidarabine for cytomegalovirus infection in renal transplant patients. *Archives of Internal Medicine* 1980;**140**(11):1441-4. [MEDLINE: 6254457]

Martin 1993 *{published data only}*

Martin M. Antiviral prophylaxis for CMV infection in liver transplantation. *Transplantation Proceedings* 1993;**25**(5 Suppl 4):10-4. [MEDLINE: 8212301]

Martin 1994 *{published data only}*

Martin M. Combination antiviral strategies in managing cytomegalovirus infection. *Transplantation Proceedings* 1994;**26**(5 Suppl 1):28-30. [MEDLINE: 7940973]

Martin 1995 *{published data only}*

Martin M. Prophylactic cytomegalovirus management strategies. *Transplantation Proceedings* 1995;**27**(5 Suppl 1):23-7. [MEDLINE: 7482812]

Mattes 2004 *{published data only}*

Mattes FM, Hainsworth EG, Geretti AM, Nebbia G, Prentice G, Potter M, et al. A randomized, controlled trial comparing ganciclovir to ganciclovir plus foscarnet (each at half dose) for preemptive therapy of cytomegalovirus infection in transplant recipients. *Journal of Infectious Diseases* 2004;**189**(8):1355-61. [MEDLINE: 15073671]

McGavin 2001 *{published data only}*

McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001;**61**(8):1153-83. [MEDLINE: 11465876]

Moreno 1999 *{published data only}*

Moreno J, Montero JL, Gavilan F, Costan G, Herrero C, Cardenas M, et al. Open clinical trial with oral acyclovir for the prophylaxis of disease by Cytomegalovirus in low risk liver transplant recipients. *Enfermedades Infecciosas y Microbiologia Clinica* 1999;**17**(8):382-5. [MEDLINE: 10563084]

Mullen 1998 *{published data only}*

Mullen GM, Silver MA, Malinowska K, Lawless CE, Lichtenberg RC, Barath PC, et al. Effective oral ganciclovir prophylaxis against cytomegalovirus disease in heart transplant recipients. *Transplantation Proceedings* 1998;**30**(8):4110-2. [MEDLINE: 9865316]

Murray 1997 *{published data only}*

Murray BM, Blas S. Cost comparison of two approaches to the management of CMV infection in renal transplant recipients [abstract]. *Journal of the American Society of Nephrology* 1997;**8**(Program & Abstracts):695A.

Paya 2002 *{published data only}*

Paya CV, Wilson JA, Espy MJ, Sia IG, DeBernardi MJ, Smith TF, et al. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *Journal of Infectious Diseases* 2002;**185**(7):854-60. [MEDLINE: 11920308]

Pescovitz 2009 *{published data only}*

* Pescovitz MD, Bloom R, Pirsch J, Johnson J, Gelone S, Villano SA. A randomized, double-blind, pharmacokinetic study of oral maribavir with tacrolimus in stable renal transplant recipients. *American Journal of Transplantation* 2009;**9**(10):2324-30. [MEDLINE: 19663892]

Pouteil 1991 *{published data only}*

Pouteil-Noble C, Betuel H, Raffaele P, Megri K, Louvier C, Lefrancois N, et al. Influence of HLA compatibility on cytomegalovirus infection in kidney transplantation [Influence de la compatibilite HLA sur l'infection a cytomegalovirus en transplantation renale]. *Presse Medicale* 1991;**20**(40):2022-4. [MEDLINE: 1662376]

PROTECT Study 2010 *{published data only}*

Potena L. Efficacy and safety of anti-cytomegalovirus prophylaxis versus pre-emptive approaches with valganciclovir in heart transplant recipients treated with everolimus or mycophenolate. a randomized open-label study for prevention

of cardiac allograft vasculopathy (PROTECT). clinicaltrials.gov/ct2/show/NCT00966836 (accessed 21 December 2012).

Queiroga 2003 *{published data only}*

Quieroga M, Castro MC, Araujo LM, Alves CF, Kakehashi E, Panutti C, et al. A prospective, randomized controlled trial comparing oral ganciclovir with weekly monitored CMV-antigenemia in renal transplant patients with a high-risk for CMV infection [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):511.

Rayes 2001 *{published data only}*

Rayes N, Seehofer D, Schmidt CA, Oettle H, Muller AR, Steinmuller T, et al. Prospective randomized trial to assess the value of preemptive oral therapy for CMV infection following liver transplantation. *Transplantation* 2001;**72**(5):881-5. [MEDLINE: 11571454]

Reischig 2008 *{published data only}*

Reischig T, Jindra P, Hes O, Svecova M, Klaboch J, Treska V. Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *American Journal of Transplantation* 2008;**8**(1):69-77. [MEDLINE: 17973956]

Reischig T, Jindra P, Klaboch J, Svecova M, Hes O, Treska V. Valacyclovir prophylaxis for cytomegalovirus is associated with reduced risk of acute renal allograft rejection compared to preemptive valganciclovir therapy [abstract]. *Transplant International* 2007;**20**(Suppl 2):185.

Reischig T, Nemcova J, Vanecek T, Jindra P, Hes O, Bouda M, et al. Intragraft cytomegalovirus infection: a randomized trial of valacyclovir prophylaxis versus pre-emptive therapy in renal transplant recipients. *Antiviral Therapy* 2010;**15**(1):23-30. [MEDLINE: 20167988]

Reischig T, Nemcova J, Vanecek T, Jindra P, Hes O, Bouda M, et al. Preemptive valganciclovir therapy is not associated with increase in cytomegalovirus (CMV) DNA in renal allograft biopsy specimens compared with valacyclovir prophylaxis [abstract]. *Transplantation* 2008;**86**(2S):131.

Reischig T, Nmcov J, Vanek T, Jindra P, Hes O, Bouda M, et al. Cytomegalovirus infection in the graft: Results of a randomised study comparing valacyclovir prophylaxis and preemptive treatment after renal transplantation [abstract]. *Kidney & Blood Pressure Research* 2010;**33**(4):324. [EMBASE: 70448142]

Sagedal 2003 *{published data only}*

Sagedal S, Nordal KP, Hartmann A, Midvedt K, Foss A, Asberg A, et al. Pre-emptive therapy of CMVpp65 antigen positive renal transplant recipients with oral ganciclovir: a randomized, comparative study. *Nephrology Dialysis Transplantation* 2003;**18**(9):1899-908. [MEDLINE: 12937241]

Said 2007 *{published data only}*

* Said T, Nampoory MR, Pacsa AS, Essa S, Madi N, Fahim N, et al. Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplantation Proceedings* 2007;**39**(4):997-9. [MEDLINE: 17524873]

Schafers 1988 *{published data only}*

Schafers H-J, Wahlers T, Jurmann M, Fieguth H-G, Milbradt H, Flik J, et al. Hyperimmuneglobulin for cytomegalovirus prophylaxis following heart transplantation. *Journal of Hospital Infection* 1988;**12**(Suppl D):61-5. [MEDLINE: 2902131]

Schnitzler 2000 *{published data only}*

Schnitzler MA, Metheney TG, Rueda JF, Woodward RS, Lowell JA, Singer GG, et al. A 3-year follow-up of pre-emptive vs deferred treatment of cytomegalovirus disease in renal transplantation. *Clinical Drug Investigation* 2000;**19**(5):367-74. [EMBASE: 2000190076]

Singh 1994 *{published data only}*

Sing N, Yu VL, Mieles L, Wagener MM, Miner RC, Gayowsky T. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. *Annals of Internal Medicine* 1994;**120**(5):375-81. [MEDLINE: 8304654]

Singh 1995 *{published data only}*

Singh TP, Gruber SA, Lempert N, Freed B, Conti DJ. Efficacy of cytomegalovirus prophylaxis in renal retransplantation. *Transplantation Proceedings* 1995;**27**(1):964-5. [MEDLINE: 7879247]

Singh 2000 *{published data only}*

* Singh N, Paterson DL, Gayowsky T, Wagener MM, Marino IR. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus iv ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients. *Transplantation* 2000;**70**(5):717-22. [MEDLINE: 11003347]

Singh N, Yu VL, Gayowski T, Marino IR. CMV antigenemia directed preemptive prophylaxis with oral ganciclovir for the prevention of CMV disease in liver transplant recipients: a prospective, randomised, controlled trial. [abstract]. *Transplantation* 1998;**65**(12):S113.

Snydman 1991a *{published data only}*

Snydman DR. Cytomegalovirus infections in the immunocompromised transplant patient. Prevention of cytomegalovirus disease with intravenous immune globulin. *Transplantation Proceedings* 1991;**23**(2 Suppl 1):20-5. [MEDLINE: 1647560]

Snydman 1991b *{published data only}*

Snydman DR, Werner BG, Tilney NL, Kirkman RL, Milford EL, Cho SI, et al. Final analysis of primary cytomegalovirus disease prevention in renal transplant recipients with a cytomegalovirus-immune globulin: comparison of the randomized and open-label trials. *Transplantation Proceedings* 1991;**23**(1 Pt 2):1357-60. [MEDLINE: 1846464]

Snydman 1994 *{published data only}*

Snydman DR, Werner BG, Dougherty NN, Griffith J, Rohrer RH, Freeman R, et al. A further analysis of the use of cytomegalovirus immune globulin in orthotopic liver transplant patients at risk for primary infection. Boston Center for Liver Transplantation CMVIG-Study Group. *Transplantation Proceedings* 1994;**26**(5 Suppl 1):23-7. [MEDLINE: 7940972]

Snydman 2001 *{published data only}*

Snydman DR. Historical overview of the use of cytomegalovirus hyperimmune globulin in organ transplantation. *Transplant Infectious Disease* 2001;**3**(Suppl 2):6-13. [MEDLINE: 11926753]

Speich 1999 *{published data only}*

Speich R, Thurnheer R, Gaspert A, Weder W, Boehler A. Efficacy and cost effectiveness of oral ganciclovir in the prevention of cytomegalovirus disease after lung transplantation. *Transplantation* 1999;**67**(2):315-20. [MEDLINE: 10075601]

Stratta 1992 *{published data only}*

Stratta RJ, Shaefer MS, Cushing KA, Markin RS, Reed EC, Langnas AN, et al. A randomized prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients receiving OKT3 therapy. *Archives of Surgery* 1992;**127**(1):55-64. [MEDLINE: 1310385]

Tong 2002 *{published data only}*

Tong CY, Bakran A, Williams H, Cheung CY, Peiris JS. Association of human herpesvirus 7 with cytomegalovirus disease in renal transplant recipients. *Transplantation* 2000;**70**(1):213-6. [MEDLINE: 10919606]

Turgeon 1998 *{published data only}*

Turgeon N, Fishman JA, Basgoz N, Tolkoff-Rubin NE, Doran M, Cosimi AB, et al. Effect of oral acyclovir or ganciclovir therapy after preemptive intravenous ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus seropositive renal and liver transplant recipients receiving antilymphocyte antibody therapy. *Transplantation* 1998;**66**(12):1780-6. [MEDLINE: 9884276]

Valantine 1995 *{published data only}*

Valantine HA. Prevention and treatment of cytomegalovirus disease in thoracic organ transplant patients: Evidence for a beneficial effect of hyperimmune globulin. *Transplantation Proceedings* 1995;**27**(5 Suppl 1):49-57. [MEDLINE: 7482821]

VICTOR Study 2007 *{published data only}*

Asberg A, Humar A, Jardine AG, Rollag H, Pescovitz MD, Mouas H, et al. Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. *American Journal of Transplantation* 2009;**9**(5):1205-13. [MEDLINE: 19422345]

Asberg A, Humar A, Rollag H, Jardine AG, Mouas H, Pescovitz MD, et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *American Journal of Transplantation* 2007;**7**(9):2106-13. [MEDLINE: 17640310]

Asberg A, Jardine AG, Bignamini AA, Rollag H, Pescovitz MD, Gahlemann CC, et al. Effects of the intensity of immunosuppressive therapy on outcome of treatment for CMV disease in organ transplant recipients. *American Journal of Transplantation* 2010;**10**(8):1881-8. [MEDLINE: 20486914]

Asberg A, Pescovitz MD, Humar A, Jardine AG, Rollag H, Mouas H, et al. Oral valganciclovir and intravenous ganciclovir results in comparable long-term outcomes in transplant recipients with CMV disease: the VICTOR study [abstract]. *Transplantation* 2008;**86**(2S):222.

Boivin G, Goyette N, Rollag H, Jardine AG, Pescovitz MD, Asberg A, et al. Cytomegalovirus resistance in solid organ transplant recipients treated with intravenous ganciclovir or oral valganciclovir. *Antiviral Therapy* 2009;**14**(5):697-704. [MEDLINE: 19704173]

Humar A, Asberg A, Kumar D, Hartmann A, Moussa G, Jardine A, et al. An assessment of herpesvirus co-infections in patients with CMV disease: correlation with clinical and virologic outcomes. *American Journal of Transplantation* 2009;**9**(2):374-81. [MEDLINE: 19120074]

Manual O, Emery V, Asberg A, Hartmann A, Pescovitz M, Pang X, et al. A prospective study of viral genetic polymorphisms in CMV glycoprotein B and their association with clinical and virologic outcomes in patients with CMV disease: results from the VICTOR Study [abstract]. *Transplantation* 2008;**86**(2S):221.

Manuel O, Asberg A, Pang X, Rollag H, Emery VC, Preiksaitis JK, et al. Impact of genetic polymorphisms in cytomegalovirus glycoprotein B on outcomes in solid-organ transplant recipients with cytomegalovirus disease. *Clinical Infectious Diseases* 2009;**49**(8):1160-6. [MEDLINE: 19751151]

Pescovitz M, Hartmann A, Humar A, Rollag H, Jardine AG, Bignamini AA, et al. Management of post transplant CMV disease: lessons learned from the VICTOR trial [abstract]. *American Journal of Transplantation* 2008;**8**(Suppl 2):183.

Yang 1998 *{published data only}*

Yang CW, An HJ, Kim YO, Shin YS, Chang YS, Bang BK. Indication of ganciclovir treatment during early cytomegalovirus (cmv) viremia in CMV seropositive recipients. a longitudinal study of CMV pp65 antigenemia (Ag) assay [abstract]. *Journal of the American Society of Nephrology* 1996;**7**(9):1928.

* Yang CW, Kim YO, Kin YS, Kin SY, Moon IS, Ahn HJ, et al. Clinical course of cytomegalovirus (CMV) viremia with and without ganciclovir treatment in CMV-seropositive kidney transplant recipients. *American Journal of Nephrology* 1998;**18**(5):373-8. [MEDLINE: 9730559]

Yang 1999 *{published data only}*

Yang HC, Holman MJ, Langhoff E, Dellock CA, Gupta M, Ulsh PJ, et al. A comparative study of 500 mg BID and 250 mg BID of prophylactic oral ganciclovir in post-kidney transplant 'CMV at risk' recipients. *Transplantation Proceedings* 1999;**31**(1-2):1125-6. [MEDLINE: 10083502]

References to ongoing studies

Villano 2010 *{published data only}*

Villano SA. Maribavir versus oral ganciclovir for the prevention of cytomegalovirus (CMV) disease in liver transplant recipients. clinicaltrials.gov/ct2/show/NCT00497796 (accessed 7 Jul 2011).

Additional references

Baliga 2004

Baliga RS, Kadambi PV, Javaid B, Harland R, Williams JW, Thistlethwaite JR, et al. A nationwide survey of cytomegalovirus prophylaxis and treatment in the transplant community [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):495.

Basgoz 1995

Basgoz N, Preiksaitis J. Post-transplant lymphoproliferative disorder. *Infectious Diseases Clinics of North America* 1995;**9**(4):901-23. [MEDLINE: 8747772]

Camacho-Gonzalez 2011

Camacho-Gonzalez AF, Gutman J, Hymes LC, Leong T, Hilinski JA. 24 weeks of valganciclovir prophylaxis in children after renal transplantation: a 4-year experience. *Transplantation* 2011;**91**(2):245–50. [MEDLINE: 21076375]

Couchoud 1998a

Couchoud C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD001320.pub2]

Couchoud 1998b

Couchoud C, Cucherat M, Haugh M, Pouteil-Noble C. Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: a meta-analysis. *Transplantation* 1998;**65**(5):641-7. [MEDLINE: 9521197]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 7718048]

Emery 2000

Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. *Lancet* 2000;**355**(9220):2032-6. [MEDLINE: 10885354]

Fiddian 2002

Fiddian P, Sabin CA, Griffiths PD. Valacyclovir provides optimum acyclovir exposure for prevention of cytomegalovirus and related outcomes after organ transplantation. *Journal of Infectious Diseases* 2002;**186 Suppl 1**:110-5. [MEDLINE: 12353195]

Fishman 1995

Fishman JA. Pneumocystis carinii and parasitic infections in transplantation. *Infectious Disease Clinics of North America* 1995;**9**(4):1005-44. [MEDLINE: 8747777]

Fishman 1998

Fishman JA, Rubin RH. Infection in organ-transplant recipients. *New England Journal of Medicine* 1998;**338**(24):1741-51. [MEDLINE: 9624195]

George 1997

George MJ, Snydman DR, Werner BG, Griffith J, Falagas ME, Dougherty NN, et al. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG-Study Group. Cytogam, MedImmune, Inc. Gaithersburg, Maryland. *American Journal of Medicine* 1997;**103**(2):106-13. [MEDLINE: 9274893]

Gourishankar 2001

Gourishankar S, Wong W, Dorval M. Meta-analysis of prophylaxis of CMV disease in solid organ transplantation: is Ganciclovir a superior agent to acyclovir?. *Transplantation Proceedings* 2001;**33**(1-2):1870-2. [MEDLINE: 11267547]

Grattan 1989

Grattan MT, Moreno-Cabral CE, Starnes BA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989;**261**(24):3561-6. [MEDLINE: 2542633]

Hadley 1995

Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. *Infectious Disease Clinics of North America* 1995;**9**(4):1045-74. [MEDLINE: 8747778]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hodson 2007

Hodson EM, Jones CA, Strippoli GFM, Webster AC, Craig JC. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005129.pub2]

Humar 2009

Humar A, Snydman D. Cytomegalovirus in solid organ transplant recipients. *American Journal of Transplantation* 2009;**9**(Suppl 4):S78-S86. [EMBASE: 2010005064]

Jassal 1998

Jassal SV, Roscoe JM, Zaltzman JS, Mazzulli T, Krajden M, Gadawski M, et al. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. *Journal of the American Society of Nephrology* 1998;**9**(9):1697-708. [MEDLINE: 9727379]

Kalil 2005

Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Annals of Internal Medicine* 2005;**143**(12):870-80. [MEDLINE: 16365468]

KDIGO 2009

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Chapter 13.2: Cytomegalovirus. *American Journal of Transplantation* 2009;**9**(Suppl 3):S46-8. [MEDLINE: 19845597]

Keenan 1991

Keenan RJ, Lega ME, Dummer JS, Paradis IL, Dauber JH, Rabinowich H, et al. Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. *Transplantation* 1991;**51**(2):433-8. [MEDLINE: 1847251]

Kotton 2010

Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 2010;**89**(7):779-95. [MEDLINE: 20224515]

Lefebvre 1996

Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomised controlled trials in Embase. Fourth International Cochrane Colloquium; 1996 Oct 20-24; Adelaide (Australia). 1996.

Linden 2000

Linden PK. Infections in liver transplant recipients. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:295-322.

Master List 2007

United States Cochrane Center. Master list of journals being searched. http://apps1.jhsph.edu/cochrane/masterlist.asp (accessed May 2007).

Michaels 2000

Michaels M, Green M. Infections in lung and heart-lung transplant recipients. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:363-93.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13. [MEDLINE: 9746022]

Owers 2013

Owers DS, Webster AC, Strippoli GFM, Kable K, Hodson EM. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD005133.pub3]

Rubin 1989

Rubin RH. The indirect effects of cytomegalovirus infection on the outcome of organ transplantation. *JAMA* 1989;**261**(24):3607-9. [MEDLINE: 2542634]

Rubin 2000

Rubin RH, Rosenberg E. Infection in solid organ transplant: an introduction. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:246-65.

Schultz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Strippoli 2006a

Strippoli GFM, Hodson EM, Jones CA, Craig JC. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD005133.pub2]

Strippoli 2006b

Strippoli GF, Hodson EM, Jones CA, Craig JC. Preemptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Transplantation* 2006;**81**(2):139-45. [MEDLINE: 16436954]

Valentine 1999

Valantine HA. Role of CMV in transplant coronary artery disease and survival after heart transplantation. *Transplant Infectious Disease* 1999;**1 Suppl 1**:25-30. [MEDLINE: 11565583]

Van den Berg 1996

Van den Berg AP, Klompmaker IJ, Haagsma EB, Peeters PM, Meerman L, Verwer R, et al. Evidence for increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. *Clinical Transplantation* 1996;**10**(2):224-31. [MEDLINE: 8664524]

Van der Bij 2001

Van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clinical Infectious Diseases* 2001;**33 Suppl 1**:32-7. [MEDLINE: 11389520]

References to other published versions of this review

Hodson 2005a

Hodson EM, Barclay PG, Craig JC, Jones C, Kable K, Strippoli GF, et al. Antiviral medication for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD003774]

Hodson 2005b

Hodson EM, Barclay PG, Craig JC, Jones C, Kable K, Strippoli GF, et al. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD003774.pub2]

Hodson 2005c

Hodson EM, Jones CA, Webster AC, Strippoli GF, Barclay BG, Kable K, et al. Antiviral medications to prevent cytomegalovirus disease and early death in solid-organ transplant recipients: a systematic review of randomised controlled trials. *Lancet* 2005;**365**(9477):2105-15. [MEDLINE: 15964447]

Hodson 2008

Hodson EM, Craig JC, Strippoli GF, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD003774.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

2VAL Study 2010 Kidney

Methods	• Study design: parallel RCT • Time frame: November 2007 and ongoing • Follow-up period: 4 months (preliminary data); planned for 36 months • Loss to follow-up: 0%
Participants	• Country: Czech Republic • Setting: tertiary single centre • Kidney transplant recipients aged ≥ 18 years; D/R+, D+/R-, D-/R- Treatment group 1 • Number: 19 • Mean age ± SD: 46 ± 14 years • Sex (M/F): 13/6 Treatment group 2 • Number: 17 • Mean age ± SD: 47 ± 10 years • Sex (M/F): 10/7 Exclusion criteria • Unknown or D-/R- serology; systemic antiviral drug intake within 2 weeks; active viral infection; significant leukopenia or thrombocytopenia; participation in another study; allergy to study medications
Interventions	Treatment group 1 • VGCV: 900 mg orally/d for 12 weeks Treatment group 2 • VACV: 2000 mg 4 times/d for 12 weeks Co-interventions • CSA, TAC, MMF, prednisone, ALG 1/19 valganciclovir, 5/17 valaciclovir
Outcomes	1. CMV disease 2. CMV infection: CMV DNA by PCR 3. Graft loss 4. Acute rejection 5. Adverse effects

2VAL Study 2010 Kidney *(Continued)*

Notes	Preliminary results at 4 months only. Full data to be analysed when all patients have completed 12 months. Information on results and randomisation sequence obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table, block randomisation (1:1 ratio, blocks of 4)
Allocation concealment (selection bias)	Low risk	Sealed envelopes opened after patient enrolled
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence clinical assessment of symptoms of possible CMV disease
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label. Lack of blinding could influence clinical assessment of symptoms of possible CMV disease
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Full data on follow-up not yet reported
Selective reporting (reporting bias)	Unclear risk	Full data on outcomes not yet reported
Other bias	Low risk	Grants from Ministry of Health

Ahsan 1997 Kidney

Methods	• Study design: parallel RCT • Time frame: March 1995 to December 1995 • Follow-up period: 9 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Kidney transplant recipients; D/R+, D+/R-, D-/R-; if diabetic or receiving OKT-3 Treatment group • Number: 22 • Mean age ± SEM: 50.4 ± 2.3 years • Sex (M/F): 10/11 • CD/LD: 18/3 Control group • Number: 22 • Mean age ± SEM: 47.6 ± 2.1 years • Sex (M/F): 12/11 • CD/LD: 7/15

Ahsan 1997 Kidney *(Continued)*

	Exclusion criteria: NS
Interventions	Treatment group • GCV: 750 mg orally twice/d for 12 weeks starting day 1 Control group • No treatment Co-interventions • CSA, AZA, prednisone, OKT-3 (CD recipients)
Outcomes	1. CMV disease 2. CMV infection: CMV culture, IgM3 3. All-cause mortality 4. Death due to CMV disease 5. Acute rejection 6. Graft loss 7. Opportunistic infections
Notes	1. Exclusions post randomisation but pre-intervention: none 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised generated code with 4 patients in each block
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient excluded but reason unlikely to be related to true outcome
Selective reporting (reporting bias)	High risk	Incomplete reporting of adverse effects
Other bias	Unclear risk	No information about pharmaceutical sponsorship

Badley 1997 Liver

Methods	• Study design: parallel RCT

Badley 1997 Liver *(Continued)*

- Time frame: January 1991 to June 1994
- Follow-up period: 1 year
- Loss to follow-up: 0%

Participants	• Country: USA • Setting: tertiary multicentre • First liver transplant Treatment group • Number: 83 • Age range: 16 to 68 years • Sex (M/F): 50/33 Control group • Number: 84 • Age range: 16 to 68 years • Sex (M/F): 46/38 Exclusion criteria • Allergy to GCV/ACV; creatinine > 3 mg/dL or GFR < 10; stage 3/4 coma post-transplant; existing CMV infection
Interventions	Treatment group • GCV: 5 mg/kg IV twice/d for 14 days starting first day post-transplant • ACV: 800 mg orally 4 times/d to 120 days Control group • ACV: 800 mg orally 4 times/d to 120 days Co-interventions • CSA, AZA (one centre), prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: 3 excluded 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomisation scheme was used to generate a series of 150 randomly selected treatment assignments for each transplant centre"

Badley 1997 Liver *(Continued)*

Allocation concealment (selection bias)	Low risk	Patient randomisation and all statistical analyses were performed at coordinating centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medications schedules differ between intervention groups. Assessment of primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Medications schedules differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients excluded but exclusions unlikely to be related to outcomes
Selective reporting (reporting bias)	High risk	No graft loss reported
Other bias	Low risk	Study carried out under NIH contracts

Balfour 1989 Kidney

Methods	• Study design: parallel RCT • Time frame: August 1985 to May 1988 • Follow-up period: 1 year • Loss to follow-up: 6% at 1 year, 0% at 6 months
Participants	• Country: USA • Setting: tertiary single centre • Cadaveric kidney transplant recipients > 10 years Treatment group • Number: 53 • Median age (range): 43 years (15 to 67) • Sex (M/F): 36/17 Control group • Number: 51 • Median age (range): 42 years (17 to 68) • Sex (M/F): 34/17 Exclusion criteria • Intolerance of ACV
Interventions	Treatment group • ACV: 800 mg orally 4 times/d for 12 weeks starting day of transplant Control group • Placebo: 1 tablet 4 times/d for 12 weeks starting day of transplant Co-interventions

Balfour 1989 Kidney *(Continued)*

	• CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, rising CMV antibody 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10. Adverse events
Notes	1. Exclusions post randomisation but pre-intervention: none reported 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation scheme generated by computer program
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled. Placebo tablets identical in appearance to acyclovir
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo controlled. Placebo tablets identical in appearance to acyclovir
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 patients (6 intervention, 8 placebo) excluded but reasons unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Report partial support from NIH, Minnesota Medical Foundation and Burroughs Wellcome

Barkholt 1999 Liver

Methods	• Study design: parallel RCT • Time frame: May 1993 to December 1994 • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: Sweden • Setting: tertiary single centre

Barkholt 1999 Liver *(Continued)*

- Liver transplant recipients; all CMV serostatus

Treatment group

- Number: 28
- Mean age ± SD: 41 ± 17 years
- Sex (M/F): 16/12

Control group

- Number: 27
- Mean age± SD: 47 ± 15 years
- Sex (M/F): 12/15

Exclusion criteria

- Age < 6 years; HIV infection; CMV therapy in previous 4 weeks

Interventions	Treatment group • ACV: 800 mg (1 tablet) orally 4 times/d for 12 weeks starting 6 hours pre-transplant Control group • Placebo: 1 tablet orally 4 times/d for 12 weeks starting 6 hours pre-transplant Co-interventions • CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV infection: CMV culture, CMV DNA, IgM 3. All-cause mortality 4. Death due to CMV disease 5. Acute rejection 6. Graft loss 7. Opportunistic infections 8. Adverse reactions
Notes	1. Exclusions post randomisation but pre-intervention: 5 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias)	Low risk	Placebo controlled. Patients with verified CMV infection were withdrawn from study drug without breaking the code

Barkholt 1999 Liver *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 excluded (3 given acyclovir outside study; 2 under 6 years) but reasons unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Supported by Wellcome Research Laboratories

Brennan 1997 Kidney

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Kidney transplant recipients; D/R+, D+/R- recipients Treatment group • Number: 19 • Mean age ± SEM: 50.6 ± 2.8 years • Sex (M/F): 13/6 Control group • Number: 23 • Mean age ± SEM: 44.2 ± 3.0 years • Sex (M/F): 5/18 Exclusion criteria • D-/R- recipients
Interventions	Treatment group • GCV: 1000 mg orally 3 times/d for 12 weeks starting at transplant Control group • No treatment except ACV low dose to prevent Herpes simplex Co-interventions • CSA, AZA, prednisone, ATG
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV DNA 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections

Brennan 1997 Kidney *(Continued)*

	8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd and even numbers according to last digit of medical record number. Information obtained from authors
Allocation concealment (selection bias)	High risk	Odd and even numbers according to last digit of medical record number. Information obtained from authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data on primary outcome
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No report of graft loss
Other bias	High risk	Hoffman-La Roche Laboratory pharmaceutical sponsorship

Cohen 1993 Liver

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 18 months • Loss to follow-up: 0%
Participants	• Country: UK • Setting: tertiary single centre • Liver transplant recipients; D/R+, D+/R- Treatment group • Number: 33 • Mean age: 42.4 years • Sex (M/F): 15/18 Control group • Number: 32 • Mean age: 46.3 years • Sex (M/F): 16/16

Cohen 1993 Liver *(Continued)*

	Exclusion criteria • Acute kidney injury; multiple organ system failure; D-/R- recipients
Interventions	Treatment group • GCV: 5 mg/kg IV twice/d for 14 days starting on day 14 Control group • No treatment Co-interventions • CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"65 patients were randomised in a distribution determined by random numbers"
Allocation concealment (selection bias)	Low risk	Information obtained from authors that method used would not allow investigator/participant to know allocation before participant entered study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. No or limited report on other infections or adverse effects
Other bias	Unclear risk	No report on pharmaceutical sponsorship

Conti 1995 Kidney

Methods	• Study design: parallel RCT • Time frame: January 1992 to January 1994 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Kidney transplant recipients; D/R+; receiving ALG for induction or rejection Treatment group • Number: 22 • Mean age: 43 years • Sex (M/F): 11/11 Control group • Number: 18 • Mean age: 45 years • Sex (M/F): 12/6 Exclusion criteria: NS
Interventions	Treatment group • GCV: 5 mg/kg/d IV during ALG therapy (median 10 days) starting on first day of ALG Control group • No treatment Co-interventions • CSA, AZA, prednisone, ALG
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. All-cause mortality 5. Acute rejection 6. Graft loss 7. Opportunistic infections 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned" but method of sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned" but no information provided on method used

Conti 1995 Kidney *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants in control group received no specific intervention. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants in control group received no specific intervention. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients evaluated
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. No report or limited reporting of CMV infection/adverse effects
Other bias	Unclear risk	Supported in part by grant from National Kidney Foundation. No report on pharmaceutical sponsorship

Duncan 1993 Lung

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Lung transplant recipients; D/R+, D+/R-; neutrophils > 1000/mm^3, creatinine > 2.5 mg/dL Treatment group • Number: 13 • Age: 41.8 ± 9.6 years (mean ± SD) • Sex (M/F): 9/4 Control group • Number: 12 • Age: 45.6 ± 8.4 years • Sex (M/F): 7/5 Exclusion criteria • D-/R-
Interventions	Treatment group • GCV: 5 mg/kg 4 times/d IV x 14 days starting day 7; 5 mg/kg/d IV for days 21 to 28; 5 mg/kg IV 5 times/wk to day 90 Control group • GCV: 5 mg/kg 4 times/d IV x 14 days starting day 7; 5 mg/kg/d IV for days 21 to 28 • ACV: 800 mg orally 4 times/d to day 90 Co-interventions

Duncan 1993 Lung *(Continued)*

	• CSA, AZA
Outcomes	1. CMV tissue invasive disease 2. CMV infection: CMV culture of bronchial lavage 3. All-cause mortality 4. Death due to CMV disease 5. Obliterative bronchiolitis 6. Graft loss 7. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided other than that patients were stratified according to CMV serostatus and type of transplant
Allocation concealment (selection bias)	Unclear risk	Said to be "randomly assigned" but no other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consecutive lung transplant recipients randomised. Results from all reported.
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of CMV disease, acute rejection, opportunistic infections
Other bias	Unclear risk	No report of pharmaceutical sponsorship

Egan 2002 Heart

Methods	• Study design: parallel RCT • Time frame: September 1994 to February 1998 • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: UK • Setting: tertiary single centre • Heart transplant recipients; D/R+ Treatment group • Number: 14

Egan 2002 Heart *(Continued)*

- Mean age (range): 51.6 years (39 to 63)
- Sex (M/F): 11/1

Control group

- Number: 13
- Mean age (range): 50.4 years (31 to 62)
- Sex (M/F): 10/3

Exclusion criteria

- Active herpes infection; required other antiviral agents

Interventions	Treatment group • VACV: 2000 mg orally 4 times/d for 90 days starting within 72 hours of transplant Control group • ACV: 200 mg orally 4 times/d for 90 days starting within 72 hours of transplant for herpes simplex Co-interventions • CSA, AZA, prednisone, ATG
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: none 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomization schedule (block size 4)"
Allocation concealment (selection bias)	Low risk	"Allocation by opening sealed envelopes corresponding to patient number in sequence"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Control group given low dose acyclovir to "maintain double blind by effective prophylaxis of herpes simplex outbreaks" but no information that acyclovir and valacyclovir tablets were indistinguishable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Control group given low dose acyclovir to "maintain double blind by effective prophylaxis of herpes simplex outbreaks" but no information that acyclovir and valacyclovir tablets were indistinguishable

Egan 2002 Heart *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients were included in the analysis including 2 patients randomised in error
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Funding provided by Glaxo Wellcome Research and Development

Flechner 1998 Kidney

Methods	• Study design: parallel RCT • Time frame: April 1996 to December 1997 • Follow-up period: 6 to 27 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Kidney transplant recipients > 18 years and < 101 kg; D/R+, D+/R- Treatment group • Number: 40 • Mean age: 47.9 years • Sex (M/F): 30/10 Control group • Number: 39 • Mean age: 50.2 years • Sex (M/F): 31/8 Exclusion criteria • D-/R-; Allergy to GCV/ACV; AIDS; WBC < 3000; platelets < 100,000; previous viral hepatitis
Interventions	Treatment group • GCV: 1000 mg orally 3 times/d for 84 days starting on day 1 Control group • ACV: 800 mg orally 4 times/d for 84 days starting on day 1 Co-interventions • CMV IgG given to D+/R- recipients in each group; CSA, AZA (⅓), MMF (⅔), OKT-3
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Opportunistic infections

Flechner 1998 Kidney *(Continued)*

Notes	1. Exclusions post-randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list. Information provided by authors
Allocation concealment (selection bias)	Low risk	Central research coordinator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Medications differ between intervention groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed to death/graft loss or June 1998
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No report of graft loss
Other bias	Unclear risk	No information provided about pharmaceutical sponsorship

Gane 1997 Liver

Methods	• Study design: parallel RCT • Time frame: December 1993 to April 1995 • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA, Europe • Setting: tertiary multicentre • Primary liver transplant recipients aged > 18 years; D/R+, D+/R- Treatment group • Number: 150 • Mean age ± SD: 46.8 ± 11.6 years • Sex (M/F): 92/58 Control group • Number: 154 • Mean age ± SD: 48.1 ± 10.9 years • Sex (M/F): 82/72 Exclusion criteria

Gane 1997 Liver *(Continued)*

	• Multiple organ transplant; D-/R- (2 patients inadvertently randomised and included in analysis); unable to take oral medications; neutrophils < 1000; platelets < 25,000; creatinine > 300
Interventions	Treatment group • GCV: 1000 mg (4 tablets) orally 3 times/d until day 98 starting within 10 days of transplant Control group • Matching placebo: 4 tablets orally 3 times/d until day 98 starting within 10 days of transplant Co-interventions • CSA, TAC (52 patients), ALG (61 patients)
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, IgM, CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infection 10. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"Randomised trial" but no further information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching placebo capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete 12 month data available on all participants
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Grant support from Roche Global Development

Gavalda 1997 Liver

Methods	• Study design: parallel RCT • Time frame: June 1991 to November 1993 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: Spain • Setting: tertiary single centre • Primary liver transplant recipient; D/R+ Treatment group • Number: 37 • Median age (range): 57 years (34 to 66) • Sex (M/F): 25/12 Control group • Number: 36 • Median age (range): 54 years (20 to 65) • Sex (M/F): 23/13 Exclusion criteria • Second transplant recipients
Interventions	Treatment group • ACV: 400 mg orally 5 times/d for 16 weeks starting 3 to 30 days (median 7 days) post-transplant Control group • No treatment Co-interventions CSA, prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"Randomized study" but no other information provided

Gavalda 1997 Liver *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no medication. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no medication. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consecutive adult recipients enrolled. 7 did not complete study. All included in analysis
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of acute rejection, adverse effects
Other bias	Unclear risk	No information provided on pharmaceutical sponsorship

Green 1997 Liver

Methods	• Study design: parallel RCT • Time frame: July 1992 to March 1994 • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • First liver transplant recipients aged < 18 years Treatment group • Number: 24 • Mean age: 4.9 years • Sex (M/F): NS Control group • Number: 24 • Mean age: 4.3 years • Sex (M/F): NS Exclusion criteria • Multi-organ recipients
Interventions	Treatment group • GCV: 5 mg/kg twice/d IV for 14 days starting day 1 • ACV: 800 mg/m^2 orally 4 times/d to 1 year Control group • GCV: 5 mg/kg twice/d IV for 14 days starting day 1 Co-interventions • TAC, prednisone

Green 1997 Liver *(Continued)*

Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive tissue disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified according to donor/recipient serostatus. Method not reported.
Allocation concealment (selection bias)	Unclear risk	"A randomized trial" but no further information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no medication after initial two weeks of ganciclovir therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no medication after initial two weeks of ganciclovir therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled in study were included in analysis
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. No or limited reporting of acute rejection, graft loss, adverse effects
Other bias	Unclear risk	Study ended following interim analysis which showed no benefit of prolonged course of acyclovir and families requesting that their children receive acyclovir rather than enter trial. No information provided on pharmaceutical sponsorship

Hertz 1998 Heart/lung

Methods	• Study design: parallel RCT • Time frame: January 1993 to January 1996 • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Lung or heart/lung transplant recipients; D/R+; D+/R- Treatment group • Number: 35

Hertz 1998 Heart/lung *(Continued)*

- Mean age ± SD: 46.4 ± 11.4 years
- Sex (M/F): 15/20

Control group

- Number: 37
- Mean age ± SD: 49.1 ± 8.7 years
- Sex (M/F): 14/23

Exclusion criteria

- D-/R-

Interventions	Treatment group • GCV: 5 mg/kg twice/d IV on days 8 to 21; 5 mg/kg IV 3 times/wk to 90 days Control group • GCV: 5 mg/kg twice/d IV on days 8 to 21; 5 mg/kg IV daily to 90 days Co-interventions • CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV tissue invasive disease 4. CMV infection: CMV culture of bronchial lavage 5. All-cause mortality 6. Death due to CMV disease 7. Opportunistic infections 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"Randomized trial" in title but no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient unable to complete therapy but included in analyses

Hertz 1998 Heart/lung *(Continued)*

Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of graft loss, adverse effects
Other bias	Unclear risk	No information provided about pharmaceutical sponsorship

Hibberd 1995 Kidney

Methods	• Study design: parallel RCT • Time frame: November 1990 to September 1992 • Follow-up period: 6 months • Loss to follow-up: 1.8% (2 lost at 32 days and 78 days)
Participants	• Country: USA • Setting: tertiary multicentre • Kidney transplant recipients; receiving ALG preparations for induction or treatment of rejection; D/R+ Treatment group • Number: 64 • Mean age ± SEM: 44.2 ± 1.62 years • Sex (M/F): 36/28 Control group • Number: 49 • Mean age ± SEM: 42.8 ± 1.99 years • Sex (M/F): 33/16 Exclusion criteria • Aged < 20 years; pregnant; multi-organ recipient; treatment with other antiviral agent
Interventions	Treatment group • GCV: 2.5 mg/kg/d IV during ALG therapy (median duration 9 days) starting within 24 hours of first dose of ALG Control group • No treatment Co-interventions • CSA, AZA, prednisone, ALG or OKT-3
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Graft loss 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Hibberd 1995 Kidney *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Separate randomization lists for each center" but no other information available
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned" but no other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Investigators at each site knew which patients received the study drug". Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Investigators at each site knew which patients received the study drug". Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analyses
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of acute rejection, adverse effects
Other bias	High risk	Supported in part by a grant from Ortho Pharmaceutical Corporation. Ganciclovir provided by Syntex Laboratories Inc

IMPACT 2010 Kidney

Methods	• Study design: parallel RCT • Time frame: March 2006 to August 2008 (final data collection date for primary outcome measure) • Follow-up period: 24 months • Loss to follow-up: 6/326 did not receive experimental therapy. 103 subsequently withdrew from treatment but all who received at least one dose of medication and underwent post randomisation safety assessment were included in ITT analysis for safety. All who received at least one dose of therapy and were D+/R- were included in efficacy study
Participants	• Countries: 65 transplant centres in 13 countries • Setting: tertiary multicentre • Kidney transplant recipients Treatment group 1 • Number: 156 • Mean age ± SD: 47 ± 13.5 years • Sex (M/F): 116/40 Treatment group 2 • Number: 164 • Mean age ± SD: 48.5 ± 13.8 years • Sex (M/F): 119/45 Exclusion criteria

IMPACT 2010 Kidney *(Continued)*

	• CMV disease; HIV; hepatitis B; hepatitis C at enrolment; received CMV IgG in previous 1 month; multi-organ transplant
Interventions	Treatment group 1 • 200 days group * VGCV: 900 mg/d orally for 200 days started as soon as able to tolerate oral medications and by 10 days post-transplant Treatment group 2 • 100 days group • VGCV: 900 mg/d orally for 100 days started as soon as able to tolerate oral medications and by 10 days post-transplant followed by placebo orally for 100 days Co-interventions • Induction therapy with ATG (52, 52) or IL2Ra (79, 72)
Outcomes	1. CMV disease 2. CMV infection: CMV DNA by PCR, CMV antigenaemia 3. All-cause mortality 4. Acute rejection 5. Graft loss 6. Opportunistic infections 7. Adverse effects 8. Death due to CMV disease 9. Ganciclovir resistant mutations
Notes	Further Information sought from the authors on sequence generation and allocation concealment but no response obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients randomized sequentially in a 1:1 ratio at each study centre in the order in which they were enrolled". No other information provided
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. Placebo and active drug "were indistinguishable"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study investigators, site staff and sponsors were fully blinded to treatment allocation until after analysis of the primary endpoint"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Patients excluded who did not receive at least one dose of medication but only 8 patients excluded and numbers unlikely to influence true outcome
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

IMPACT 2010 Kidney *(Continued)*

Other bias	High risk	Funded by F Hoffman-La-Roche. Medical writers funded by sponsors. "There is an agreement between the Principal Investigators and the Sponsor that restricts the principal investigators' rights to discuss or publish trial results after the trial is completed"

Kletzmayr 1996 Kidney

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year • Loss to follow-up: 5.6%
Participants	Country: Austria • Setting: tertiary single centre • Kidney transplant recipients; D+/R- Treatment group • Number: 22 • Mean age ± SD: 46 ± 14 years • Sex (M/F): 17/5 Control group • Number: 10 • Mean age ± SD: 44 ± 13 years • Sex (M/F): 7/3 Exclusion criteria: NS
Interventions	Treatment group • ACV: 800 mg 3 times/d orally for 3 months starting first post-op day Control group • No treatment Co-interventions • CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV infection: CMV antigenaemia, CMV culture, IgM 3. All-cause mortality 4. Acute rejection 5. Graft loss
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Kletzmayr 1996 Kidney *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients randomized... in a 2:1 ratio". No information on sequence generation provided
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned". No information provided on method
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no specific treatment. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no specific treatment. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/36 excluded from analysis
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of opportunistic infections/adverse effects
Other bias	Unclear risk	No information provided on pharmaceutical sponsorship

Leray 1995 Kidney

Methods	• Study design: parallel RCT • Time frame: January 1991 to July 1994 • Follow-up period: Unclear • Loss to follow-up: 0%
Participants	• Country: France • Setting: tertiary single centre • Kidney transplant recipients; D+/R- Treatment group • Number: 13 • Age: NS • Sex (M/F): NS Control group • Number: 10 • Age: NS • Sex (M/F): NS Exclusion criteria: NS
Interventions	Treatment group • GCV: 5 mg/kg IV twice/d for 14 days starting 14 days post-transplant Control group • No treatment

Leray 1995 Kidney *(Continued)*

	Co-interventions • CSA, AZA, prednisone, ALG
Outcomes	1. CMV disease 2. CMV infection: CMV antigenaemia, CMV culture, IgM 3. Acute rejection 4. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: none reported 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"On day 14 patients were randomized". No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any patients were excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Abstract only available
Other bias	Unclear risk	No information provided on sponsorship

Lowance 1999 Kidney

Methods	• Study design: parallel RCT • Time frame: July 1992 to December 1996 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: USA/Europe • Setting: tertiary multicentre • Kidney transplant recipients; D/R+, D+/R- Treatment group • Number: 306; D/R+ (204); D+/R- (102) • Mean age ± SD: D/R+ (43.6 ± 13.1 years); D+/R- (40.3 ± 14.2 years)

Lowance 1999 Kidney *(Continued)*

	• Sex (M/F): D/R+ 153/51; D+/R- 60/42 Control group • Number: 310; D/R+ (204); D+/R- (106) • Mean age ± SD: D/R+ (45.1 ± 13 years); D+/R- (45.6 ± 13.5 years) • Sex (M/F): D/R+ 124/80; D+/R- 65/41 Exclusion criteria • D-/R-; active herpes infection; antiviral therapy in previous 2 months
Interventions	Treatment group • VACV: 2000 mg orally 4 times/d for 90 days starting within 3 days of transplant Control group • Placebo: orally 4 times/d for 90 days starting within 3 days of transplant Co-interventions • CSA, AZA, TAC (6), MMF (7), ATG or ALG (251), OKT-3 (102)
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Opportunistic infections 9. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned in 1:1 ratio according to study site". No other information provided
Allocation concealment (selection bias)	Unclear risk	"Randomly assigned" but method of allocation unstated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching placebo tablets
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in intention to treat analysis

Lowance 1999 Kidney *(Continued)*

Selective reporting (reporting bias)	High risk	Not all expected outcomes reported. No graft loss data reported
Other bias	High risk	Supported by Glaxo Wellcome. Employees included as authors

Macdonald 1995 Heart

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: Australia • Setting: tertiary single centre • Heart transplant recipients; D/R+, D+/R- Treatment group • Number: 28 • Mean age ± SD: 48 ± 15 years • Sex (M/F): 24/4 Control group • Number: 28 • Mean age ± SD: 45 ± 15 years • Sex (M/F): 25/3 Exclusion criteria • D-/R-
Interventions	Treatment group • GCV: 5 mg/kg IV 3 times/wk for 6 weeks starting pre-transplant Control group • Placebo: IV 3 times/wk for 6 weeks starting pre-transplant Co-interventions • CSA, AZA, prednisone, ATG
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Macdonald 1995 Heart *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers. Separate randomisation sequences were used according to serostatus
Allocation concealment (selection bias)	Unclear risk	Method of allocation not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo administered to control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching placebo administered to control group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consecutive patients enrolled and all included in analysis
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No report of graft loss
Other bias	Unclear risk	No report on pharmaceutical sponsorship

Martin 1994 Liver

Methods	• Study design: parallel RCT • Time frame: February 1991 to August 1991 • Follow-up period: 24 weeks • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Liver transplant recipients aged > 18 years Treatment group • Number: 68 • Mean age ± SD: 48.1 ± 13.2 years • Sex (M/F): 43/25 Control group • Number: 71 • Mean age ± SD: 47 ± 12.9 years Sex (M/F): 35/36 Exclusion criteria • Fulminant hepatic failure; stage 3/4 hepatic coma; hepatic malignancies with pre-operative chemotherapy
Interventions	Treatment group

Martin 1994 Liver *(Continued)*

	• GCV: 5 mg/kg twice/d IV for 14 days starting 2 days post-transplant • ACV: 800 mg orally 4 times/d to 10 weeks Control group • ACV: 800 mg orally 4 times/d for 10 weeks starting 2 days post-transplant Co-interventions • TAC
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive tissue disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Acute rejection 7. Graft loss 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: none 2. Stop or end point: NS 3. Four excluded after randomisation (active CMV (1), death from sepsis (2), unable to take medication (1)) and one randomised to ganciclovir given acyclovir and analysed in acyclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Fixed block randomization scheme (block size = 4)"
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Groups received different medications by different routes. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Groups received different medications by different routes. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/143. Missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	High risk	Did not report opportunistic infections
Other bias	Unclear risk	No information on pharmaceutical sponsorship provided

Merigan 1992 Heart

Methods	• Study design: parallel RCT

Merigan 1992 Heart *(Continued)*

- Time frame: NS
- Follow-up period: 120 days
- Loss to follow-up: 0%

Participants	• Country: USA • Setting: tertiary multicentre • Heart transplant recipients; D/R+, D+/R-. Treatment group • Number: 76 • Mean age ± SEM: 47.1 ± 1.55 years • Sex (M/F): 68/8 Control group • Number: 73 • Mean age ± SEM: 47.6 ± 1.4 years • Sex (M/F): 63/10 Exclusion criteria • D-/R-; combined heart-lung transplant recipients; antiviral agents in previous 7 days; WBC < 1500; platelets < 50,000; GFR < 10 or > 400
Interventions	Treatment group • GCV: 5 mg/kg IV twice/d for 14 days starting on day 1 post-transplant but delay for 2 to 7 days in 21% Control group • Placebo: IV twice/d for 14 days starting on day 1 post-transplant but delay for 2 to 7 days in 23% Co-interventions • CSA, AZA, prednisone, OKT-3
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: Study stopped after interim assessment after 80 patients enrolled when difference between treatment groups evident

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Stratified at randomization according to their CMV serostatus". Otherwise no information provided
Allocation concealment (selection bias)	Unclear risk	Patients were... randomly assigned". No information provided on allocation

Merigan 1992 Heart *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients in control group received infusions of placebo medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients in control group received infusions of placebo medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analysis
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No report of graft loss
Other bias	High risk	Supported by Public Health Service grant and by grant from Syntex Corporation (employees included as authors)

Nafar 2005 Kidney

Methods	• Study design: parallel RCT • Time frame: September 2001 to November 2001 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: Iran • Setting: tertiary single centre • Kidney transplant recipients; D+/R+; ATG required for rejection; second transplant; deceased donor transplant • Mean age ± SD: 37.8 ± 9.8 years Treatment group • Number: 16 (17 entered the study) • Age: NS • Sex (M/F): 11/5 Control group • Number: 14 (17 entered study) • Age: NS • Sex (M/F): 9/5 Exclusion criteria: NS
Interventions	Treatment group • GCV: 1000 mg oral 3 times/d for 3 months Control group • GCV: 5 mg/kg/d IV for 2 weeks Co-interventions • ATG for induction or rejection; other immunosuppression NS

Nafar 2005 Kidney *(Continued)*

Outcomes	1. CMV disease 2. CMV viraemia: CMV antigenaemia 3. Acute rejection 4. Adverse effects 5. Kidney function at 12 months
Notes	1. Exclusions post randomisation but pre-intervention: None 2. One patient from treatment group excluded following graft loss; 3 excluded from control group (graft loss 1, pre-existing CMV antigenaemia, refusal to be followed). 3. Stop or end point: NS 4. Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"Randomized prospective trial" in title but no other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	4/34 excluded. 3 excluded from !V ganciclovir arm
Selective reporting (reporting bias)	High risk	Drug toxicity and side effects not reported
Other bias	Unclear risk	No information provided on pharmaceutical sponsorship

Nakazato 1993 Liver

Methods	• Study design: parallel RCT • Time frame: August 1990 to November 1991 • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Liver transplant recipients Treatment group • Number: 52

Nakazato 1993 Liver *(Continued)*

	• Mean age ± SD: 38.7 ± 21.5 years • Sex (M/F): NS Control group • Number: 52 • Mean age ± SD: 34.9 ± 22.8 years • Sex (M/F): NS Exclusion criteria: NS
Interventions	Treatment group • GCV: 5 mg/kg/d IV during inpatient periods in first 3 months post-transplant • ACV: 5 mg/kg/d oral to 3 months Control group • ACV: 5 mg/kg/d IV during inpatient periods in first 3 months post-transplant • ACV: 5 mg/kg/d oral to 3 months Co-interventions • IgG IV 200 mg/kg/d during inpatient periods in first 3 months post-transplant; CSA (81), TAC (23), prednisone
Outcomes	1. CMV disease: CMV culture/histopathology and symptoms 2. All-cause mortality 3. Acute rejection 4. Graft loss 5. Opportunistic infections 6. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"Preliminary report of a randomized trial..." in title. Otherwise no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses

Nakazato 1993 Liver *(Continued)*

Selective reporting (reporting bias)	High risk	No CMV infection or adverse effects reported
Other bias	High risk	Supported in part by Sandoz Pharmaceuticals

Palmer 2010 Lung

Methods	• Study design: parallel RCT • Time frame: July 2003 to January 2007 • Follow-up period: 13 months • Loss to follow-up: 45/136 withdrawn but all included in analysis
Participants	• Country: USA • Setting/Design: tertiary multicentre (11 centres) • Single or double first lung transplant recipient; aged ≥ 18 years; adequate haematological, kidney and liver function; D/R+, D+/R-; received IV GCV for 2 weeks post-transplant; able to tolerate oral medications; negative PCR/bronchoscopy for CMV at baseline and at day 75 when randomisation occurred Treatment group 1 • Number: 70 • Age (IQR): 56 (45 to 62) years • Sex (M/F): 29/41 Treatment group 2 • Number: 66 • Age (IQR): 55 (42 to 61) years • Sex (M/F): 38/28 Exclusion criteria • Re-transplant, on ventilator; current/previous GCV outside study; invasive fungal disease; using disallowed medications; previous severe reaction to GCV; diarrhoea; malabsorption; liver/kidney/haematological dysfunction

Interventions	Treatment group 1
	
	• 12 months group
	  * IV GCV: for 2 weeks starting within 24 hours of transplant
	  * Oral VGCV: 900 mg/d for 3 months
	  * Oral VGCV: 900 mg/d for 9 months
	
	Treatment group 2
	
	• 3 months group
	  * IV GCV: for 2 weeks starting within 24 hours of transplant
	  * Oral VGCV: 900 mg/d for 3 months
	  * Placebo: for 9 months
	
	Co-interventions
	
	• TAC 50/70 and 46/66. ALG 23/70 and 21/66

Outcomes	1. CMV disease 2. CMV infection: CMV-DNA by PCR on blood and/or broncholavage 3. All-cause mortality (data from 1 centre)

Palmer 2010 Lung *(Continued)*

	4. Acute rejection 5. Opportunistic infections 6. Adverse reactions
Notes	• Information on absolute numbers with outcomes requested from investigators. Response received but information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1.1 stratified by site at 3 months. Computer-generated randomised list managed centrally
Allocation concealment (selection bias)	Low risk	Randomised at 3 months. Independent pharmacist dispensed medically centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Bronchoscopies performed by investigators blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analysis
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. Reports of deaths only available for one institution
Other bias	High risk	Funded by Roche Pharmaceuticals. All data analyses performed at Duke Clinical Research Institute

Pavlopoulou 2005 Kidney

Methods	• Study design: parallel RCT • Time frame: April 1999 to September 2000 • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: Greece • Setting: tertiary single centre • Kidney transplant recipient; D/R+, D+/R- Treatment group • Number: 43 • Mean age ± SD: 40.7 ± 12 years • Sex (M/F): 34/9 Control group • Number: 40

Pavlopoulou 2005 Kidney *(Continued)*

	• Mean age ± SD: 43.1 ± 15 years • Sex (M/F): 29/11 Exclusion criteria • Active herpes viral infection; antiviral therapy in previous 14 days
Interventions	Treatment group • VACV: 2000 mg oral 4 times/d starting within 72 hours of transplant for 3 months Control group • GCV: 1000 mg oral 3 times/d starting within 72 hours of transplant for 3 months Co-interventions • CSA or TAC, sirolimus (11), IL2R antagonists 23 (treatment) and 25 (control), ATG 4 (treatment) and 2 (control)
Outcomes	1. CMV disease 2. CMV infection: CMV-DNA 3. All-cause mortality 4. Acute rejection 5. Opportunistic infections 6. Adverse reactions 7. Kidney function at 6 months
Notes	1. Exclusions post randomisation but pre-intervention: NS 2. Stop or end point: NS 3. Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned randomly in 1:1 ratio but no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label. Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. Limited reporting of adverse effects

Pavlopoulou 2005 Kidney *(Continued)*

Other bias	Unclear risk	No information provided on pharmaceutical sponsorship

Paya 2004 All

Methods	• Study design: parallel RCT • Time frame: April 2000 to August 2001 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: USA/Europe/Canada/Australia • Setting: tertiary multicentre • Solid organ transplant recipient aged >12 years (liver, kidney, heart, kidney-pancreas); D+/R-; first transplant; adequate liver and kidney function Treatment group • Number: 245 • Mean age: 45.7 years • Sex (M/F): 179/66 Control group • Number: 127 • Mean age: 45.3 years • Sex (M/F): 95/32 Exclusion criteria • Retransplant; history of CMV infection/disease; CMV therapy in previous 30 days; severe uncontrolled diarrhoea; malabsorption
Interventions	Treatment group • VGCV: 900 mg oral daily starting within 10 days of transplant for 100 days Control group • GCV: 1000 mg oral 3 times/d starting within 10 days of transplant for 100 days Co-interventions • Immunosuppression according to protocol of centre
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV tissue invasive disease 4. CMV infection: CMV-DNA; infection confirmed in central lab 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10.Adverse reactions
Notes	Exclusions post-randomisation but pre-intervention: 2 excluded from safety analysis as did not receive medication, 8 excluded from primary outcome analysis as not D+/R-

Paya 2004 All *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified according to organ transplanted and assigned in 2:1 ratio at each centre
Allocation concealment (selection bias)	Low risk	"Treatment randomization numbers were assigned by telephone via a central randomization center"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy. Placebo tablets given to both groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	End points adjudicated by independent (of sponsor and study) blinded Endpoint Committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT population included 364/372 patients. Safety 370/372. Reasons for missing outcomes data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Expected outcomes all reported
Other bias	High risk	Study funded by Hoffman-La Roche

Pouteil-Noble 1996 Kidney

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: France • Setting: tertiary single centre • Kidney transplant recipients; all CMV serostatus Treatment group • Number: 24 • Age: NS • Sex (M/F): NS Control group • Number: 26 • Age: NS • Sex (M/F): NS Exclusion criteria: NS
Interventions	Treatment group • GCV: 5 mg/kg/d IV for 14 days starting on day of transplant

Pouteil-Noble 1996 Kidney *(Continued)*

	• ACV: 800 mg oral 3 times/d from day 14 to 3 months Control group • Placebo: given as for treatment arm Co-interventions: NS
Outcomes	1. CMV disease 2. CMV infection: CMV culture, IgM 3. All-cause mortality
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided except stratification for CMV serostatus
Allocation concealment (selection bias)	Low risk	Adequate allocation (information received from authors)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Control group received placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Control group received placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	Unclear risk	Abstract only
Other bias	Unclear risk	Work supported by Wellcome Laboratories and Hospices Civils de Lyon

Reischig 2005 Kidney

Methods	• Study design: parallel RCT • Time frame: April1999 to December 2000; January 2001 to January 2003 • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: Czech Republic • Setting: tertiary single centre • Kidney transplant recipients; D/R+, D+/R- Treatment group

Reischig 2005 Kidney *(Continued)*

- Number: 35
- Mean age ± SD: 45 ± 12 years
- Sex (M/F): 26/9

Control group

- Number: 36
- Mean age ± SD: 48 ± 11 years
- Sex (M/F): 25/11

Exclusion criteria

- D-/R-; unknown CMV status; active CMV infection; treatment with antiviral agents; WBC < 4000; platelets < 150,000; allergy to study drugs

Interventions	Treatment group • VACV: 2000 mg oral 4 times/d starting within 3 days of transplant for 3 months Control group • GCV: 1000 mg oral 3 times/d starting within 3 days of transplant for 3 months Co-interventions • ACV low dose to prevent herpes simplex; CSA, MMF, prednisone, ATG or OKT-3 (9), anti-IL2R monoclonal antibody/sirolimus (6)
Outcomes	1. CMV disease 2. CMV infection: CMV-DNA, CMV antigenaemia, CMV culture 3. All-cause mortality 4. Acute rejection 5. Graft loss 6. Adverse reactions
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS 3. Additional data requested from authors: data on quality assessment and results obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator used. (Information from authors)
Allocation concealment (selection bias)	Low risk	Adequate allocation based on information from authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different medication schedules in each group. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different medication schedules in each group. Primary outcome of CMV disease could be influenced by lack of blinding

Reischig 2005 Kidney *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised consecutive patients. All patients included in analyses
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No data of opportunistic infections
Other bias	Low risk	"The study was independent and not funded by any commercial sources"

Rondeau 1993 Kidney

Methods	• Study design: parallel RCT • Time frame: January 1990 to July 1992 • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: France • Setting: tertiary multicentre • Kidney transplant recipients; D+/R- Treatment group • Number: 17 • Mean age ± SEM: 43.8 ± 2.9 years • Sex (M/F): 13/4 Control group • Number: 15 • Mean age ± SEM: 43.5 ± 3.3 years • Sex (M/F): 6/9 Exclusion criteria • Living related donor transplant recipients; WBC < 1500; platelets < 50,000; treatment with another antiviral agent
Interventions	Treatment group • GCV: 5 mg/kg IV twice/d for 14 days starting day 14 post-transplant Control group • No treatment Co-interventions: NS
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Acute rejection 7. Graft loss
Notes	1. Exclusions post randomisation but pre-intervention: None reported

Rondeau 1993 Kidney *(Continued)*

2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"On day 14 after transplantation, patients were randomized...". No further information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No or limited reporting of opportunistic infections/adverse effects
Other bias	Low risk	Work supported in part by grants from non-pharmaceutical sources

Rostaing 1994 Kidney

Methods

- Study design: parallel RCT
- Time frame: April 1992 to February 1993
- Follow-up period: mean 12 months
- Loss to follow-up: 0%

Participants

- Country: France
- Setting: tertiary single centre
- Kidney transplant recipients; D/R+

Treatment group

- Number: 19
- Mean age ± SD: 50.4 ± 11.3 years
- Sex (M/F): 13/6

Control group

- Number: 18
- Mean age ± SD: 45.1 ± 11.1 years
- Sex (M/F): 14/4

Exclusion criteria

- D+/R-; D-/R- recipients

Rostaing 1994 Kidney *(Continued)*

Interventions	Treatment group • ACV: 6 mg/kg/d IV for 3 days starting day 1 then ACV 800 mg oral 4 times/d for 3 months Control group • No treatment Co-interventions • CSA, AZA, prednisone, ATG
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Acute rejection 7. Graft loss 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None reported 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"The patients were randomized to receive either acyclovir or nothing..". No other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analysis
Selective reporting (reporting bias)	High risk	No data on opportunistic infections or adverse reactions
Other bias	Unclear risk	No information provided about pharmaceutical sponsorship

Rubin 2002 All

Methods	• Study design: parallel RCT • Time frame: November 1996 to January 1999

Rubin 2002 All *(Continued)*

- Follow-up period: 12 months
- Loss to follow-up: 0% of evaluated patients

Participants	• Country: USA • Setting: tertiary multicentre • First kidney, liver or heart transplant recipients aged >12 years; D+/R- Treatment group • Number: 77 • Mean age ± SD: 46 ± 13 years • Sex (M/F): 60/17 Control group • Number: 78 • Mean age ± SD: 45 ± 12 years • Sex (M/F): 61/17 Exclusion criteria • D/R+; D-/R-
Interventions	Treatment group • GCV: 5 mg/kg/d IV for 5 to 10 days starting within 72 hours of transplant, then GCV 1000 mg oral 3 times/d to 12 weeks Control group • GCV: 5 mg/kg/d IV for 5 to 10 days starting within 72 hours of transplant then ACV 400 mg oral 3 times/d to 12 weeks Co-interventions • CSA (141), TAC (27), AZA (57), MMF (101), antibody therapy (56)
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, CMV culture 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections 8. Adverse effects 9. Time to CMV disease
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS 3. 11 (5 acyclovir, 6 ganciclovir) were deemed unable to be evaluated: 7 did not qualify for protocol, 1 died, 3 lost to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratification for organ transplanted. Central randomisation. Otherwise no information available

Rubin 2002 All *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients received different oral medications. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients received different oral medications. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/166 excluded from analyses. Reasons for missing data unlikely to be related to true outcome
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. No report of graft loss
Other bias	High risk	Funded in part by a grant from F. Hoffman-LaRoche

Saliba 1993 Liver

Methods	• Study design: parallel RCT • Time frame: February 1990 to February 1991 • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: France • Setting/Design: tertiary single centre • Liver transplant recipients; D/R+ Treatment group • Number: 60 • Mean age ± SD: 45.3 ± 12 years • Sex (M/F): 36/24 Control group • Number: 60 • Mean age ± SD: 44.5 ± 13 years • Sex (M/F): 35/35 Exclusion criteria • D+/R-; D-/R- recipients
Interventions	Treatment group • ACV: 500 mg/m^2/d IV for 10 days, then 800 mg oral 4 times/d to 3 months Control group • No treatment Co-interventions

Saliba 1993 Liver *(Continued)*

	• CSA, AZA, prednisone
Outcomes	1. CMV disease 2. CMV infection: CMV culture 3. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment (information from authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group received no specific therapy. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consecutive recruitment. All patients included in analyses
Selective reporting (reporting bias)	Unclear risk	Abstract only
Other bias	Unclear risk	No information provided on pharmaceutical sponsorship

Winston 1995 Liver

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 4 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • First liver transplant recipients aged > 12 years; all serologies Treatment group • Number: 124 • Mean age (range): 52 years (20 to 72) • Sex (M/F): 67/57 Control group

Winston 1995 Liver *(Continued)*

- Number: 126
- Mean age (range): 47 years (20 to 74)
- Sex (M/F): 67/59

Exclusion criteria

- Second transplants

Interventions	Treatment group • GCV: 6 mg/kg/d IV to day 30; GCV 6 mg/kg/d IV Monday to Friday to day 100 Control group • ACV: 10 mg/kg IV 8 hourly until discharge; ACV 800 mg oral 4 times/d to day 100 Co-interventions • CSA, TAC (38), AZA, prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, isolation from any site 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Opportunistic infections 9. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified according to CMV status but no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients given different medications by different routes. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients given different medications by different routes. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Winston 1995 Liver *(Continued)*

Other bias	High risk	Supported in part by non-pharmaceutical grants. Ganciclovir from Syntex Research

Winston 2003 Liver

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Liver transplant recipients; D/R+ Treatment group • Number: 110 • Mean age (range): 51 years (7 to 78) • Sex (M/F): 58/52 Control group • Number: 109 • Mean age (range): 51 years (7 to 71) • Sex (M/F): 58/51 Exclusion criteria • D+/R-; D-/R- recipients
Interventions	Treatment group • GCV: 6 mg/kg/d IV to day 14 starting day of transplant; GCV 1000 mg oral 3 times/d to day 100 Control group • GCV: 6 mg/kg/d IV to day 14 starting day of transplant; ACV 800 mg oral 4 times/d to day 100 Co-interventions • CSA (58), TAC (164), AZA (128), MMF (85), prednisone
Outcomes	1. CMV disease: CMV DNA, CMV culture 2. CMV syndrome 3. CMV tissue invasive disease 4. All-cause mortality 5. Death due to CMV disease 6. Acute rejection 7. Opportunistic infections 8. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: Unclear 2. Stop or end point: NS

Risk of bias

Winston 2003 Liver *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	"Patients were assigned randomly" but no other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions given to groups with different dose frequency. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different interventions given to groups with different dose frequency. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes. No report of CMV infection and graft loss
Other bias	High risk	Supported in part by a research grant from Roche Laboratories

Winston 2004 Liver

Methods	• Study design: parallel RCT • Time frame: June 1997 to April 2000 • Follow-up period: 1 year • Loss to follow-up: 0%
Participants	• Country: USA • Setting: tertiary single centre • Liver transplant recipients; D+/R- Treatment group • Number: 32 • Mean age (range): 49 years (13 to 67) • Sex (M/F): 24/8 Control group • Number: 32 • Mean age (range): 46 years (6 to 73) • Sex (M/F): 23/9 Exclusion criteria • D/R+; D-/R-
Interventions	Treatment group • GCV: 6 mg/kg IV daily days 1 to 14; GCV 1000 mg oral 3 times/d on days 15 to 86

Winston 2004 Liver *(Continued)*

	Control group • GCV: 6 mg/kg IV daily days 1 to 14; GCV 6 mg/kg IV Monday to Friday from days 15 to 86 Co-interventions • CSA (10), TAC (54), MMF (29), AZA (3), prednisone
Outcomes	1. CMV disease 2. CMV syndrome 3. CMV tissue invasive disease 4. All-cause mortality 5. Opportunistic infections 6. Adverse effects
Notes	1. Exclusions post randomisation but pre-intervention: None 2. Stop or end point: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"Randomized controlled trial" in title but no other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different interventions given to groups. Primary outcome of CMV disease could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed for 1 year or until death
Selective reporting (reporting bias)	High risk	Incomplete outcome reporting. No report of CMV infection, graft loss
Other bias	Unclear risk	Supported in part by research grant from Roche Laboratories

ACV - aciclovir; AIDS - acquired immunodeficiency syndrome; ALG - antilymphocyte globulin; AT - antithymocyte globulin; AZA - azathioprine; CD/LD - cadaveric donor/living donor; CMV, cytomegalovirus; CMVIgG - cytomegalovirus gamma G immunoglobulin; CSA - cyclosporin; D/R+ - donor CMV positive or negative/recipient CMV positive; D+/R- - donor CMV positive/recipient CMV negative; D-/R- - donor CMV negative/recipient CMV negative; DNA - deoxyribonucleic acid; GCV - ganciclovir; GFR - glomerular filtration rate; HI -, human immunovirus; IgG - immunoglobulin G; IgM - immunoglobulin M; IgM 3 - immunoglobulin M 3; IL2Ra - interleukin 2 receptor alpha; IQR - interquartile range; ITT - intention-to-treat; IV - intravenous; MMF - mycophenolate mofetil; NS - not stated; OKT-3 - monoclonal anti CD3 antibody; PCR - polymerase chain reaction; TAC - tacrolimus; VACV - valaciclovir; VGCV - valganciclovir; WBC - white blood cell

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahsan 1998	Not RCT (sequential)
Arbo 2000	Economic evaluation of previous study
Brennan 1997	Pre-emptive study
Brennan 2001	Review article
Devolder 2010	Ineligible intervention. Compares different methods to encourage compliance
Dickinson 1996	IgG to prevent CMV
Falagas 1997	Included both non-randomised patients and patients from a previous study
Fehir 1989	Nonrandomised patients included
Ferreira 2004	Prospective study of different immunosuppressive regimens. Not RCT
Fishman 2000	Retrospective study
Gerna 2003	Diagnostic test systematic review
Gerna 2008	Pre-emptive therapy compared with prophylaxis
Greger 1988	Ineligible intervention
Griffiths 1997	Review article
Griffiths 2010	Study of pre-emptive therapy vs. monitoring
Grundmann 1986	Ineligible intervention. CMV IgG
Hecht 1988	Not an RCT
Huurman 2006	RCT of ATG versus daclizumab, not antiviral medication
Jung 2001	Pre-emptive study
Jurim 1996	Subgroup of previous study; outcome hepatitis B
Khoury 2006	Pre-emptive study
Kim 2000	Economic evaluation of previous study
Kletzmayr 2000	Not RCT. Historical controls
Kliem 2008	Pre-emptive study
Koetz 2001	Pre-emptive study
Kuypers 1999	Review article
Laske 1991	Review article
Laske 1992	Review article

Study	Reason for exclusion
Luan 2009	Retrospective study
Lumbreras 1993	Not RCT. Historical controls
MacDonald 1991	Ineligible intervention. CMV IgG
Marker 1980	Treatment not prophylaxis of CMV disease
Martin 1993	Review article
Martin 1994	Review article
Martin 1995	Review article
Mattes 2004	Ineligible intervention. Comparing 2 pre-emptive regimens. Results cannot be separated for bone marrow and solid organ transplant recipients
McGavin 2001	GCV review
Moreno 1999	Not RCT
Mullen 1998	Retrospective study
Murray 1997	Pre-emptive study
Paya 2002	Pre-emptive study
Pescovitz 2009	Pharmacokinetic study
Pouteil 1991	Study of influence of HLA on CMV infection within RCT of different immunosuppressive regimens
PROTECT Study 2010	Comparing pre-emptive therapy with prophylaxis
Queiroga 2003	Pre-emptive study
Rayes 2001	Pre-emptive study
Reischig 2008	Pre-emptive study
Sagedal 2003	Pre-emptive study
Said 2007	Appears to be sequential study not RCT
Schafers 1988	Not RCT (sequential)
Schnitzler 2000	Re-analysis of previous study (1992)
Singh 1994	Pre-emptive study
Singh 1995	Not RCT
Singh 2000	Pre-emptive study
Snydman 1991a	Review article

Study	Reason for exclusion
Snydman 1991b	Compares results to previous study
Snydman 1994	Compares results to previous study
Snydman 2001	Historical controls
Speich 1999	Not RCT (sequential)
Stratta 1992	Non-randomised patients included
Tong 2002	Not an RCT
Turgeon 1998	Not RCT (sequential)
Valantine 1995	IgG study
VICTOR Study 2007	Treatment of CMV disease not prophylaxis
Yang 1998	Pre-emptive study
Yang 1999	Unable to determine if patients randomised

ATG - antithymocyte globulin; CMV - cytomegalovirus; GCV - ganciclovir; HLA - human leukocyte antigen; IgG - Immunoglobulin G; RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Villano 2010

Trial name or title	A randomized, double-blind study to assess the efficacy and safety of prophylactic use of maribavir versus oral ganciclovir for the prevention of cytomegalovirus disease in recipients of orthotopic liver transplants
Methods	• Allocation: randomized • Endpoint classification: safety/efficacy study • Intervention model: parallel assignment • Masking: double blind (subject, caregiver, investigator) • Primary purpose: prevention
Participants	Inclusion criteria • Male and female, ≥ 18 years • Orthotopic liver transplant recipient • Donor CMV seropositive / Recipient CMV seronegative • Enrolled within 10 days after liver transplant • Able to swallow tablets Exclusion criteria • Multiple organ transplant • HIV infection • CMV disease • Use of other anti-CMV therapy at time of enrolment
Interventions	• Maribavir: 100 mg twice a day for 14 weeks

Villano 2010 *(Continued)*	• Ganciclovir: 1000 mg 3 times/d for 14 weeks
Outcomes	• CMV disease 6 months post-transplant • CMV disease 100 days and 12 months post-transplant • Incidence of CMV infection 100 days and 12 months post-transplant • Incidence of graft rejection 100 days and 12 months post-transplant • Incidence of retransplantation 100 days and 12 months post-transplant • Mortality 100 days and 12 months post-transplant
Starting date	July 2007
Contact information	Stephen Villano, MD, Viropharma, Inc.
Notes	Study completed 2009

DATA AND ANALYSES

Comparison 1. Antiviral prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All symptomatic CMV disease	19	1981	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.52]
1.2 CMV syndrome	11	1570	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.29, 0.57]
1.3 CMV organ involvement	12	1628	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.21, 0.55]
1.4 Total CMV infection	17	1786	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.48, 0.77]
2 All symptomatic CMV disease stratified by antibody status	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV antibody +ve recipients	13	1348	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.24, 0.50]
2.2 CMV +ve donor / CMV -ve recipient	10	423	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.37, 0.73]
2.3 CMV -ve donor / CMV -ve recipient	4	38	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.09, 11.03]
2.4 CMV +ve donor / CMV +ve recipient	5	276	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.09, 0.37]

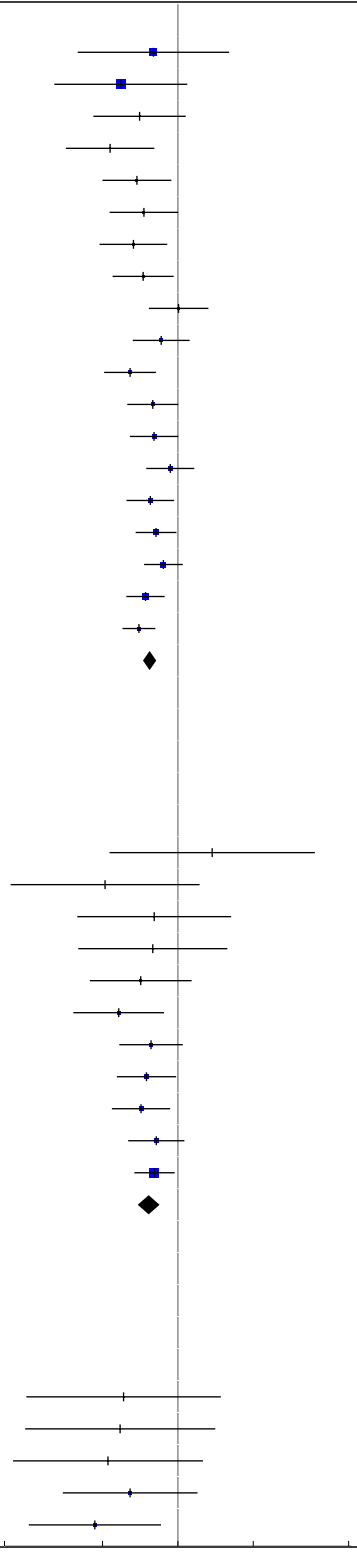
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 CMV -ve donor / CMV +ve recipient	5	160	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.95]
3 CMV disease in all patients by antiviral medication	19	1981	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.52]
3.1 Aciclovir	6	421	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.29, 0.69]
3.2 Ganciclovir	11	917	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.34, 0.58]
3.3 Valaciclovir	2	643	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.19, 0.49]
4 CMV disease for different organ transplants	19	1980	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.35, 0.55]
4.1 Kidney transplant recipients	11	1132	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.57]
4.2 Liver transplant recipients	5	616	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.29, 0.84]
4.3 Heart transplant recipients	3	232	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.63]
5 CMV disease and ganciclovir duration	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Six weeks or less	7	478	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.36, 0.68]
5.2 More than 6 weeks	4	439	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.21, 0.53]
6 ATG therapy and antiviral efficacy	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 CMV disease in all treated patients	11	666	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.55]
6.2 All-cause mortality	10	643	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.33, 2.02]
7 Immunosuppression without ATG induction and antiviral efficacy	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 CMV disease in all treated patients	6	649	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.76]
7.2 All-cause mortality	5	529	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.00]
8 Mortality due to CMV disease or other causes	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 CMV disease	7	1300	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.78]
8.2 Other causes	7	1300	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 All-cause mortality according to antiviral medication	17	1838	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
9.1 Aciclovir	5	301	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.38, 1.20]
9.2 Ganciclovir	10	894	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.65]
9.3 Valaciclovir	2	643	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.15]
10 All-cause mortality according to CMV status	9	1026	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.41, 1.32]
10.1 CMV +ve recipients	7	738	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.18]
10.2 CMV -ve recipients of CMV +ve organs	4	288	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.44, 4.66]
11 All-cause mortality for different organ transplants	17	1838	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
11.1 Kidney transplant recipients	10	1109	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.24, 1.00]
11.2 Liver transplant patients	4	497	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.00]
11.3 Heart transplant recipients	3	232	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.39, 8.51]
12 All-cause mortality and ganciclovir duration	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Six weeks or less	6	455	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.17, 4.92]
12.2 More than 6 weeks	4	439	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.30, 1.30]
13 Additional outcomes - all medications	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Graft loss	10	825	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.47, 1.17]
13.2 Acute rejection	13	1420	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
13.3 Herpes simplex and H. zoster infection	9	1483	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.19, 0.40]
13.4 Invasive fungal infection	3	189	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.19, 1.73]
13.5 Bacterial infection	3	174	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.96]
13.6 EBV-associated PTLD	2	359	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.51]
13.7 Protozoal infections	2	114	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 0.99]

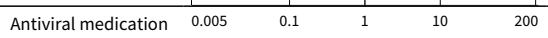
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Acute rejection according to method of diagnosis	13	1420	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
14.1 Biopsy-proven acute rejection	5	821	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.32]
14.2 Clinical diagnosis of acute rejection or method not stated	8	599	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
15 Valaciclovir - additional outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Acute rejection in donor CMV +ve / recipient CMV -ve grafts	1	208	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.35, 0.74]
15.2 Acute rejection in CMV +ve recipients	1	408	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.63, 1.10]
15.3 Total with acute rejection	2	643	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.55, 1.19]
16 Adverse effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Leucopenia with aciclovir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Kidney dysfunction with aciclovir	2	159	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.27, 4.70]
16.3 Neurological dysfunction with aciclovir	1	55	Risk Ratio (M-H, Random, 95% CI)	10.62 [0.62, 183.26]
16.4 Leucopenia with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.37, 2.65]
16.5 Kidney dysfunction with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.91, 6.15]
16.6 Neurological dysfunction with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.98, 2.58]
16.7 Leucopenia with valaciclovir	1	616	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.62, 1.78]
16.8 Kidney dysfunction with valaciclovir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.9 Neurological dysfunction with valaciclovir	1	616	Risk Ratio (M-H, Random, 95% CI)	8.78 [2.69, 28.71]

Analysis 1.1. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 1 CMV disease and CMV infection in all treated patients.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All symptomatic CMV disease					
Rostaing 1994 Kidney	1/19	2/18		0.76%	0.47[0.05,4.78]
Ahsan 1997 Kidney	1/21	6/22		0.98%	0.17[0.02,1.33]
Egan 2002 Heart	2/14	6/13		1.97%	0.31[0.08,1.27]
Conti 1995 Kidney	2/22	13/18		2.14%	0.13[0.03,0.49]
Saliba 1993 Liver	4/60	14/60		3.42%	0.29[0.1,0.82]
Gavalda 1997 Liver	4/37	11/36		3.45%	0.35[0.12,1.01]
Balfour 1989 Kidney	4/53	15/51		3.54%	0.26[0.09,0.72]
Brennan 1997 Kidney	4/19	14/23		4.28%	0.35[0.14,0.88]
Kletzmayr 1996 Kidney	9/22	4/10		4.45%	1.02[0.41,2.54]
Macdonald 1995 Heart	6/28	10/28		4.87%	0.6[0.25,1.43]
Gane 1997 Liver	7/150	31/154		5.73%	0.23[0.11,0.51]
Pouteil-Noble 1996 Kidney	6/24	14/26		5.86%	0.46[0.21,1.01]
Barkholt 1999 Liver	7/28	14/27		6.44%	0.48[0.23,1.01]
Cohen 1993 Liver	9/33	11/32		6.48%	0.79[0.38,1.65]
Hibberd 1995 Kidney	9/64	16/49		6.59%	0.43[0.21,0.89]
Leray 1995 Kidney	6/13	9/10		8.52%	0.51[0.28,0.96]
Rondeau 1993 Kidney	8/17	11/15		9.29%	0.64[0.36,1.16]
Merigan 1992 Heart	12/76	31/73		9.42%	0.37[0.21,0.67]
Lowance 1999 Kidney	18/306	60/310		11.81%	0.3[0.18,0.5]
Subtotal (95% CI)	**1006**	**975**		**100%**	**0.42[0.34,0.52]**
Total events: 119 (Antiviral medication), 292 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=20.59, df=18(P=0.3); I^2=12.59%					
Test for overall effect: Z=8.35(P<0.0001)					
1.1.2 CMV syndrome					
Rostaing 1994 Kidney	1/19	0/18		1.12%	2.85[0.12,65.74]
Gavalda 1997 Liver	0/37	4/36		1.33%	0.11[0.01,1.94]
Cohen 1993 Liver	1/33	2/32		2%	0.48[0.05,5.09]
Egan 2002 Heart	1/14	2/13		2.13%	0.46[0.05,4.53]
Balfour 1989 Kidney	2/53	6/51		4.58%	0.32[0.07,1.52]
Conti 1995 Kidney	2/22	10/18		5.77%	0.16[0.04,0.65]
Brennan 1997 Kidney	4/19	11/23		11.76%	0.44[0.17,1.16]
Hibberd 1995 Kidney	6/64	12/49		13.46%	0.38[0.15,0.95]
Gane 1997 Liver	6/150	19/154		13.97%	0.32[0.13,0.79]
Merigan 1992 Heart	7/76	13/73		14.92%	0.52[0.22,1.22]
Lowance 1999 Kidney	14/306	29/310		28.96%	0.49[0.26,0.91]
Subtotal (95% CI)	**793**	**777**		**100%**	**0.41[0.29,0.57]**
Total events: 44 (Antiviral medication), 108 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=5.02, df=10(P=0.89); I^2=0%					
Test for overall effect: Z=5.27(P<0.0001)					
1.1.3 CMV organ involvement					
Rostaing 1994 Kidney	0/19	2/18		2.51%	0.19[0.01,3.71]
Brennan 1997 Kidney	0/19	3/23		2.61%	0.17[0.01,3.13]
Conti 1995 Kidney	0/22	3/18		2.62%	0.12[0.01,2.15]
Egan 2002 Heart	1/14	4/13		4.74%	0.23[0.03,1.82]
Gane 1997 Liver	1/150	13/154		4.88%	0.08[0.01,0.6]

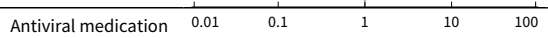


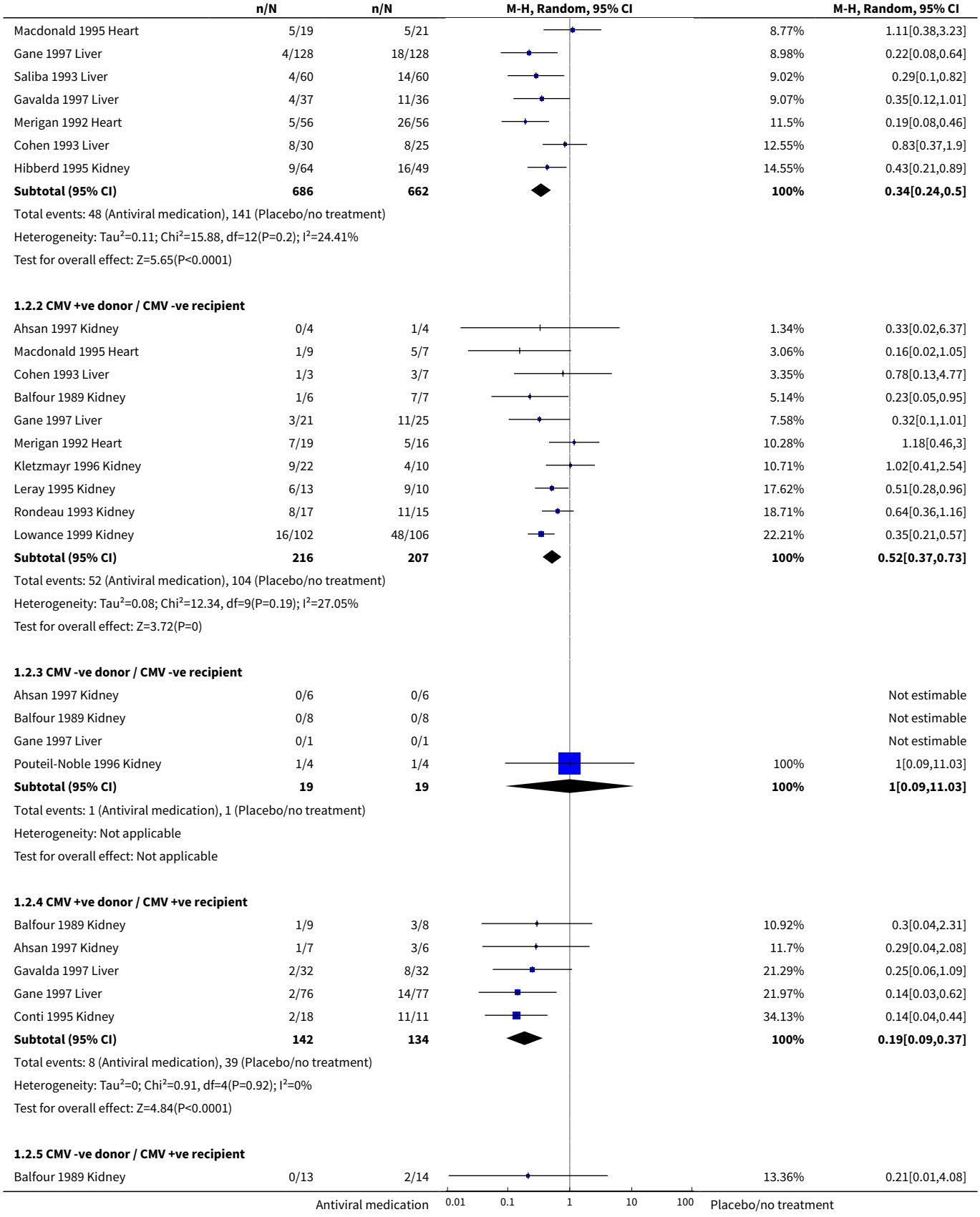
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Balfour 1989 Kidney	2/53	9/51		7.83%	0.21[0.05,0.94]
Hibberd 1995 Kidney	3/64	4/49		8.08%	0.57[0.13,2.45]
Gavalda 1997 Liver	4/37	7/38		10.99%	0.59[0.19,1.84]
Lowance 1999 Kidney	4/306	31/310		12.35%	0.13[0.05,0.37]
Merigan 1992 Heart	5/76	20/73		13.75%	0.24[0.1,0.61]
Macdonald 1995 Heart	6/28	9/28		14.27%	0.67[0.27,1.62]
Cohen 1993 Liver	8/33	9/32		15.37%	0.86[0.38,1.95]
Subtotal (95% CI)	**821**	**807**		**100%**	**0.34[0.21,0.55]**
Total events: 34 (Antiviral medication), 114 (Placebo/no treatment)					
Heterogeneity: Tau²=0.24; Chi²=16.88, df=11(P=0.11); I²=34.85%					
Test for overall effect: Z=4.32(P<0.0001)					
1.1.4 Total CMV infection					
Ahsan 1997 Kidney	1/21	6/22		1.16%	0.17[0.02,1.33]
Macdonald 1995 Heart	4/21	9/20		3.39%	0.42[0.15,1.16]
Gavalda 1997 Liver	6/37	14/36		4.18%	0.42[0.18,0.97]
Rostaing 1994 Kidney	5/19	11/18		4.18%	0.43[0.19,1]
Kletzmayr 1996 Kidney	15/22	5/10		5.1%	1.36[0.69,2.7]
Hibberd 1995 Kidney	11/64	17/49		5.24%	0.5[0.26,0.96]
Saliba 1993 Liver	11/60	23/60		5.49%	0.48[0.26,0.89]
Merigan 1992 Heart	11/58	31/55		5.79%	0.34[0.19,0.6]
Leray 1995 Kidney	7/13	9/10		6.05%	0.6[0.35,1.03]
Pouteil-Noble 1996 Kidney	13/24	18/26		6.75%	0.78[0.5,1.23]
Barkholt 1999 Liver	16/28	17/27		6.87%	0.91[0.59,1.4]
Cohen 1993 Liver	16/33	24/32		7.07%	0.65[0.43,0.97]
Rondeau 1993 Kidney	12/17	12/15		7.12%	0.88[0.59,1.31]
Gane 1997 Liver	37/150	79/154		7.68%	0.48[0.35,0.66]
Brennan 1997 Kidney	13/19	23/23		7.75%	0.69[0.51,0.94]
Lowance 1999 Kidney	48/306	119/310		7.84%	0.41[0.3,0.55]
Egan 2002 Heart	13/14	12/13		8.34%	1.01[0.81,1.25]
Subtotal (95% CI)	**906**	**880**		**100%**	**0.61[0.48,0.77]**
Total events: 239 (Antiviral medication), 429 (Placebo/no treatment)					
Heterogeneity: Tau²=0.16; Chi²=67.22, df=16(P<0.0001); I²=76.2%					
Test for overall effect: Z=4.13(P<0.0001)					

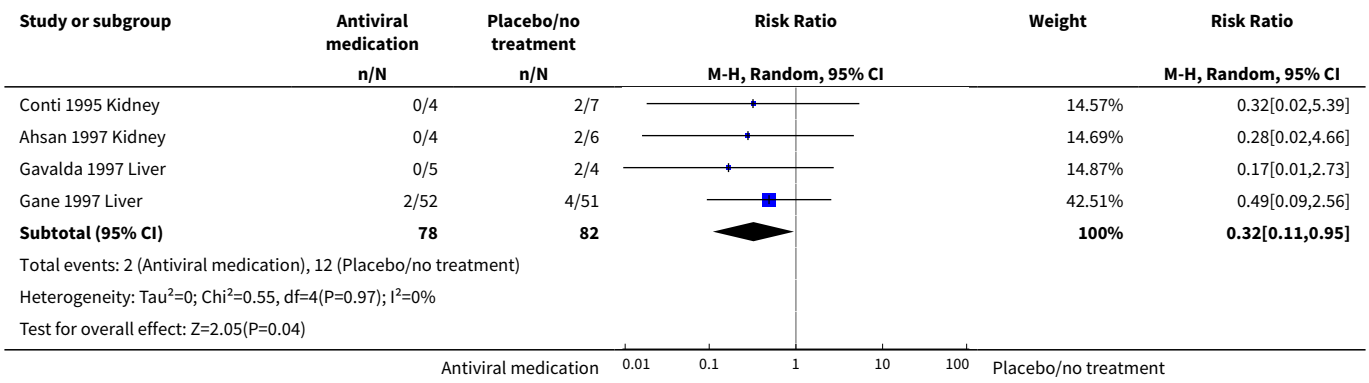


Analysis 1.2. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 2 All symptomatic CMV disease stratified by antibody status.

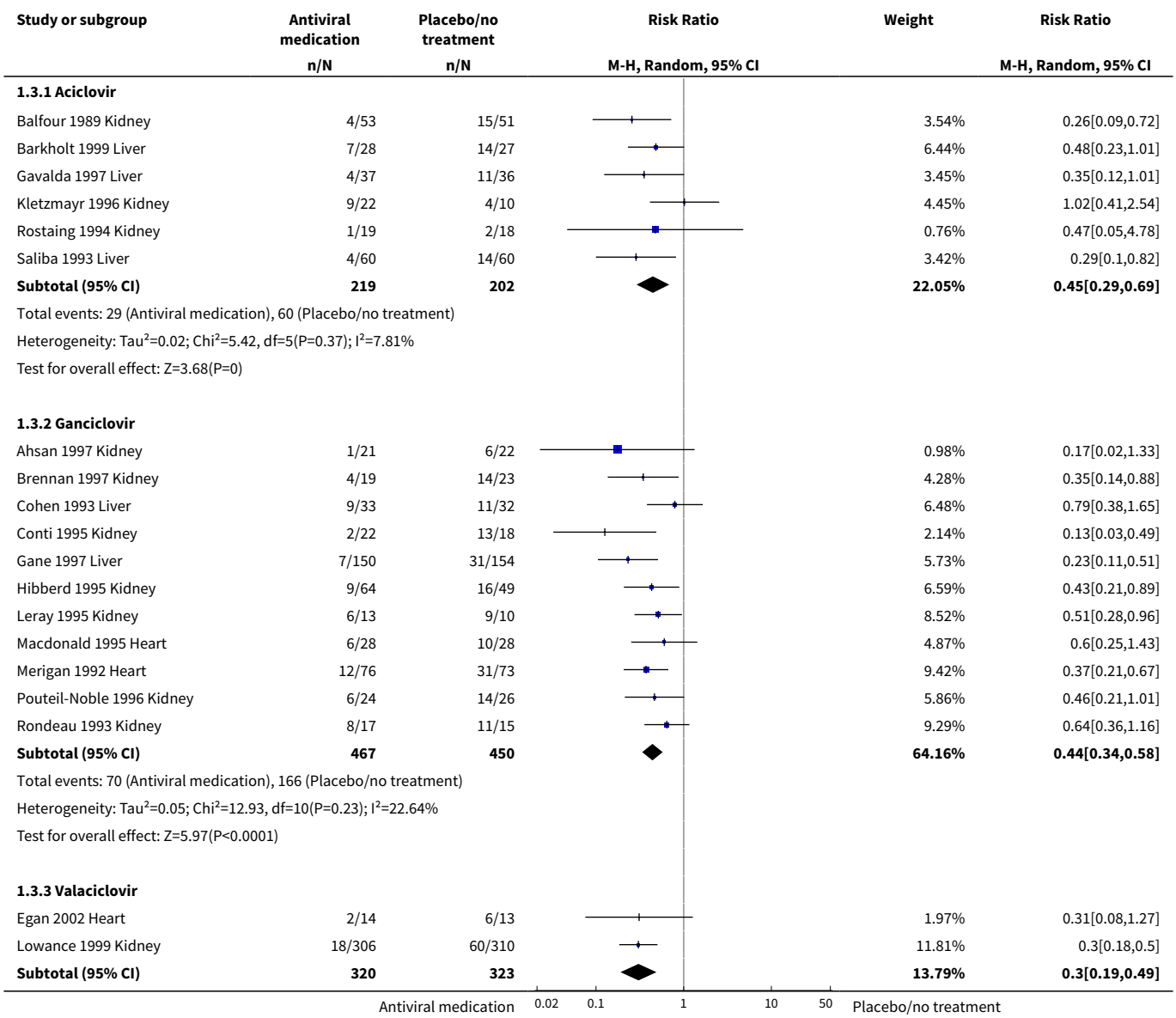
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 CMV antibody +ve recipients					
Rostaing 1994 Kidney	1/19	2/18		2.39%	0.47[0.05,4.78]
Balfour 1989 Kidney	1/22	5/22		2.94%	0.2[0.03,1.58]
Ahsan 1997 Kidney	1/11	5/12		3.16%	0.22[0.03,1.59]
Lowance 1999 Kidney	2/204	12/204		5.25%	0.17[0.04,0.74]
Egan 2002 Heart	2/14	6/13		5.71%	0.31[0.08,1.27]
Conti 1995 Kidney	2/22	13/18		6.12%	0.13[0.03,0.49]







Analysis 1.3. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 3 CMV disease in all patients by antiviral medication.



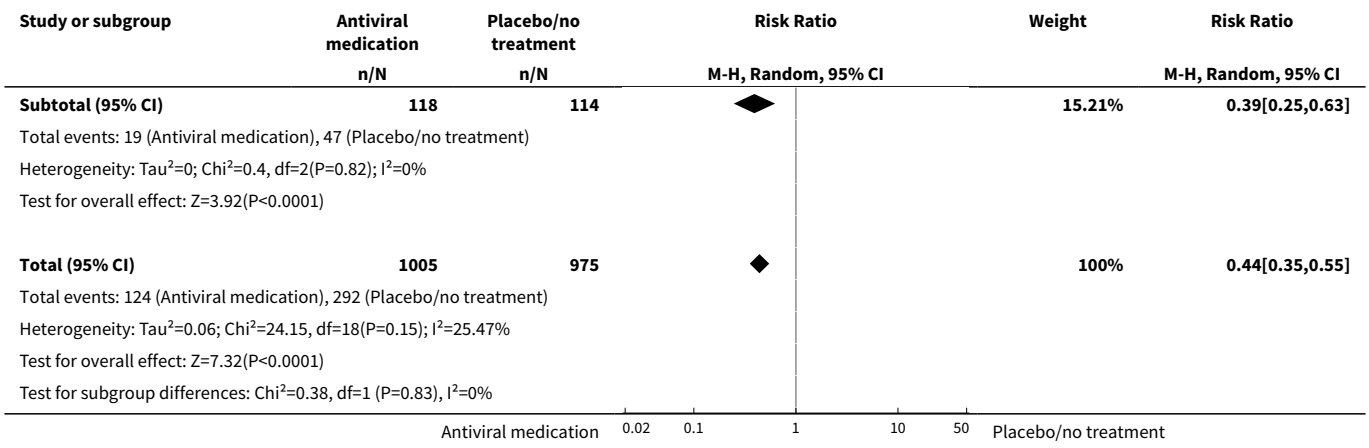
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 20 (Antiviral medication), 66 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.98); I²=0%					
Test for overall effect: Z=4.92(P<0.0001)					
Total (95% CI)	**1006**	**975**	◆	**100%**	**0.42[0.34,0.52]**
Total events: 119 (Antiviral medication), 292 (Placebo/no treatment)					
Heterogeneity: Tau²=0.03; Chi²=20.59, df=18(P=0.3); I²=12.59%					
Test for overall effect: Z=8.35(P<0.0001)					
Test for subgroup differences: Chi²=1.91, df=1 (P=0.38), I²=0%					

Antiviral medication 0.02 0.1 1 10 50 Placebo/no treatment

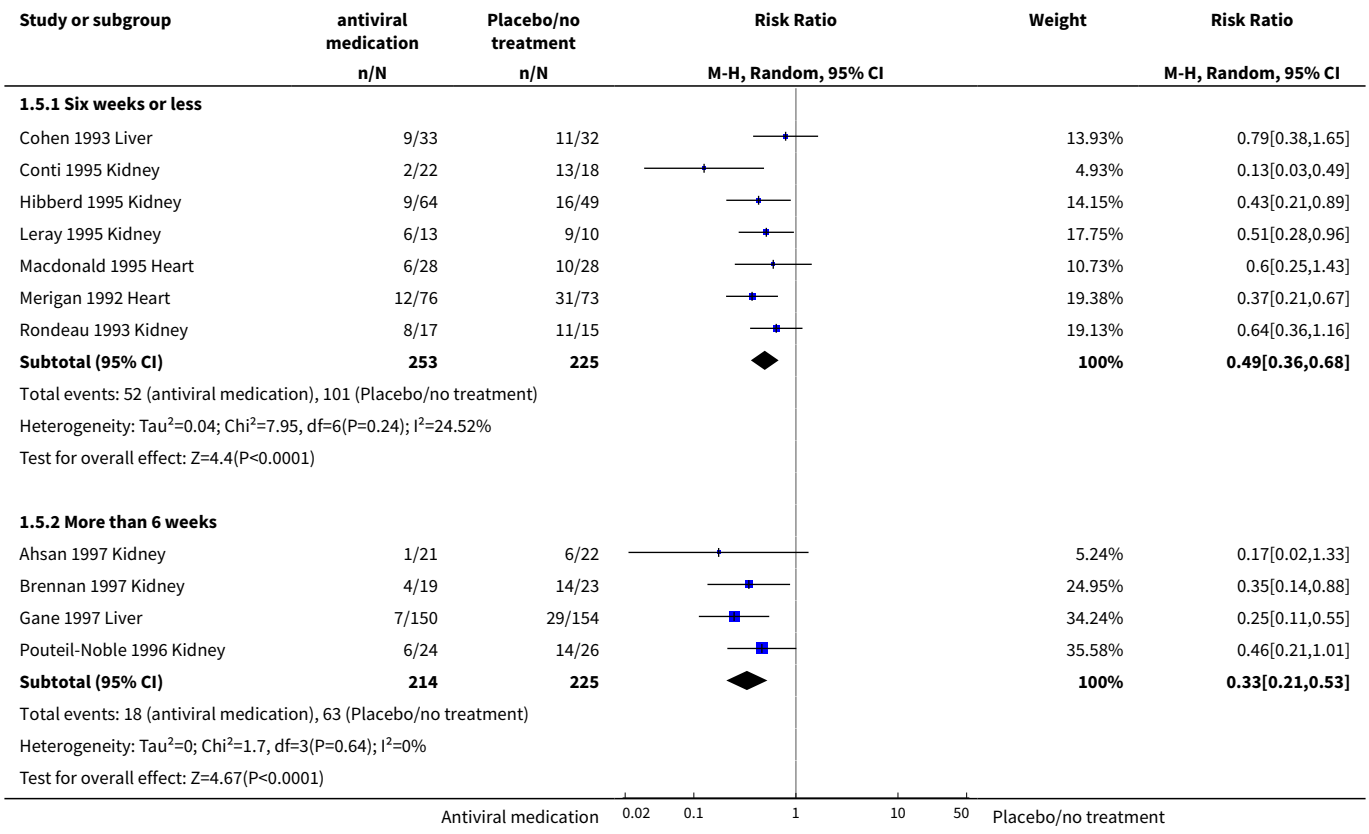
Analysis 1.4. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 4 CMV disease for different organ transplants.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Kidney transplant recipients					
Ahsan 1997 Kidney	1/21	6/22		1.11%	0.17[0.02,1.33]
Balfour 1989 Kidney	4/53	15/51		3.75%	0.26[0.09,0.72]
Brennan 1997 Kidney	4/19	14/23		4.46%	0.35[0.14,0.88]
Conti 1995 Kidney	2/22	13/18		2.36%	0.13[0.03,0.49]
Hibberd 1995 Kidney	9/64	16/49		6.46%	0.43[0.21,0.89]
Kletzmayr 1996 Kidney	9/22	4/10		4.61%	1.02[0.41,2.54]
Leray 1995 Kidney	6/13	9/10		7.96%	0.51[0.28,0.96]
Lowance 1999 Kidney	18/306	60/310		10.22%	0.3[0.18,0.5]
Pouteil-Noble 1996 Kidney	6/24	14/26		5.85%	0.46[0.21,1.01]
Rondeau 1993 Kidney	8/17	11/15		8.52%	0.64[0.36,1.16]
Rostaing 1994 Kidney	1/19	2/18		0.87%	0.47[0.05,4.78]
Subtotal (95% CI)	**580**	**552**	◆	**56.17%**	**0.42[0.31,0.57]**
Total events: 68 (Antiviral medication), 164 (Placebo/no treatment)					
Heterogeneity: Tau²=0.07; Chi²=13.75, df=10(P=0.18); I²=27.25%					
Test for overall effect: Z=5.64(P<0.0001)					
1.4.2 Liver transplant recipients					
Barkholt 1999 Liver	7/28	14/27		6.33%	0.48[0.23,1.01]
Cohen 1993 Liver	9/33	11/32		6.36%	0.79[0.38,1.65]
Gane 1997 Liver	7/150	31/154		5.74%	0.23[0.11,0.51]
Gavalda 1997 Liver	10/36	11/36		6.53%	0.91[0.44,1.87]
Saliba 1993 Liver	4/60	14/60		3.65%	0.29[0.1,0.82]
Subtotal (95% CI)	**307**	**309**	◆	**28.62%**	**0.49[0.29,0.84]**
Total events: 37 (Antiviral medication), 81 (Placebo/no treatment)					
Heterogeneity: Tau²=0.22; Chi²=9.33, df=4(P=0.05); I²=57.13%					
Test for overall effect: Z=2.57(P=0.01)					
1.4.3 Heart transplant recipients					
Egan 2002 Heart	2/14	6/13		2.19%	0.31[0.08,1.27]
Macdonald 1995 Heart	5/28	10/28		4.41%	0.5[0.2,1.28]
Merigan 1992 Heart	12/76	31/73		8.61%	0.37[0.21,0.67]

Antiviral medication 0.02 0.1 1 10 50 Placebo/no treatment

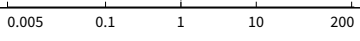


Analysis 1.5. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 5 CMV disease and ganciclovir duration.



Analysis 1.6. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 6 ATG therapy and antiviral efficacy.

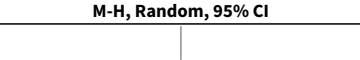
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 CMV disease in all treated patients					
Ahsan 1997 Kidney	1/21	6/22		1.6%	0.17[0.02,1.33]
Balfour 1989 Kidney	4/53	15/51		6.16%	0.26[0.09,0.72]
Brennan 1997 Kidney	4/19	14/23		7.61%	0.35[0.14,0.88]
Conti 1995 Kidney	2/22	13/18		3.6%	0.13[0.03,0.49]
Egan 2002 Heart	2/14	6/13		3.31%	0.31[0.08,1.27]
Hibberd 1995 Kidney	9/64	16/49		12.46%	0.43[0.21,0.89]
Leray 1995 Kidney	6/13	9/10		16.99%	0.51[0.28,0.96]
Macdonald 1995 Heart	6/28	10/28		8.78%	0.6[0.25,1.43]
Merigan 1992 Heart	12/76	31/73		19.31%	0.37[0.21,0.67]
Rondeau 1993 Kidney	8/17	11/15		18.95%	0.64[0.36,1.16]
Rostaing 1994 Kidney	1/19	2/18		1.23%	0.47[0.05,4.78]
Subtotal (95% CI)	**346**	**320**		**100%**	**0.43[0.33,0.55]**
Total events: 55 (Antiviral medication), 133 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=8.99, df=10(P=0.53); I^2=0%					
Test for overall effect: Z=6.52(P<0.0001)					
1.6.2 All-cause mortality					
Ahsan 1997 Kidney	0/21	1/22		8.3%	0.35[0.01,8.11]
Balfour 1989 Kidney	2/53	3/51		26.91%	0.64[0.11,3.68]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Conti 1995 Kidney	0/22	0/18			Not estimable
Egan 2002 Heart	1/14	2/13		15.82%	0.46[0.05,4.53]
Hibberd 1995 Kidney	1/64	2/49		14.61%	0.38[0.04,4.1]
Macdonald 1995 Heart	3/28	0/28		9.65%	7[0.38,129.55]
Merigan 1992 Heart	3/76	1/73		16.37%	2.88[0.31,27.07]
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Rostaing 1994 Kidney	0/19	1/18		8.34%	0.32[0.01,7.3]
Subtotal (95% CI)	**333**	**310**		**100%**	**0.82[0.33,2.02]**
Total events: 10 (Antiviral medication), 10 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=4.73, df=6(P=0.58); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					



Antiviral medication — Placebo/no treatment

Analysis 1.7. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 7 Immunosuppression without ATG induction and antiviral efficacy.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 CMV disease in all treated patients					
Barkholt 1999 Liver	7/28	14/27		19.55%	0.48[0.23,1.01]
Cohen 1993 Liver	9/33	11/32		19.62%	0.79[0.38,1.65]
Gane 1997 Liver	7/150	31/154		18.35%	0.23[0.11,0.51]
Gavalda 1997 Liver	4/37	11/36		13.37%	0.35[0.12,1.01]
Kletzmayr 1996 Kidney	9/22	4/10		15.8%	1.02[0.41,2.54]



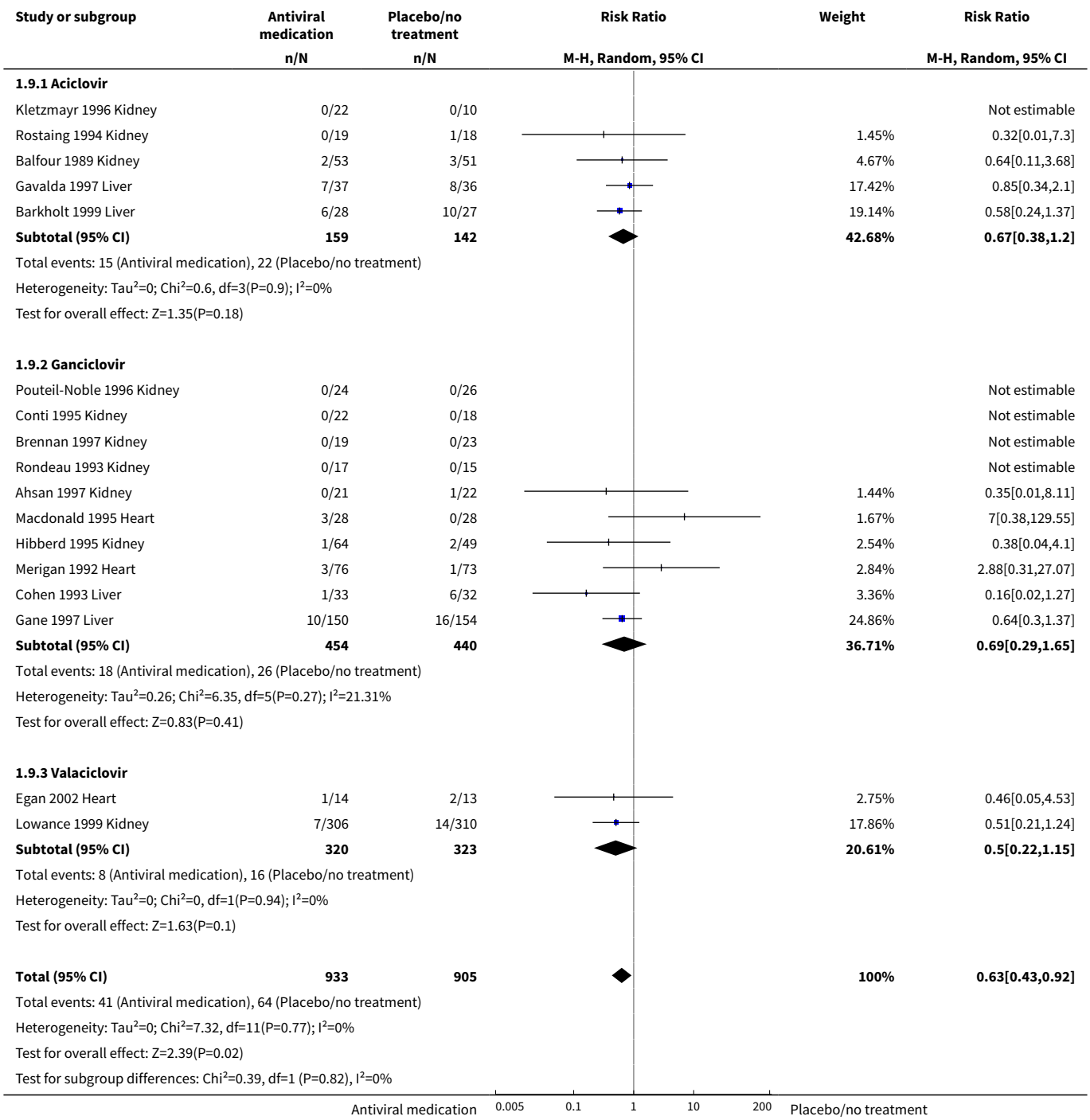
Antiviral medication — Placebo/no treatment

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Saliba 1993 Liver	4/60	14/60		13.31%	0.29[0.1,0.82]
Subtotal (95% CI)	**330**	**319**		**100%**	**0.47[0.29,0.76]**
Total events: 40 (Antiviral medication), 85 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.17; Chi^2=9.49, df=5(P=0.09); I^2=47.29%					
Test for overall effect: Z=3.07(P=0)					
1.7.2 All-cause mortality					
Barkholt 1999 Liver	6/28	10/27		29.55%	0.58[0.24,1.37]
Cohen 1993 Liver	1/33	6/32		5.19%	0.16[0.02,1.27]
Gane 1997 Liver	10/150	16/154		38.37%	0.64[0.3,1.37]
Gavalda 1997 Liver	7/37	8/36		26.9%	0.85[0.34,2.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Subtotal (95% CI)	**270**	**259**		**100%**	**0.63[0.39,1]**
Total events: 24 (Antiviral medication), 40 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.18, df=3(P=0.54); I^2=0%					
Test for overall effect: Z=1.96(P=0.05)					

Analysis 1.8. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 8 Mortality due to CMV disease or other causes.

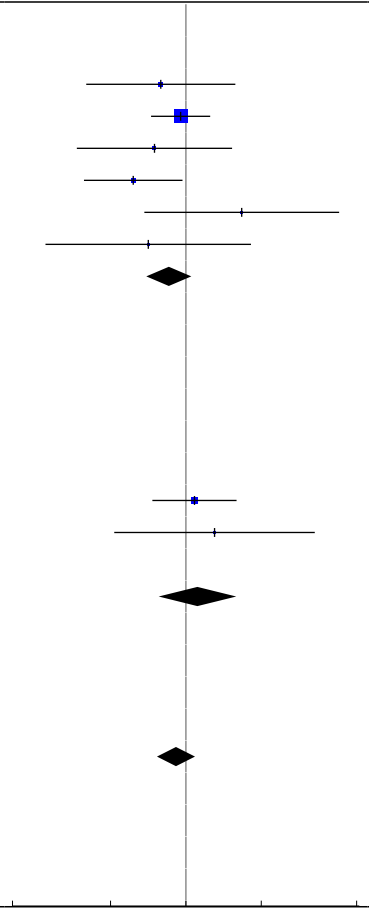
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 CMV disease					
Ahsan 1997 Kidney	0/21	1/22		12.42%	0.35[0.01,8.11]
Balfour 1989 Kidney	0/53	2/51		13.55%	0.19[0.01,3.92]
Barkholt 1999 Liver	1/28	2/27		22.43%	0.48[0.05,5.01]
Cohen 1993 Liver	0/33	1/32		12.28%	0.32[0.01,7.66]
Gane 1997 Liver	0/150	7/154		15.1%	0.07[0,1.19]
Hibberd 1995 Kidney	0/64	1/49		12.17%	0.26[0.01,6.16]
Lowance 1999 Kidney	0/306	1/310		12.04%	0.34[0.01,8.26]
Subtotal (95% CI)	**655**	**645**		**100%**	**0.26[0.08,0.78]**
Total events: 1 (Antiviral medication), 15 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.32, df=6(P=0.97); I^2=0%					
Test for overall effect: Z=2.4(P=0.02)					
1.8.2 Other causes					
Ahsan 1997 Kidney	0/21	0/22			Not estimable
Balfour 1989 Kidney	2/53	1/51		4.34%	1.92[0.18,20.58]
Barkholt 1999 Liver	5/28	8/27		25.13%	0.6[0.23,1.61]
Cohen 1993 Liver	1/33	5/32		5.57%	0.19[0.02,1.57]
Gane 1997 Liver	10/150	9/154		32.02%	1.14[0.48,2.73]
Hibberd 1995 Kidney	1/64	1/49		3.23%	0.77[0.05,11.94]
Lowance 1999 Kidney	7/306	13/310		29.72%	0.55[0.22,1.35]
Subtotal (95% CI)	**655**	**645**		**100%**	**0.71[0.44,1.17]**
Total events: 26 (Antiviral medication), 37 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.74, df=5(P=0.59); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					

Analysis 1.9. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 9 All-cause mortality according to antiviral medication.



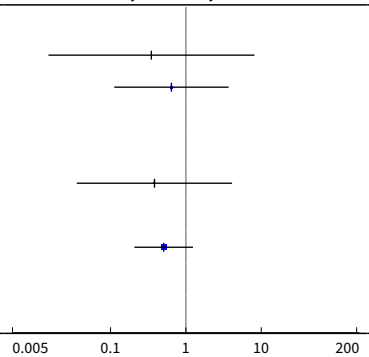
Analysis 1.10. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 10 All-cause mortality according to CMV status.

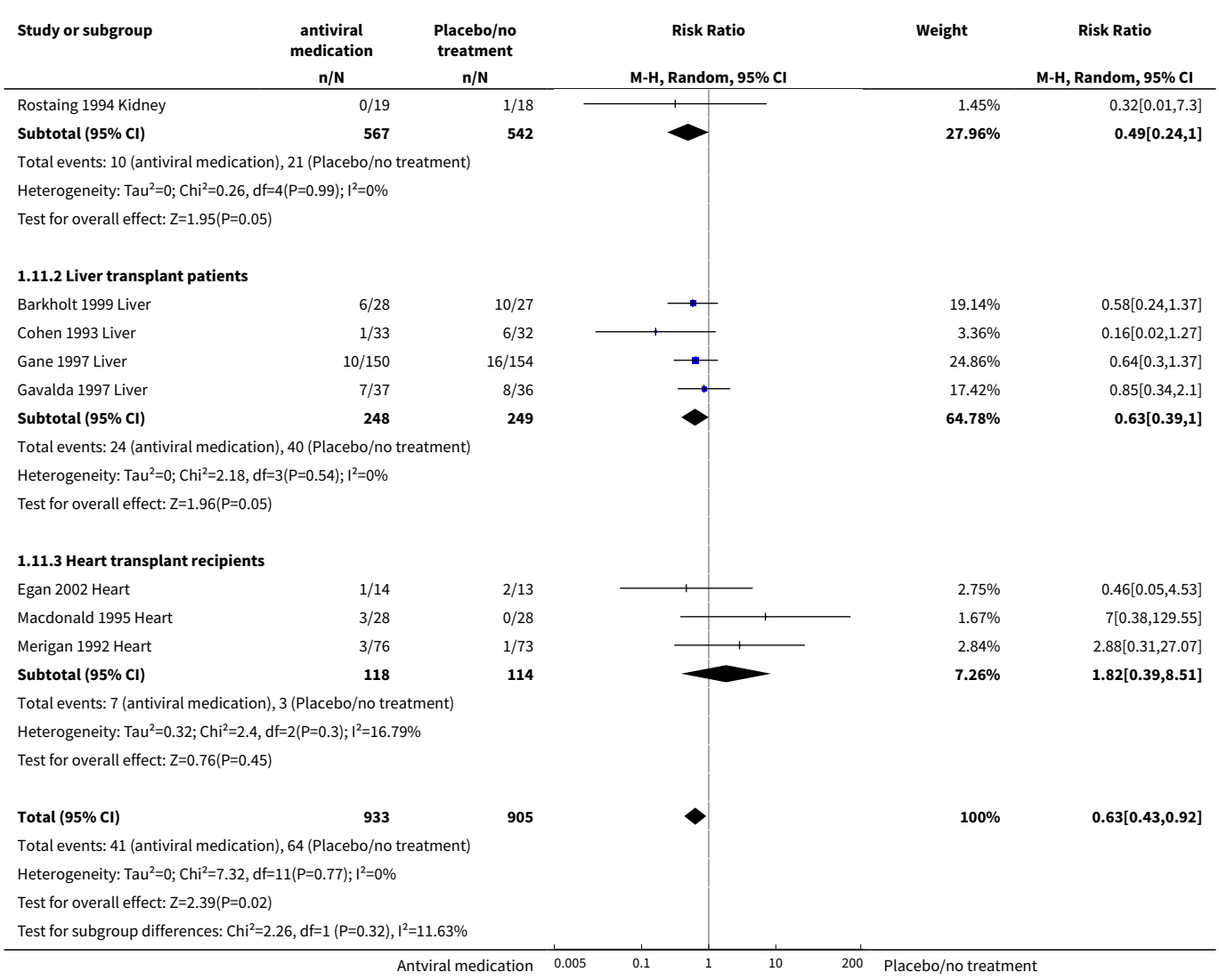
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 CMV +ve recipients					
Conti 1995 Kidney	0/22	0/18			Not estimable
Egan 2002 Heart	1/14	2/13		6.51%	0.46[0.05,4.53]
Gavalda 1997 Liver	7/37	8/36		41.3%	0.85[0.34,2.1]
Hibberd 1995 Kidney	1/64	2/49		6.01%	0.38[0.04,4.1]
Lowance 1999 Kidney	2/204	10/204		14.91%	0.2[0.04,0.9]
Macdonald 1995 Heart	2/19	0/21		3.82%	5.5[0.28,107.78]
Rostaing 1994 Kidney	0/19	1/18		3.43%	0.32[0.01,7.3]
Subtotal (95% CI)	**379**	**359**		**75.97%**	**0.59[0.3,1.18]**
Total events: 13 (Antiviral medication), 23 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=5.12, df=5(P=0.4); I^2=2.44%					
Test for overall effect: Z=1.49(P=0.14)					
1.10.2 CMV -ve recipients of CMV +ve organs					
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Lowance 1999 Kidney	5/102	4/106		20.42%	1.3[0.36,4.7]
Macdonald 1995 Heart	1/9	0/7		3.6%	2.4[0.11,51.32]
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Subtotal (95% CI)	**150**	**138**		**24.03%**	**1.42[0.44,4.66]**
Total events: 6 (Antiviral medication), 4 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					
Total (95% CI)	**529**	**497**		**100%**	**0.74[0.41,1.32]**
Total events: 19 (Antiviral medication), 27 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=6.81, df=7(P=0.45); I^2=0%					
Test for overall effect: Z=1.02(P=0.31)					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21), I^2=36.15%					



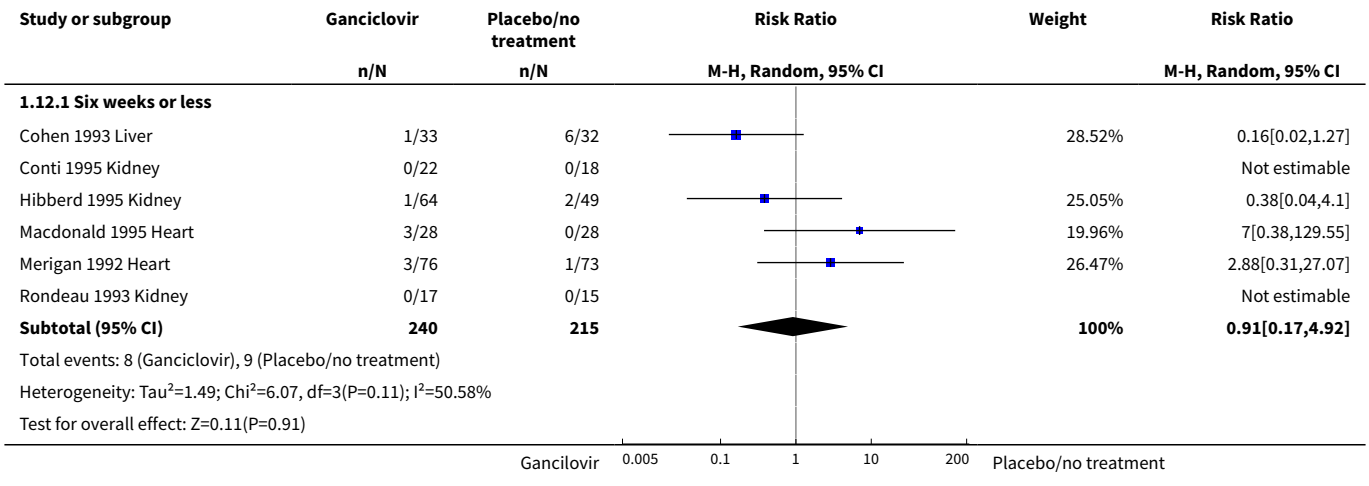
Analysis 1.11. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 11 All-cause mortality for different organ transplants.

Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Kidney transplant recipients					
Ahsan 1997 Kidney	0/21	1/22		1.44%	0.35[0.01,8.11]
Balfour 1989 Kidney	2/53	3/51		4.67%	0.64[0.11,3.68]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Conti 1995 Kidney	0/22	0/18			Not estimable
Hibberd 1995 Kidney	1/64	2/49		2.54%	0.38[0.04,4.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Lowance 1999 Kidney	7/306	14/310		17.86%	0.51[0.21,1.24]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Rondeau 1993 Kidney	0/17	0/15			Not estimable

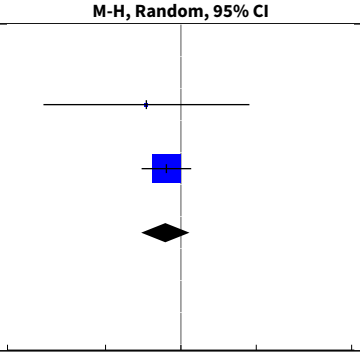




Analysis 1.12. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 12 All-cause mortality and ganciclovir duration.

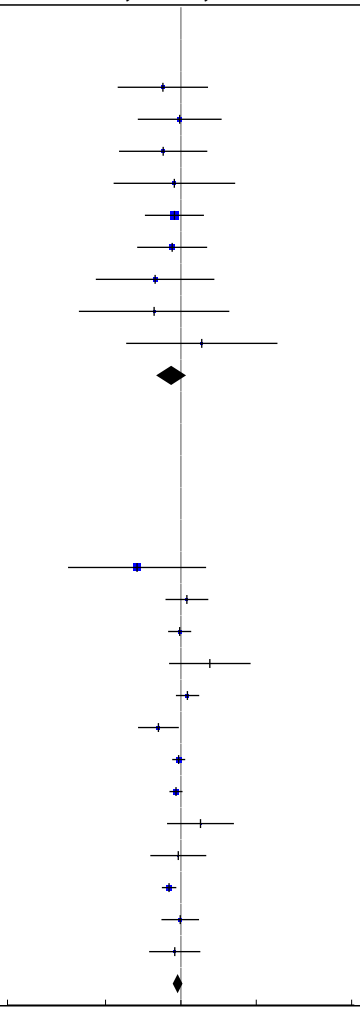


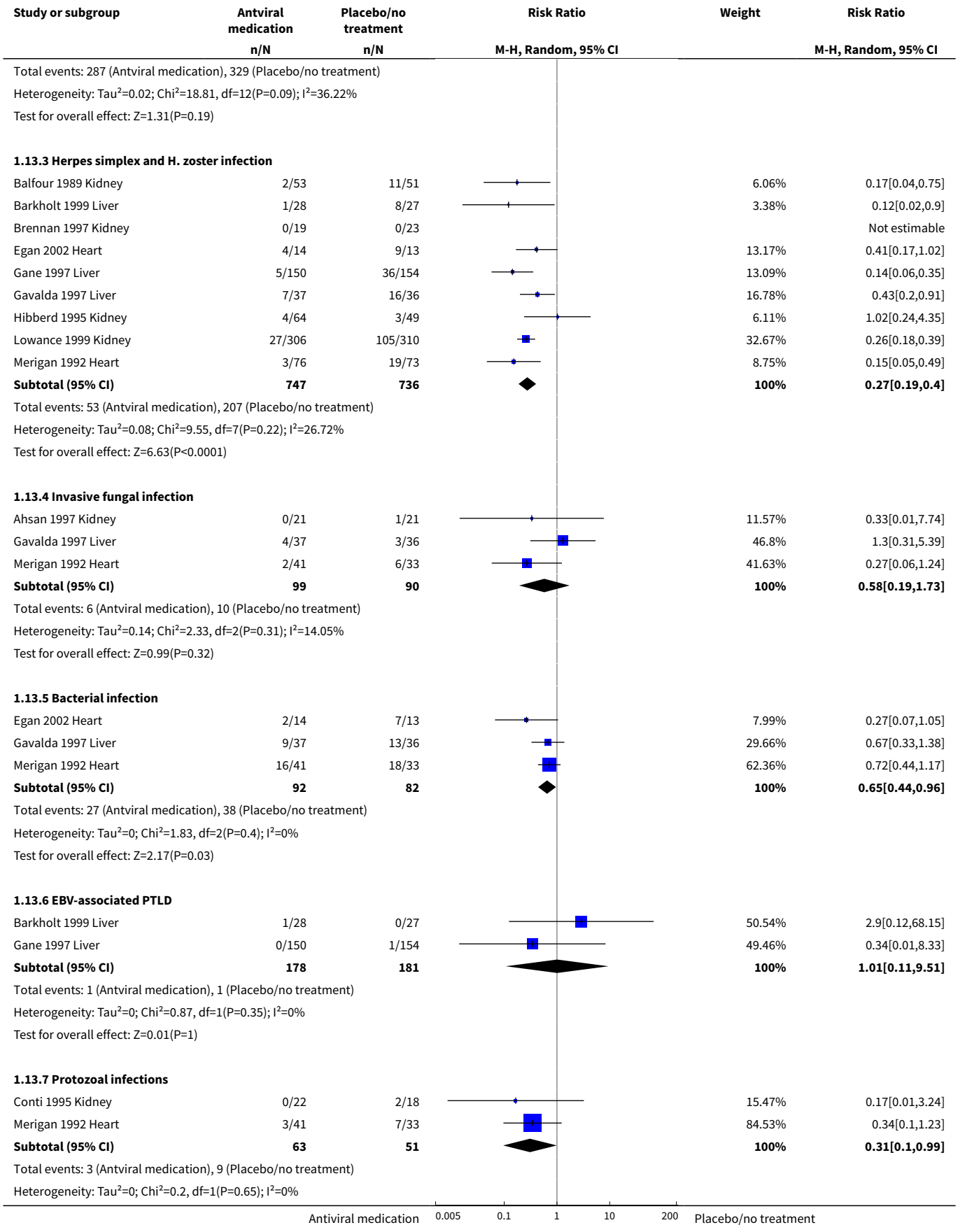
Study or subgroup	Ganciclovir n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.2 More than 6 weeks					
Ahsan 1997 Kidney	0/21	1/22		5.48%	0.35[0.01,8.11]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Gane 1997 Liver	10/150	16/154		94.52%	0.64[0.3,1.37]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Subtotal (95% CI)	**214**	**225**		**100%**	**0.62[0.3,1.3]**
Total events: 10 (Ganciclovir), 17 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					



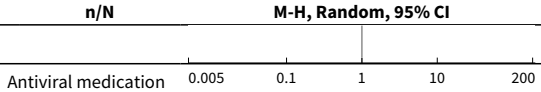
Analysis 1.13. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 13 Additional outcomes - all medications.

Study or subgroup	Antviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Graft loss					
Ahsan 1997 Kidney	0/21	0/22			Not estimable
Balfour 1989 Kidney	3/53	5/51		11.05%	0.58[0.15,2.29]
Barkholt 1999 Liver	4/28	4/27		12.79%	0.96[0.27,3.47]
Cohen 1993 Liver	3/33	5/32		11.59%	0.58[0.15,2.24]
Conti 1995 Kidney	2/22	2/18		6.08%	0.82[0.13,5.25]
Gane 1997 Liver	8/150	10/154		25.8%	0.82[0.33,2.02]
Hibberd 1995 Kidney	6/64	6/49		18.39%	0.77[0.26,2.23]
Kletzmayr 1996 Kidney	2/22	2/10		6.4%	0.45[0.07,2.78]
Rondeau 1993 Kidney	1/17	2/15		3.98%	0.44[0.04,4.39]
Rostaing 1994 Kidney	2/19	1/18		3.93%	1.89[0.19,19.13]
Subtotal (95% CI)	**429**	**396**		**100%**	**0.74[0.47,1.17]**
Total events: 31 (Antviral medication), 37 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.59, df=8(P=0.99); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					
1.13.2 Acute rejection					
Ahsan 1997 Kidney	1/21	4/22		0.5%	0.26[0.03,2.16]
Balfour 1989 Kidney	15/53	12/51		4.41%	1.2[0.63,2.31]
Barkholt 1999 Liver	19/28	19/27		10.83%	0.96[0.68,1.37]
Brennan 1997 Kidney	6/19	3/23		1.38%	2.42[0.7,8.41]
Cohen 1993 Liver	24/33	19/32		10.78%	1.22[0.86,1.75]
Conti 1995 Kidney	8/22	13/18		4.79%	0.5[0.27,0.94]
Egan 2002 Heart	13/14	13/13		18.47%	0.93[0.77,1.14]
Gane 1997 Liver	78/150	93/154		18.27%	0.86[0.7,1.05]
Kletzmayr 1996 Kidney	12/22	3/10		2.01%	1.82[0.66,5.05]
Leray 1995 Kidney	6/13	5/10		2.78%	0.92[0.39,2.17]
Lowance 1999 Kidney	88/306	128/310		17.06%	0.7[0.56,0.87]
Rondeau 1993 Kidney	10/17	9/15		5.47%	0.98[0.55,1.74]
Rostaing 1994 Kidney	7/19	8/18		3.24%	0.83[0.38,1.81]
Subtotal (95% CI)	**717**	**703**		**100%**	**0.9[0.78,1.05]**



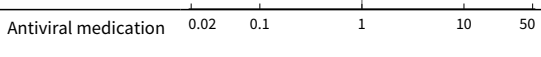


Study or subgroup	Antviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=1.97(P=0.05)					

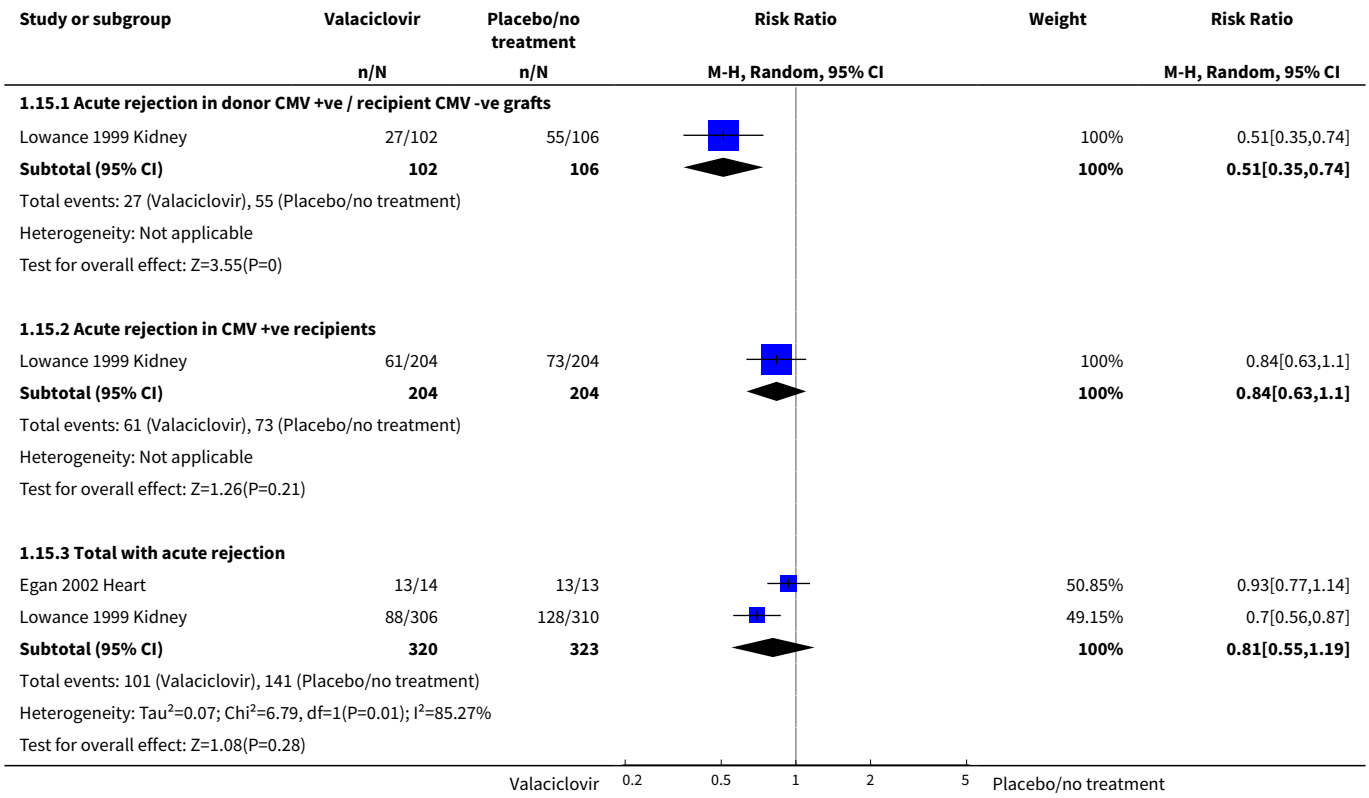


Analysis 1.14. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 14 Acute rejection according to method of diagnosis.

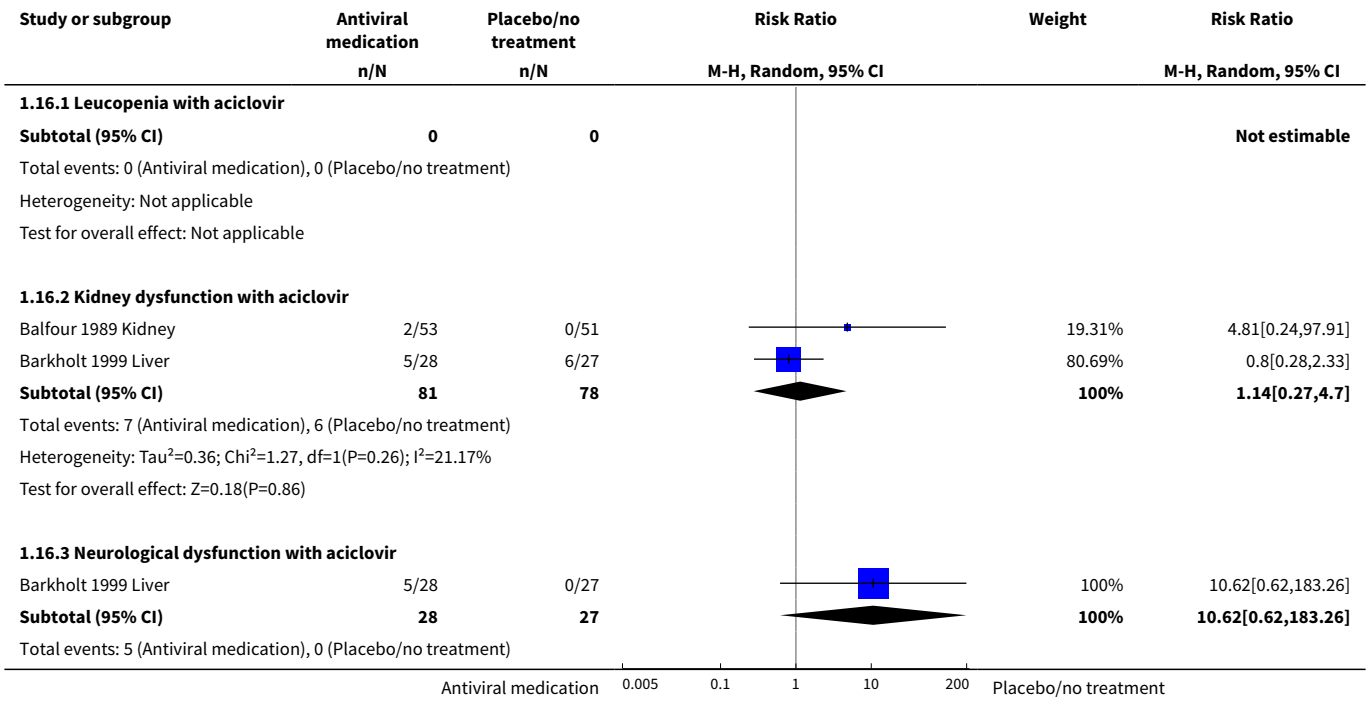
Study or subgroup	Antiviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.14.1 Biopsy-proven acute rejection					
Balfour 1989 Kidney	15/53	12/51		4.41%	1.2[0.63,2.31]
Brennan 1997 Kidney	6/19	3/23		1.38%	2.42[0.7,8.41]
Egan 2002 Heart	13/14	13/13		18.47%	0.93[0.77,1.14]
Kletzmayr 1996 Kidney	12/22	3/10		2.01%	1.82[0.66,5.05]
Lowance 1999 Kidney	88/306	128/310		17.06%	0.7[0.56,0.87]
Subtotal (95% CI)	**414**	**407**		**43.33%**	**0.97[0.71,1.32]**
Total events: 134 (Antiviral medication), 159 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.06; Chi^2=10.47, df=4(P=0.03); I^2=61.8%					
Test for overall effect: Z=0.2(P=0.84)					
1.14.2 Clinical diagnosis of acute rejection or method not stated					
Ahsan 1997 Kidney	1/21	4/22		0.5%	0.26[0.03,2.16]
Barkholt 1999 Liver	19/28	19/27		10.83%	0.96[0.68,1.37]
Cohen 1993 Liver	24/33	19/32		10.78%	1.22[0.86,1.75]
Conti 1995 Kidney	8/22	13/18		4.79%	0.5[0.27,0.94]
Gane 1997 Liver	78/150	93/154		18.27%	0.86[0.7,1.05]
Leray 1995 Kidney	6/13	5/10		2.78%	0.92[0.39,2.17]
Rondeau 1993 Kidney	10/17	9/15		5.47%	0.98[0.55,1.74]
Rostaing 1994 Kidney	7/19	8/18		3.24%	0.83[0.38,1.81]
Subtotal (95% CI)	**303**	**296**		**56.67%**	**0.91[0.76,1.08]**
Total events: 153 (Antiviral medication), 170 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=8.21, df=7(P=0.31); I^2=14.7%					
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	**717**	**703**		**100%**	**0.9[0.78,1.05]**
Total events: 287 (Antiviral medication), 329 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=18.81, df=12(P=0.09); I^2=36.22%					
Test for overall effect: Z=1.31(P=0.19)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.71), I^2=0%					

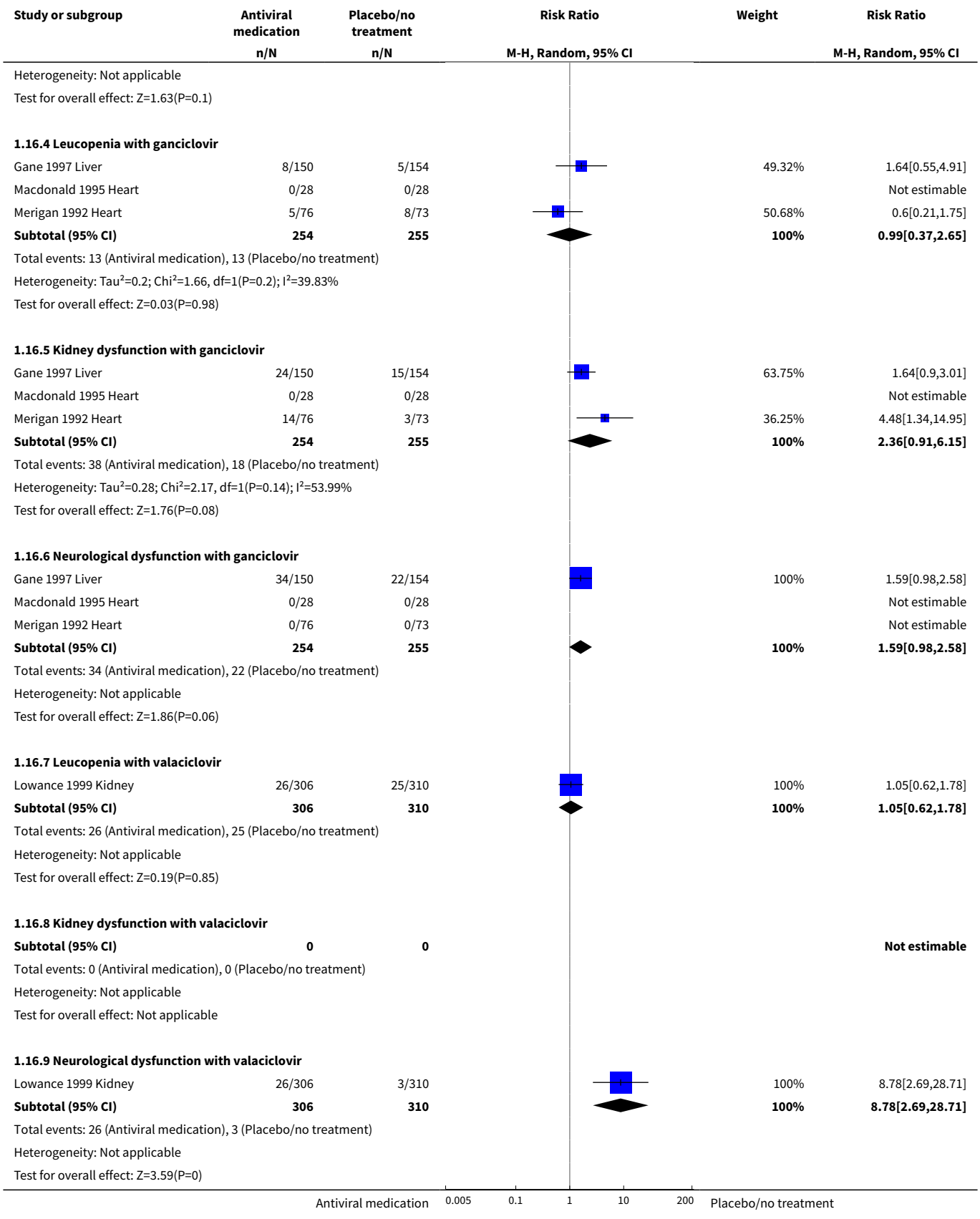


Analysis 1.15. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 15 Valaciclovir - additional outcomes.



Analysis 1.16. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 16 Adverse effects.



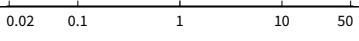


Comparison 2. Effect of methodological quality on CMV disease in studies of prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate	4	262	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.31, 0.79]
1.2 Inadequate/unclear	15	1719	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.33, 0.51]
2 Blinding of participants/investigators	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Blinding	5	1135	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
2.2 No blinding	14	846	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.59]
3 Intention-to-treat analysis (ITT)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ITT undertaken	10	1569	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.30, 0.48]
3.2 ITT not undertaken	9	412	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.68]
4 CMV disease by time of outcome assessment or trial publication date	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Outcome at 9-12 months	8	1277	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.22, 0.58]
4.2 Outcome at 3-6 months	11	704	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.36, 0.58]
4.3 Trials published before 1997	12	821	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.37, 0.63]
4.4 Trials published in 1997 and later	7	1160	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.24, 0.44]

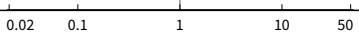
Analysis 2.1. Comparison 2 Effect of methodological quality on CMV disease in studies of prophylaxis versus placebo/no treatment, Outcome 1 Allocation concealment.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Adequate					
Cohen 1993 Liver	9/33	11/32		37.16%	0.79[0.38,1.65]
Egan 2002 Heart	2/14	6/13		10.67%	0.31[0.08,1.27]
Pouteil-Noble 1996 Kidney	6/24	14/26		33.32%	0.46[0.21,1.01]
Saliba 1993 Liver	4/60	14/60		18.86%	0.29[0.1,0.82]
Subtotal (95% CI)	**131**	**131**		**100%**	**0.5[0.31,0.79]**
Total events: 21 (Antiviral medication), 45 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=3.15, df=3(P=0.37); I^2=4.88%					
Test for overall effect: Z=2.96(P=0)					
2.1.2 Inadequate/unclear					
Ahsan 1997 Kidney	1/21	6/22		1.21%	0.17[0.02,1.33]
Balfour 1989 Kidney	4/53	15/51		4.34%	0.26[0.09,0.72]
Barkholt 1999 Liver	7/28	14/27		7.85%	0.48[0.23,1.01]
Brennan 1997 Kidney	4/19	14/23		5.25%	0.35[0.14,0.88]
Conti 1995 Kidney	2/22	13/18		2.64%	0.13[0.03,0.49]
Gane 1997 Liver	7/150	29/154		6.92%	0.25[0.11,0.55]
Gavalda 1997 Liver	4/37	11/36		4.23%	0.35[0.12,1.01]
Hibberd 1995 Kidney	9/64	16/49		8.03%	0.43[0.21,0.89]
Kletzmayr 1996 Kidney	9/22	4/10		5.46%	1.02[0.41,2.54]
Leray 1995 Kidney	6/13	9/10		10.33%	0.51[0.28,0.96]
Lowance 1999 Kidney	18/306	60/310		14.22%	0.3[0.18,0.5]
Macdonald 1995 Heart	6/28	10/28		5.96%	0.6[0.25,1.43]
Merigan 1992 Heart	12/76	31/73		11.41%	0.37[0.21,0.67]
Rondeau 1993 Kidney	8/17	11/15		11.24%	0.64[0.36,1.16]
Rostaing 1994 Kidney	1/19	2/18		0.94%	0.47[0.05,4.78]
Subtotal (95% CI)	**875**	**844**		**100%**	**0.41[0.33,0.51]**
Total events: 98 (Antiviral medication), 245 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=16.32, df=14(P=0.29); I^2=14.24%					
Test for overall effect: Z=7.75(P<0.0001)					

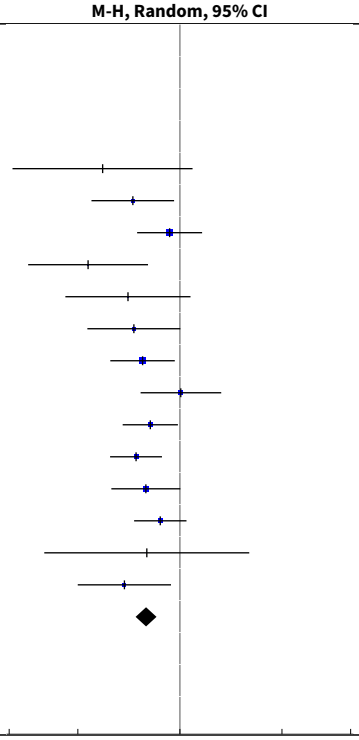


Analysis 2.2. Comparison 2 Effect of methodological quality on CMV disease in studies of prophylaxis versus placebo/no treatment, Outcome 2 Blinding of participants/investigators.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Blinding					
Balfour 1989 Kidney	4/53	15/51		9.69%	0.26[0.09,0.72]
Barkholt 1999 Liver	7/28	14/27		19.05%	0.48[0.23,1.01]
Gane 1997 Liver	7/150	29/154		16.42%	0.25[0.11,0.55]
Lowance 1999 Kidney	18/306	60/310		41.02%	0.3[0.18,0.5]
Macdonald 1995 Heart	6/28	10/28		13.81%	0.6[0.25,1.43]
Subtotal (95% CI)	**565**	**570**		**100%**	**0.35[0.25,0.48]**
Total events: 42 (Antiviral medication), 128 (Placebo/no treatment)					

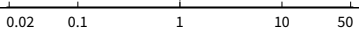


Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=3.69, df=4(P=0.45); I²=0%					
Test for overall effect: Z=6.45(P<0.0001)					
2.2.2 No blinding					
Ahsan 1997 Kidney	1/21	6/22		1.34%	0.17[0.02,1.33]
Brennan 1997 Kidney	4/19	14/23		6.15%	0.35[0.14,0.88]
Cohen 1993 Liver	9/33	11/32		9.57%	0.79[0.38,1.65]
Conti 1995 Kidney	2/22	13/18		2.99%	0.13[0.03,0.49]
Egan 2002 Heart	2/14	6/13		2.75%	0.31[0.08,1.27]
Gavalda 1997 Liver	4/37	11/36		4.89%	0.35[0.12,1.01]
Hibberd 1995 Kidney	9/64	16/49		9.75%	0.43[0.21,0.89]
Kletzmayr 1996 Kidney	9/22	4/10		6.41%	1.02[0.41,2.54]
Leray 1995 Kidney	6/13	9/10		12.93%	0.51[0.28,0.96]
Merigan 1992 Heart	12/76	31/73		14.49%	0.37[0.21,0.67]
Pouteil-Noble 1996 Kidney	6/24	14/26		8.58%	0.46[0.21,1.01]
Rondeau 1993 Kidney	8/17	11/15		14.25%	0.64[0.36,1.16]
Rostaing 1994 Kidney	1/19	2/18		1.04%	0.47[0.05,4.78]
Saliba 1993 Liver	4/60	14/60		4.86%	0.29[0.1,0.82]
Subtotal (95% CI)	**441**	**405**		**100%**	**0.47[0.37,0.59]**
Total events: 77 (Antiviral medication), 162 (Placebo/no treatment)					
Heterogeneity: Tau²=0.01; Chi²=13.8, df=13(P=0.39); I²=5.81%					
Test for overall effect: Z=6.33(P<0.0001)					

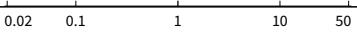


Analysis 2.3. Comparison 2 Effect of methodological quality on CMV disease in studies of prophylaxis versus placebo/no treatment, Outcome 3 Intention-to-treat analysis (ITT).

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 ITT undertaken					
Brennan 1997 Kidney	4/19	14/23		6.78%	0.35[0.14,0.88]
Cohen 1993 Liver	9/33	11/32		10.88%	0.79[0.38,1.65]
Gane 1997 Liver	7/150	29/154		9.31%	0.25[0.11,0.55]
Gavalda 1997 Liver	4/37	11/36		5.34%	0.35[0.12,1.01]
Hibberd 1995 Kidney	9/64	16/49		11.11%	0.43[0.21,0.89]
Lowance 1999 Kidney	18/306	60/310		23.26%	0.3[0.18,0.5]
Merigan 1992 Heart	12/76	31/73		17.23%	0.37[0.21,0.67]
Pouteil-Noble 1996 Kidney	6/24	14/26		9.68%	0.46[0.21,1.01]
Rostaing 1994 Kidney	1/19	2/18		1.1%	0.47[0.05,4.78]
Saliba 1993 Liver	4/60	14/60		5.31%	0.29[0.1,0.82]
Subtotal (95% CI)	**788**	**781**		**100%**	**0.38[0.3,0.48]**
Total events: 74 (Antiviral medication), 202 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=6.61, df=9(P=0.68); I²=0%					
Test for overall effect: Z=7.87(P<0.0001)					
2.3.2 ITT not undertaken					
Ahsan 1997 Kidney	1/21	6/22		2.95%	0.17[0.02,1.33]
Balfour 1989 Kidney	4/53	15/51		9.37%	0.26[0.09,0.72]



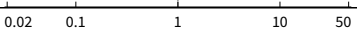
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barkholt 1999 Liver	7/28	14/27		14.98%	0.48[0.23,1.01]
Conti 1995 Kidney	2/22	13/18		6.08%	0.13[0.03,0.49]
Egan 2002 Heart	2/14	6/13		5.66%	0.31[0.08,1.27]
Kletzmayr 1996 Kidney	9/22	4/10		11.31%	1.02[0.41,2.54]
Leray 1995 Kidney	6/13	9/10		18.22%	0.51[0.28,0.96]
Macdonald 1995 Heart	6/28	10/28		12.13%	0.6[0.25,1.43]
Rondeau 1993 Kidney	8/17	11/15		19.29%	0.64[0.36,1.16]
Subtotal (95% CI)	**218**	**194**		**100%**	**0.47[0.33,0.68]**
Total events: 45 (Antiviral medication), 88 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.09; Chi^2=11.4, df=8(P=0.18); I^2=29.79%					
Test for overall effect: Z=4.04(P<0.0001)					



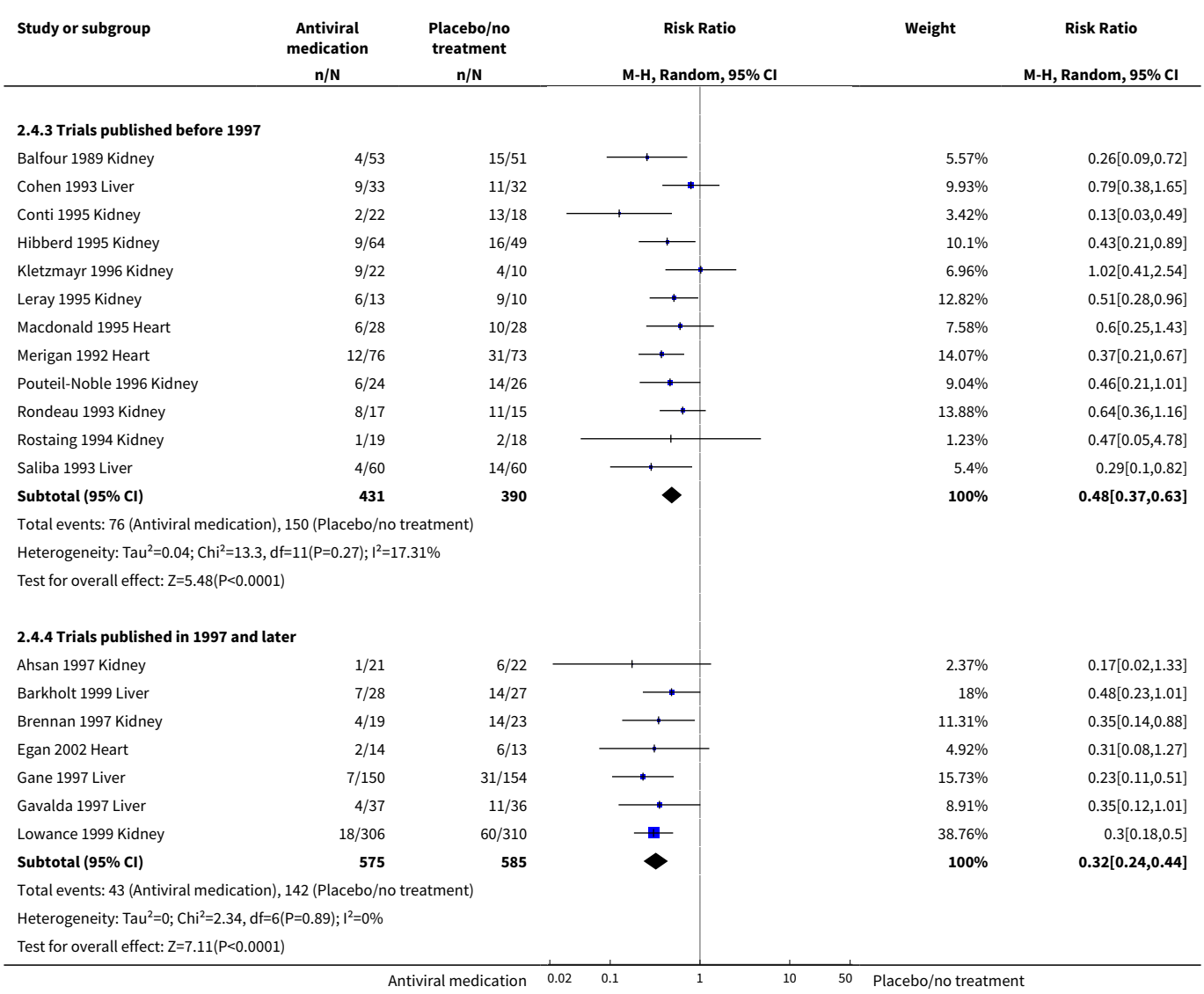
Antiviral medication — Placebo/no treatment

Analysis 2.4. Comparison 2 Effect of methodological quality on CMV disease in studies of prophylaxis versus placebo/no treatment, Outcome 4 CMV disease by time of outcome assessment or trial publication date.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Outcome at 9-12 months					
Ahsan 1997 Kidney	1/21	6/22		4.51%	0.17[0.02,1.33]
Balfour 1989 Kidney	4/53	15/51		11.59%	0.26[0.09,0.72]
Cohen 1993 Liver	9/33	11/32		15.92%	0.79[0.38,1.65]
Conti 1995 Kidney	2/22	13/18		8.33%	0.13[0.03,0.49]
Gane 1997 Liver	7/150	31/154		15.04%	0.23[0.11,0.51]
Gavalda 1997 Liver	4/37	11/36		11.41%	0.35[0.12,1.01]
Kletzmayr 1996 Kidney	9/22	4/10		13.22%	1.02[0.41,2.54]
Lowance 1999 Kidney	18/306	60/310		19.97%	0.3[0.18,0.5]
Subtotal (95% CI)	**644**	**633**		**100%**	**0.36[0.22,0.58]**
Total events: 54 (Antiviral medication), 151 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.23; Chi^2=14.91, df=7(P=0.04); I^2=53.05%					
Test for overall effect: Z=4.21(P<0.0001)					
2.4.2 Outcome at 3-6 months					
Barkholt 1999 Liver	7/28	14/27		10.3%	0.48[0.23,1.01]
Brennan 1997 Kidney	4/19	14/23		6.47%	0.35[0.14,0.88]
Egan 2002 Heart	2/14	6/13		2.81%	0.31[0.08,1.27]
Hibberd 1995 Kidney	9/64	16/49		10.6%	0.43[0.21,0.89]
Leray 1995 Kidney	6/13	9/10		14.46%	0.51[0.28,0.96]
Macdonald 1995 Heart	6/28	10/28		7.47%	0.6[0.25,1.43]
Merigan 1992 Heart	12/76	31/73		16.43%	0.37[0.21,0.67]
Pouteil-Noble 1996 Kidney	6/24	14/26		9.23%	0.46[0.21,1.01]
Rondeau 1993 Kidney	8/17	11/15		16.12%	0.64[0.36,1.16]
Rostaing 1994 Kidney	1/19	2/18		1.05%	0.47[0.05,4.78]
Saliba 1993 Liver	4/60	14/60		5.06%	0.29[0.1,0.82]
Subtotal (95% CI)	**362**	**342**		**100%**	**0.46[0.36,0.58]**
Total events: 65 (Antiviral medication), 141 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.93, df=10(P=0.95); I^2=0%					
Test for overall effect: Z=6.43(P<0.0001)					



Antiviral medication — Placebo/no treatment



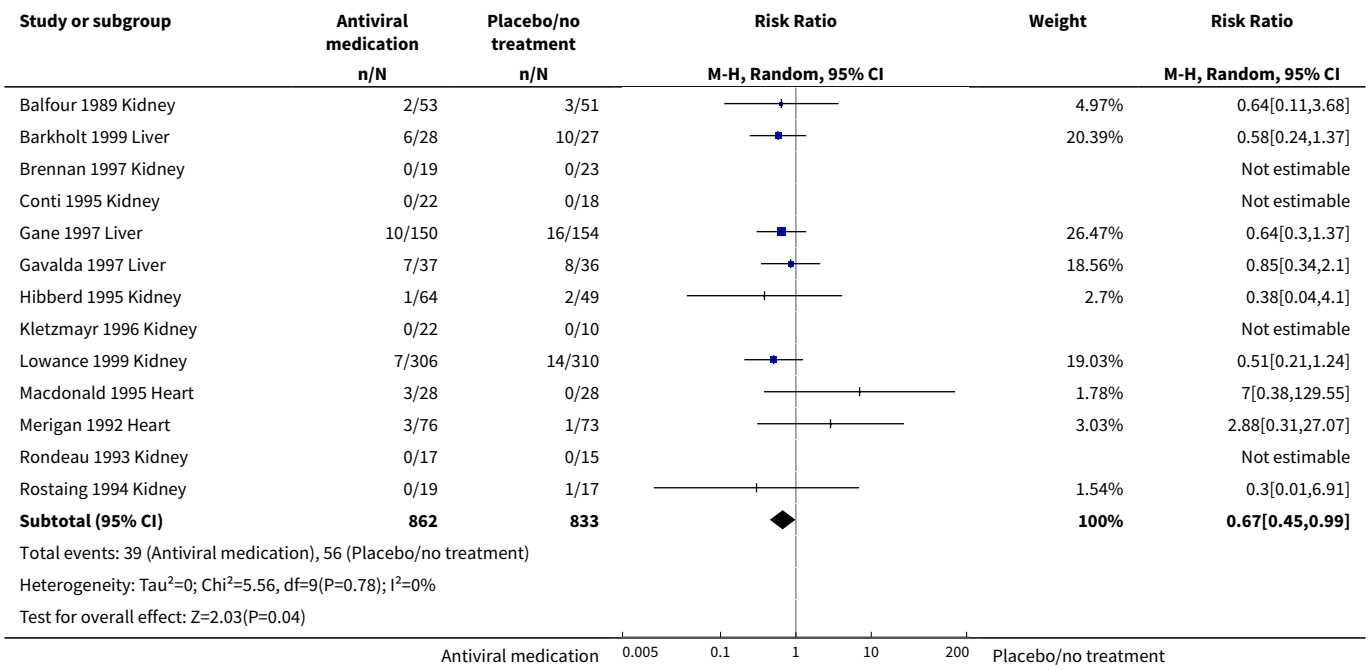
Comparison 3. Effect of methodological quality on all-cause mortality in studies of prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allocation concealment	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate	3	142	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.06, 1.20]
1.2 Inadequate/unclear	14	1695	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Blinding of participants and investigators	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Blinding	5	1135	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.39, 0.98]
2.2 No blinding	12	702	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.27]
3 Intention-to-treat analysis (ITT)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ITT undertaken	9	1448	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.98]
3.2 ITT not undertaken	8	389	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.29]
4 All-cause mortality and time of outcome assessment or trial publication date	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Outcome at 9-12 months	10	1370	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.97]
4.2 Outcome at 4-6 months	7	468	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.31, 1.33]
4.3 Outcome in trials published before 1997	10	678	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.08]
4.4 Outcome in trials published in 1997 or later	7	1160	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.41, 0.94]

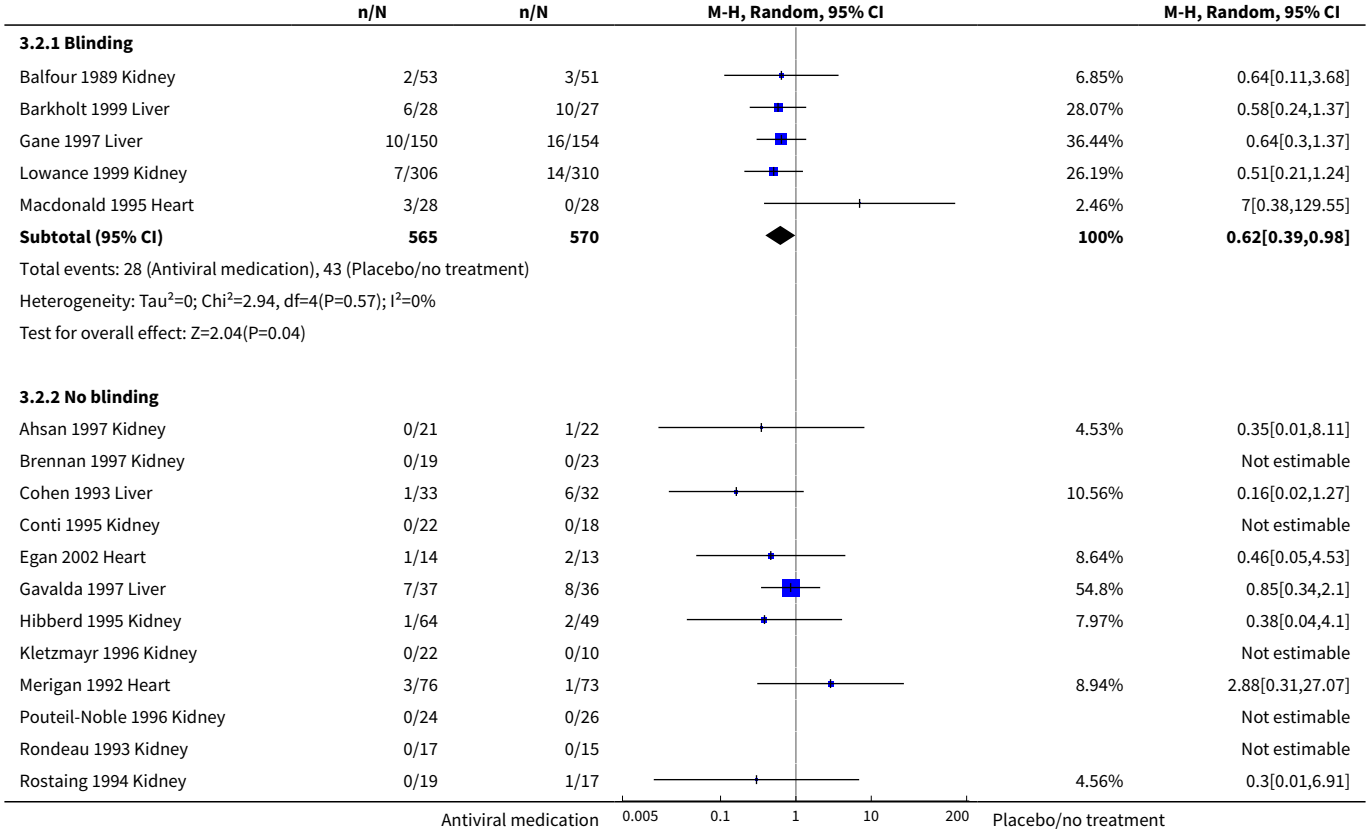
Analysis 3.1. Comparison 3 Effect of methodological quality on all-cause mortality in studies of prophylaxis versus placebo/no treatment, Outcome 1 Allocation concealment.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Adequate					
Cohen 1993 Liver	1/33	6/32		55.02%	0.16[0.02,1.27]
Egan 2002 Heart	1/14	2/13		44.98%	0.46[0.05,4.53]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Subtotal (95% CI)	**71**	**71**		**100%**	**0.26[0.06,1.2]**
Total events: 2 (Antiviral medication), 8 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
3.1.2 Inadequate/unclear					
Ahsan 1997 Kidney	0/21	1/22		1.53%	0.35[0.01,8.11]
			Antiviral medication 0.005 0.1 1 10 200 Placebo/no treatment		

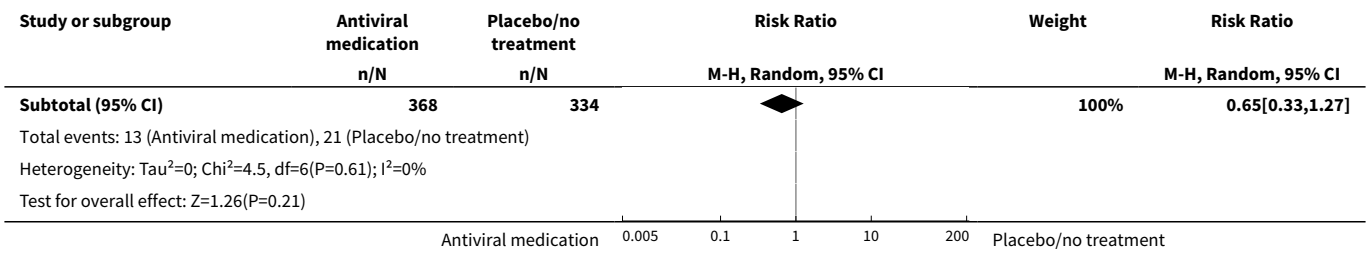


Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Balfour 1989 Kidney	2/53	3/51		4.97%	0.64[0.11,3.68]
Barkholt 1999 Liver	6/28	10/27		20.39%	0.58[0.24,1.37]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Conti 1995 Kidney	0/22	0/18			Not estimable
Gane 1997 Liver	10/150	16/154		26.47%	0.64[0.3,1.37]
Gavalda 1997 Liver	7/37	8/36		18.56%	0.85[0.34,2.1]
Hibberd 1995 Kidney	1/64	2/49		2.7%	0.38[0.04,4.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Lowance 1999 Kidney	7/306	14/310		19.03%	0.51[0.21,1.24]
Macdonald 1995 Heart	3/28	0/28		1.78%	7[0.38,129.55]
Merigan 1992 Heart	3/76	1/73		3.03%	2.88[0.31,27.07]
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Rostaing 1994 Kidney	0/19	1/17		1.54%	0.3[0.01,6.91]
Subtotal (95% CI)	**862**	**833**		**100%**	**0.67[0.45,0.99]**
Total events: 39 (Antiviral medication), 56 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=5.56, df=9(P=0.78); I²=0%					
Test for overall effect: Z=2.03(P=0.04)					

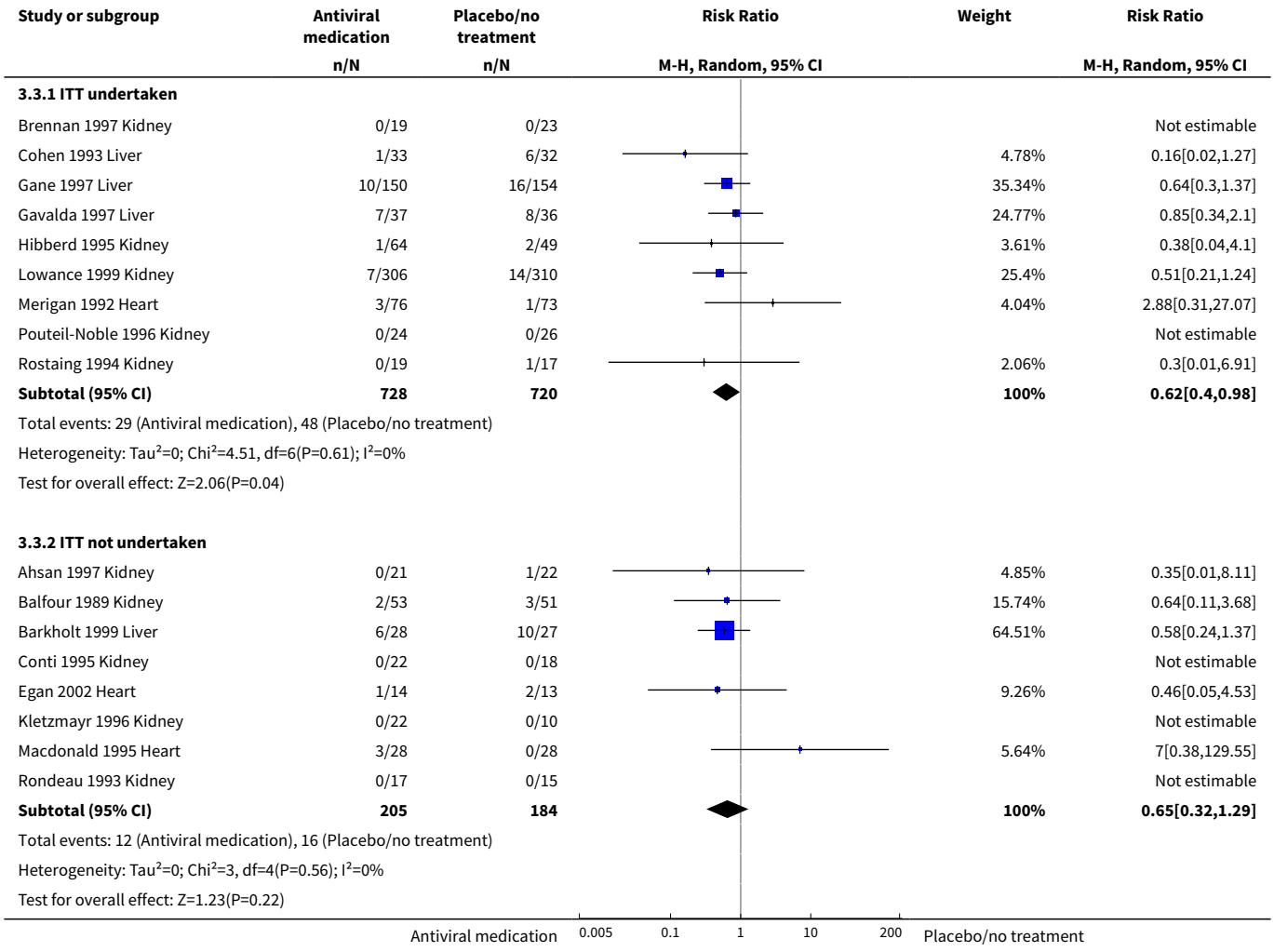
Analysis 3.2. Comparison 3 Effect of methodological quality on all-cause mortality in studies of prophylaxis versus placebo/no treatment, Outcome 2 Blinding of participants and investigators.



Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Blinding					
Balfour 1989 Kidney	2/53	3/51		6.85%	0.64[0.11,3.68]
Barkholt 1999 Liver	6/28	10/27		28.07%	0.58[0.24,1.37]
Gane 1997 Liver	10/150	16/154		36.44%	0.64[0.3,1.37]
Lowance 1999 Kidney	7/306	14/310		26.19%	0.51[0.21,1.24]
Macdonald 1995 Heart	3/28	0/28		2.46%	7[0.38,129.55]
Subtotal (95% CI)	**565**	**570**		**100%**	**0.62[0.39,0.98]**
Total events: 28 (Antiviral medication), 43 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=2.94, df=4(P=0.57); I²=0%					
Test for overall effect: Z=2.04(P=0.04)					
3.2.2 No blinding					
Ahsan 1997 Kidney	0/21	1/22		4.53%	0.35[0.01,8.11]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Cohen 1993 Liver	1/33	6/32		10.56%	0.16[0.02,1.27]
Conti 1995 Kidney	0/22	0/18			Not estimable
Egan 2002 Heart	1/14	2/13		8.64%	0.46[0.05,4.53]
Gavalda 1997 Liver	7/37	8/36		54.8%	0.85[0.34,2.1]
Hibberd 1995 Kidney	1/64	2/49		7.97%	0.38[0.04,4.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Merigan 1992 Heart	3/76	1/73		8.94%	2.88[0.31,27.07]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Rostaing 1994 Kidney	0/19	1/17		4.56%	0.3[0.01,6.91]

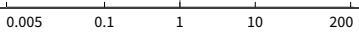


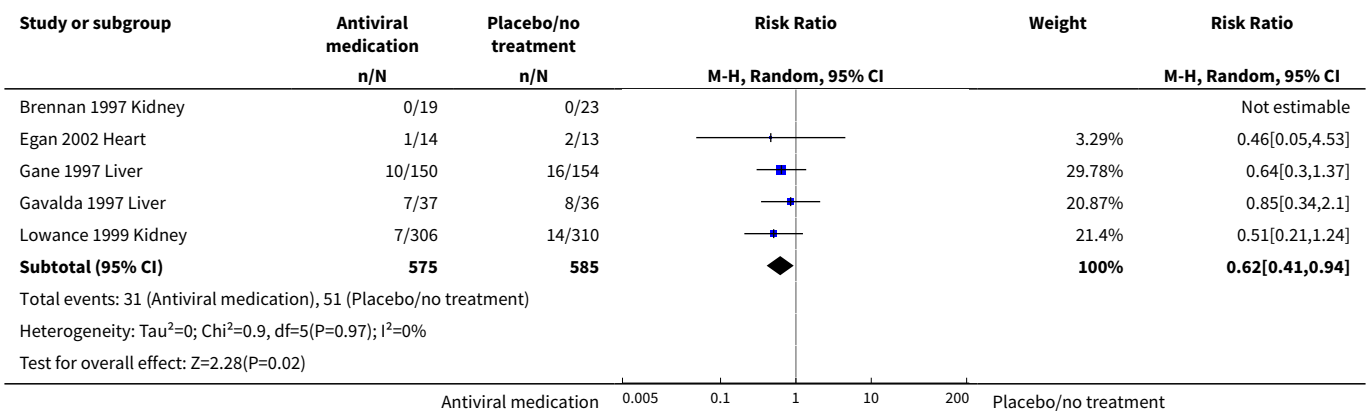
Analysis 3.3. Comparison 3 Effect of methodological quality on all-cause mortality in studies of prophylaxis versus placebo/no treatment, Outcome 3 Intention-to-treat analysis (ITT).



Analysis 3.4. Comparison 3 Effect of methodological quality on all-cause mortality in studies of prophylaxis versus placebo/no treatment, Outcome 4 All-cause mortality and time of outcome assessment or trial publication date.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Outcome at 9-12 months					
Ahsan 1997 Kidney	0/21	1/22		1.98%	0.35[0.01,8.11]
Balfour 1989 Kidney	2/53	3/51		6.42%	0.64[0.11,3.68]
Cohen 1993 Liver	1/33	6/32		4.62%	0.16[0.02,1.27]
Conti 1995 Kidney	0/22	0/18			Not estimable
Gane 1997 Liver	10/150	16/154		34.17%	0.64[0.3,1.37]
Gavalda 1997 Liver	7/37	8/36		23.95%	0.85[0.34,2.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Lowance 1999 Kidney	7/306	14/310		24.56%	0.51[0.21,1.24]
Macdonald 1995 Heart	3/28	0/28		2.3%	7[0.38,129.55]
Rostaing 1994 Kidney	0/19	1/18		1.99%	0.32[0.01,7.3]
Subtotal (95% CI)	**691**	**679**		**100%**	**0.63[0.4,0.97]**
Total events: 30 (Antiviral medication), 49 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=5.27, df=7(P=0.63); I^2=0%					
Test for overall effect: Z=2.08(P=0.04)					
3.4.2 Outcome at 4-6 months					
Barkholt 1999 Liver	6/28	10/27		70.21%	0.58[0.24,1.37]
Brennan 1997 Kidney	0/19	0/23			Not estimable
Egan 2002 Heart	1/14	2/13		10.07%	0.46[0.05,4.53]
Hibberd 1995 Kidney	1/64	2/49		9.3%	0.38[0.04,4.1]
Merigan 1992 Heart	3/76	1/73		10.42%	2.88[0.31,27.07]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Subtotal (95% CI)	**242**	**226**		**100%**	**0.64[0.31,1.33]**
Total events: 11 (Antiviral medication), 15 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=3(P=0.56); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					
3.4.3 Outcome in trials published before 1997					
Balfour 1989 Kidney	2/53	3/51		25.11%	0.64[0.11,3.68]
Cohen 1993 Liver	1/33	6/32		19.89%	0.16[0.02,1.27]
Conti 1995 Kidney	0/22	0/18			Not estimable
Hibberd 1995 Kidney	1/64	2/49		16.03%	0.38[0.04,4.1]
Kletzmayr 1996 Kidney	0/22	0/10			Not estimable
Macdonald 1995 Heart	3/28	0/28		11.4%	7[0.38,129.55]
Merigan 1992 Heart	3/76	1/73		17.52%	2.88[0.31,27.07]
Pouteil-Noble 1996 Kidney	0/24	0/26			Not estimable
Rondeau 1993 Kidney	0/17	0/15			Not estimable
Rostaing 1994 Kidney	0/19	1/18		10.06%	0.32[0.01,7.3]
Subtotal (95% CI)	**358**	**320**		**100%**	**0.71[0.25,2.08]**
Total events: 10 (Antiviral medication), 13 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.39; Chi^2=6.39, df=5(P=0.27); I^2=21.77%					
Test for overall effect: Z=0.62(P=0.54)					
3.4.4 Outcome in trials published in 1997 or later					
Ahsan 1997 Kidney	0/21	1/22		1.73%	0.35[0.01,8.11]
Barkholt 1999 Liver	6/28	10/27		22.93%	0.58[0.24,1.37]





Comparison 4. Ganciclovir versus aciclovir

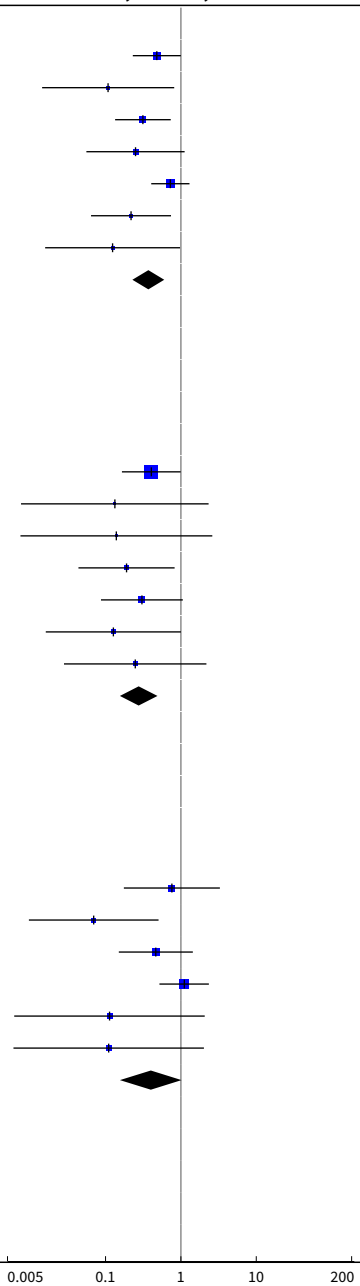
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease in all patients	7	1113	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.60]
1.2 CMV organ involvement	7	1034	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.15, 0.49]
1.3 CMV syndrome	6	1009	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.16, 1.02]
1.4 CMV infection	6	815	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.67]
1.5 CMV disease in patients treated with ganciclovir for 3 months	4	703	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.09, 0.82]
1.6 CMV disease in patients treated with ganciclovir for 2-4 weeks then aciclovir	3	410	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.22, 0.64]
2 CMV antibody +ve recipients	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All symptomatic CMV disease	5	722	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.55]
2.2 CMV infection	5	522	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.58]
3 CMV +ve donors / CMV -ve recipients	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All symptomatic CMV disease	5	246	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.41, 0.99]
3.2 CMV infection	4	228	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.09]

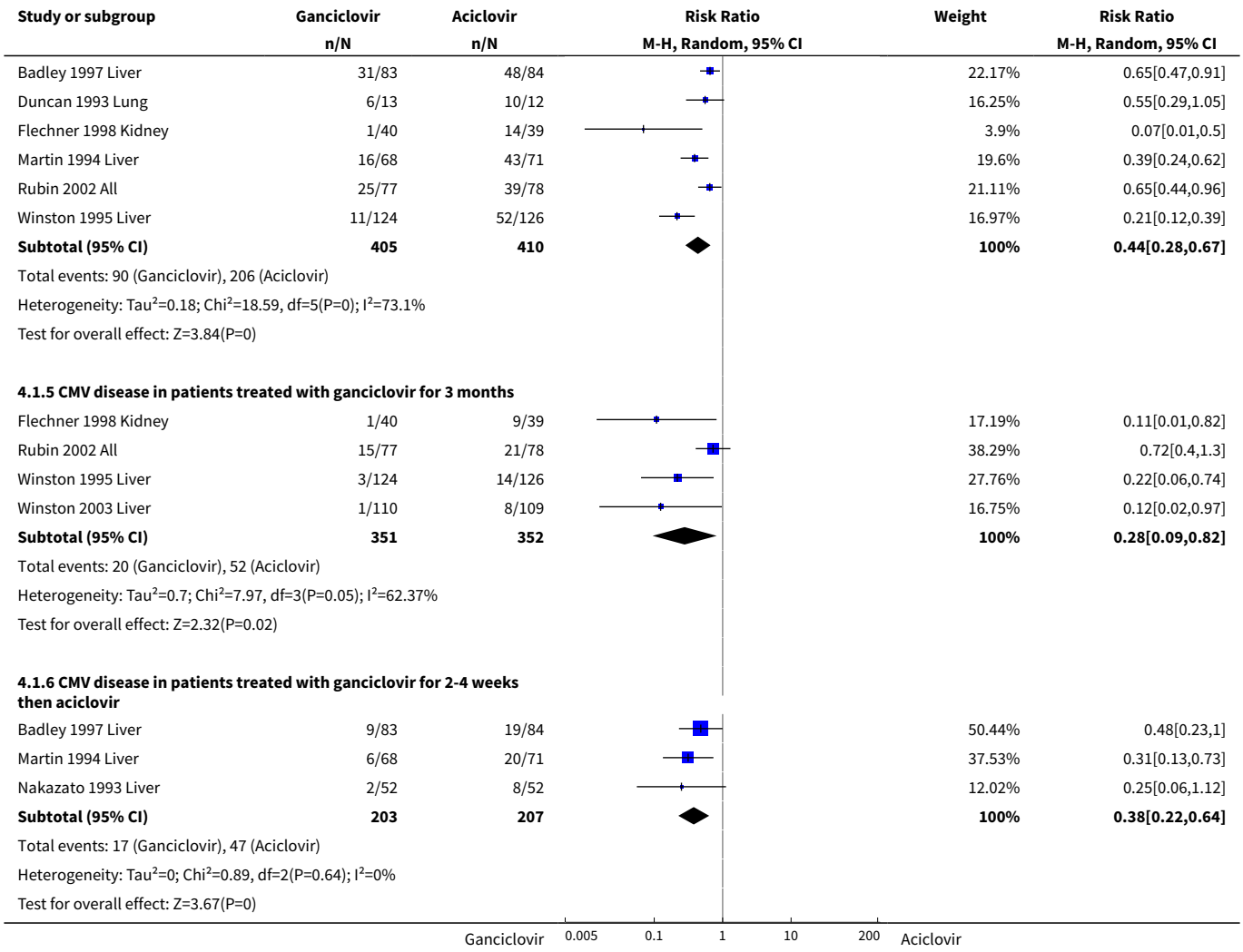
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 CMV -ve donor / CMV -ve recipient	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 CMV disease	3	41	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.07, 3.07]
5 Effect of prophylaxis for different transplanted organs	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 CMV disease in kidney transplant patients	2	168	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.35]
5.2 CMV disease in liver transplant patients	5	791	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.59]
5.3 CMV disease in heart or lung transplant patients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.10, 3.00]
5.4 CMV infection in kidney transplant patients	2	168	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.04, 0.95]
5.5 CMV infection in liver transplant patients	4	572	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.73]
5.6 CMV infection in heart or lung transplant patients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.50, 1.55]
6 Death	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Death associated with CMV disease	6	832	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.58]
6.2 All-cause mortality	8	1138	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.82, 1.58]
7 Additional outcomes	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Acute rejection	6	1009	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.10]
7.2 Graft loss	3	268	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.27, 1.13]
7.3 Other viral infections	4	740	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.32, 2.01]
7.4 Invasive fungal infections	3	401	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.40, 1.10]
7.5 Bacterial infections	1	167	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.78, 1.53]
7.6 Protozoal infections	1	167	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.16]
7.7 Obliterative bronchiolitis in lung transplant recipients	1	25	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.42, 1.54]
7.8 Leucopenia	6	955	Risk Ratio (M-H, Random, 95% CI)	3.28 [1.48, 7.25]
7.9 Kidney dysfunction	4	661	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.10 Neurological dysfunction	2	306	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.24, 4.15]

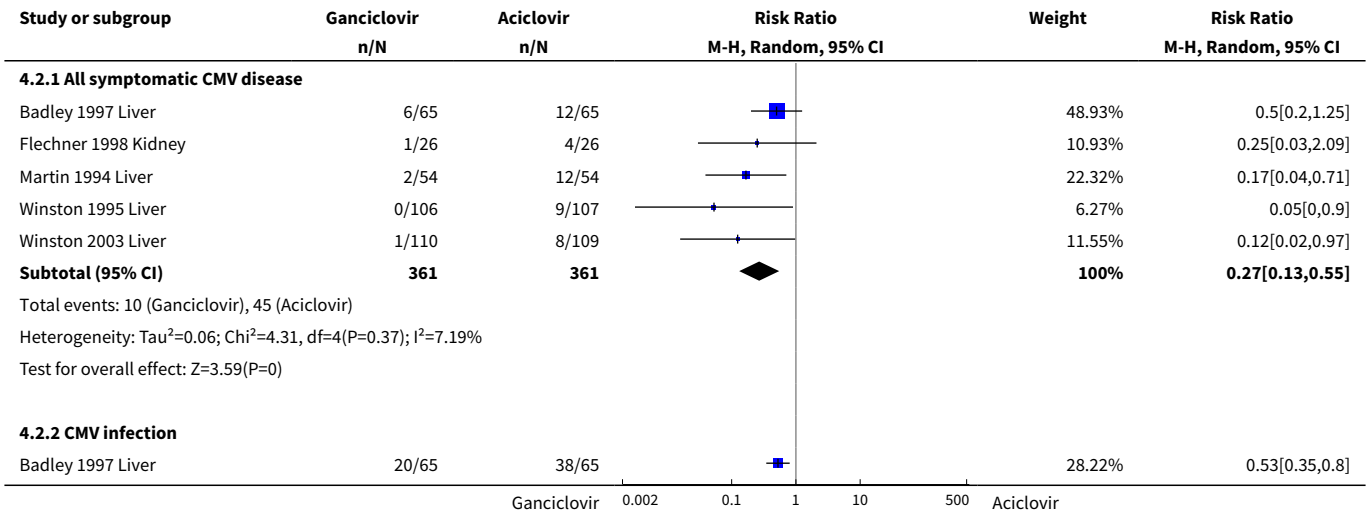
Analysis 4.1. Comparison 4 Ganciclovir versus aciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

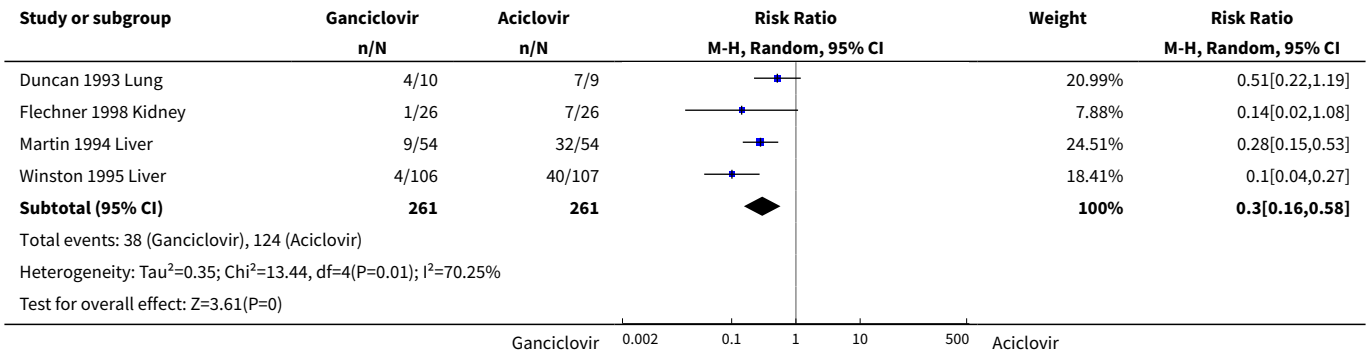
Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 CMV disease in all patients					
Badley 1997 Liver	9/83	19/84		22.56%	0.48[0.23,1]
Flechner 1998 Kidney	1/40	9/39		5.16%	0.11[0.01,0.82]
Martin 1994 Liver	6/68	20/71		19.18%	0.31[0.13,0.73]
Nakazato 1993 Liver	2/52	8/52		8.55%	0.25[0.06,1.12]
Rubin 2002 All	15/77	21/78		27.79%	0.72[0.4,1.3]
Winston 1995 Liver	3/124	14/126		11.8%	0.22[0.06,0.74]
Winston 2003 Liver	1/110	8/109		4.97%	0.12[0.02,0.97]
Subtotal (95% CI)	**554**	**559**		**100%**	**0.37[0.23,0.6]**
Total events: 37 (Ganciclovir), 99 (Aciclovir)					
Heterogeneity: Tau^2=0.13; Chi^2=9.01, df=6(P=0.17); I^2=33.38%					
Test for overall effect: Z=4.01(P<0.0001)					
4.1.2 CMV organ involvement					
Badley 1997 Liver	6/83	15/84		41.04%	0.4[0.17,0.99]
Duncan 1993 Lung	0/13	3/12		4.02%	0.13[0.01,2.33]
Flechner 1998 Kidney	0/40	3/39		3.84%	0.14[0.01,2.61]
Martin 1994 Liver	2/68	11/71		15.29%	0.19[0.04,0.83]
Rubin 2002 All	3/77	10/78		21.09%	0.3[0.09,1.06]
Winston 1995 Liver	1/124	8/126		7.75%	0.13[0.02,1]
Winston 2003 Liver	1/110	4/109		6.98%	0.25[0.03,2.18]
Subtotal (95% CI)	**515**	**519**		**100%**	**0.28[0.15,0.49]**
Total events: 13 (Ganciclovir), 54 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=2.04, df=6(P=0.92); I^2=0%					
Test for overall effect: Z=4.4(P<0.0001)					
4.1.3 CMV syndrome					
Badley 1997 Liver	3/83	4/84		18.83%	0.76[0.18,3.29]
Flechner 1998 Kidney	1/40	14/39		13.7%	0.07[0.01,0.5]
Martin 1994 Liver	4/68	9/71		23.08%	0.46[0.15,1.44]
Rubin 2002 All	12/77	11/78		28.25%	1.11[0.52,2.35]
Winston 1995 Liver	0/124	4/126		8.06%	0.11[0.01,2.07]
Winston 2003 Liver	0/110	4/109		8.07%	0.11[0.01,2.02]
Subtotal (95% CI)	**502**	**507**		**100%**	**0.4[0.16,1.02]**
Total events: 20 (Ganciclovir), 46 (Aciclovir)					
Heterogeneity: Tau^2=0.67; Chi^2=11.08, df=5(P=0.05); I^2=54.86%					
Test for overall effect: Z=1.91(P=0.06)					
4.1.4 CMV infection					



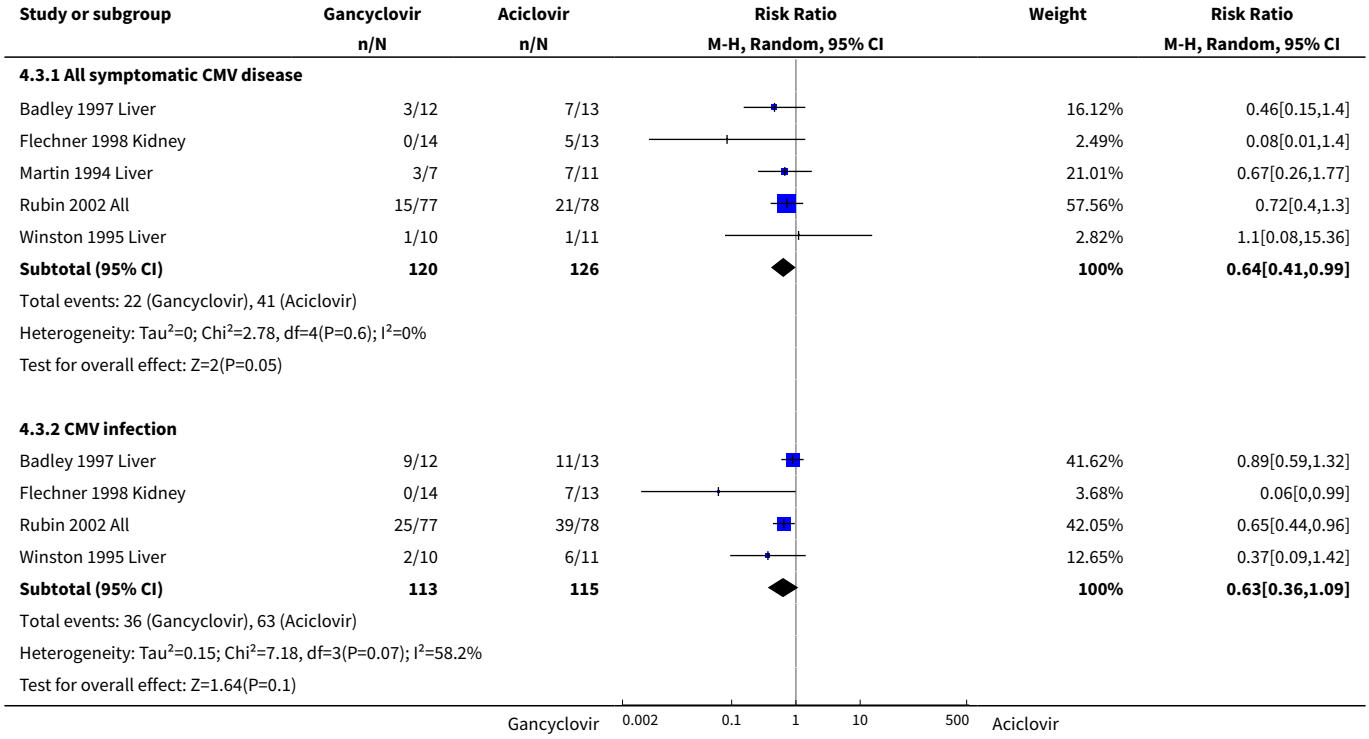


Analysis 4.2. Comparison 4 Ganciclovir versus aciclovir, Outcome 2 CMV antibody +ve recipients.

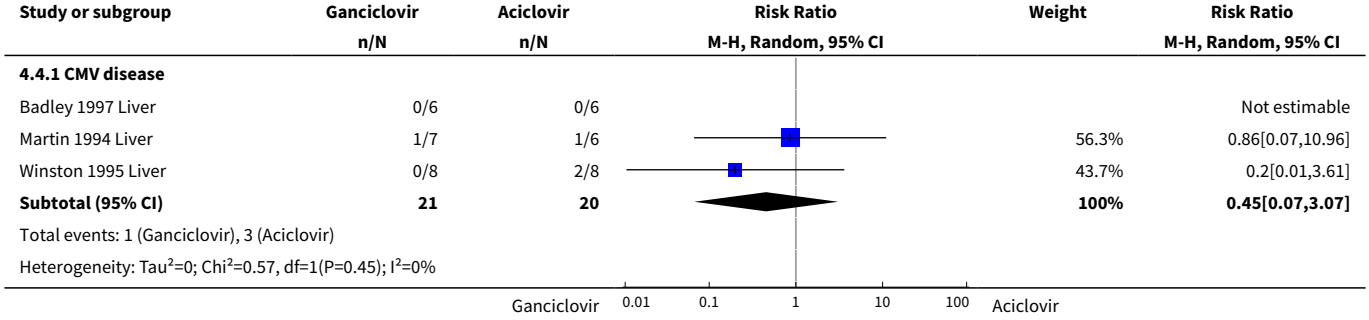




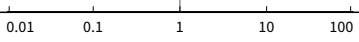
Analysis 4.3. Comparison 4 Ganciclovir versus aciclovir, Outcome 3 CMV +ve donors / CMV -ve recipients.



Analysis 4.4. Comparison 4 Ganciclovir versus aciclovir, Outcome 4 CMV -ve donor / CMV -ve recipient.

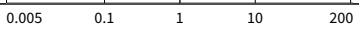


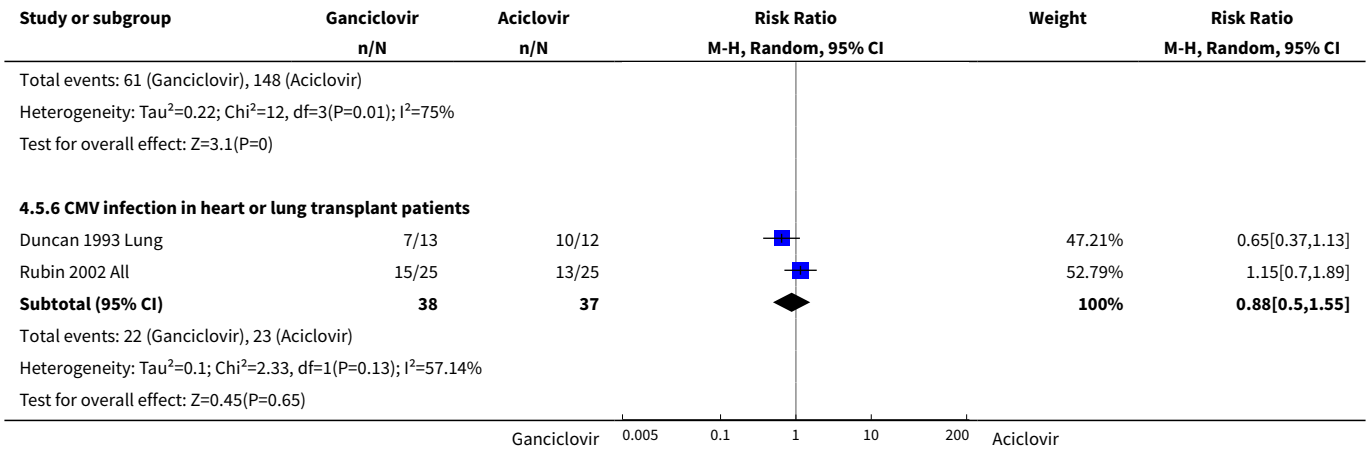
Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.81(P=0.42)					



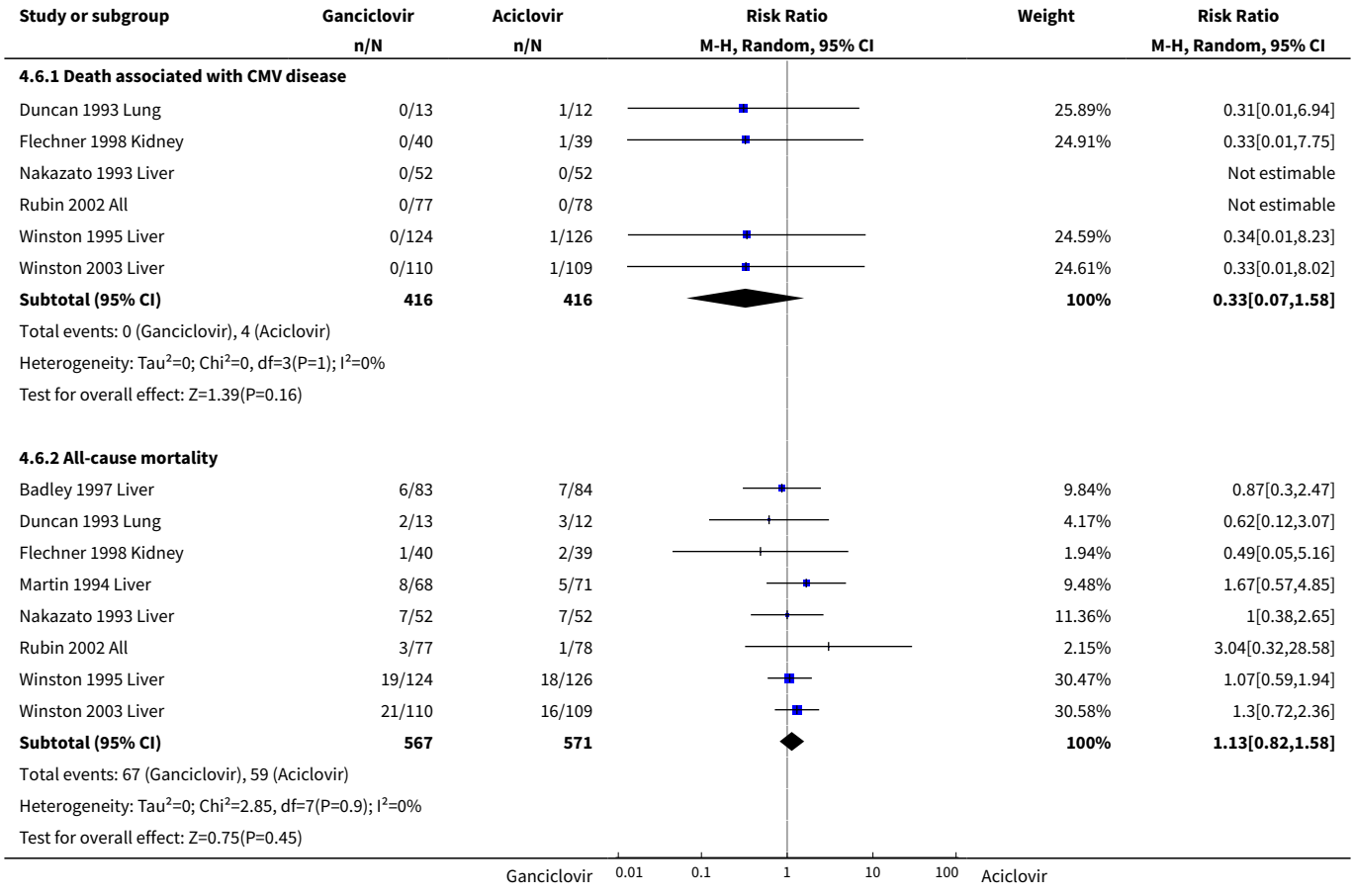
Analysis 4.5. Comparison 4 Ganciclovir versus aciclovir, Outcome 5 Effect of prophylaxis for different transplanted organs.

Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 CMV disease in kidney transplant patients					
Flechner 1998 Kidney	1/40	9/39		34.52%	0.11[0.01,0.82]
Rubin 2002 All	5/44	10/45		65.48%	0.51[0.19,1.38]
Subtotal (95% CI)	**84**	**84**		**100%**	**0.3[0.07,1.35]**
Total events: 6 (Ganciclovir), 19 (Aciclovir)					
Heterogeneity: Tau^2=0.64; Chi^2=1.98, df=1(P=0.16); I^2=49.44%					
Test for overall effect: Z=1.57(P=0.12)					
4.5.2 CMV disease in liver transplant patients					
Badley 1997 Liver	9/83	19/84		41.39%	0.48[0.23,1]
Martin 1994 Liver	6/68	20/71		30.79%	0.31[0.13,0.73]
Rubin 2002 All	2/8	2/8		7.71%	1[0.18,5.46]
Winston 1995 Liver	3/124	14/126		14.88%	0.22[0.06,0.74]
Winston 2003 Liver	1/110	8/109		5.23%	0.12[0.02,0.97]
Subtotal (95% CI)	**393**	**398**		**100%**	**0.37[0.23,0.59]**
Total events: 21 (Ganciclovir), 63 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=3.86, df=4(P=0.42); I^2=0%					
Test for overall effect: Z=4.15(P<0.0001)					
4.5.3 CMV disease in heart or lung transplant patients					
Duncan 1993 Lung	0/13	3/12		25.09%	0.13[0.01,2.33]
Rubin 2002 All	8/25	9/25		74.91%	0.89[0.41,1.93]
Subtotal (95% CI)	**38**	**37**		**100%**	**0.55[0.1,3]**
Total events: 8 (Ganciclovir), 12 (Aciclovir)					
Heterogeneity: Tau^2=0.84; Chi^2=1.73, df=1(P=0.19); I^2=42.34%					
Test for overall effect: Z=0.69(P=0.49)					
4.5.4 CMV infection in kidney transplant patients					
Flechner 1998 Kidney	1/40	14/39		34.69%	0.07[0.01,0.5]
Rubin 2002 All	7/44	21/45		65.31%	0.34[0.16,0.72]
Subtotal (95% CI)	**84**	**84**		**100%**	**0.2[0.04,0.95]**
Total events: 8 (Ganciclovir), 35 (Aciclovir)					
Heterogeneity: Tau^2=0.85; Chi^2=2.45, df=1(P=0.12); I^2=59.21%					
Test for overall effect: Z=2.02(P=0.04)					
4.5.5 CMV infection in liver transplant patients					
Badley 1997 Liver	31/83	48/84		31.45%	0.65[0.47,0.91]
Martin 1994 Liver	16/68	43/71		28.24%	0.39[0.24,0.62]
Rubin 2002 All	3/8	5/8		15.44%	0.6[0.21,1.7]
Winston 1995 Liver	11/124	52/126		24.86%	0.21[0.12,0.39]
Subtotal (95% CI)	**283**	**289**		**100%**	**0.42[0.25,0.73]**



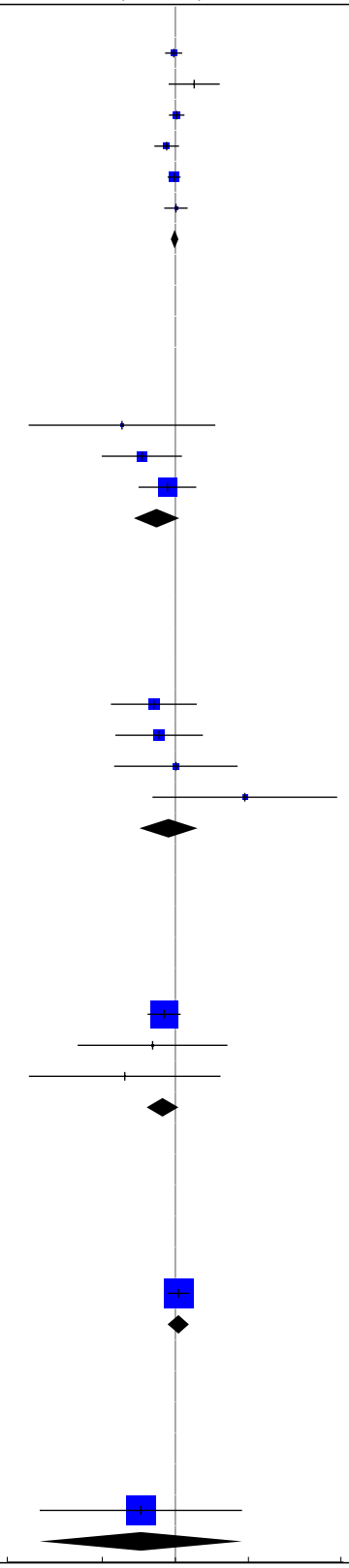


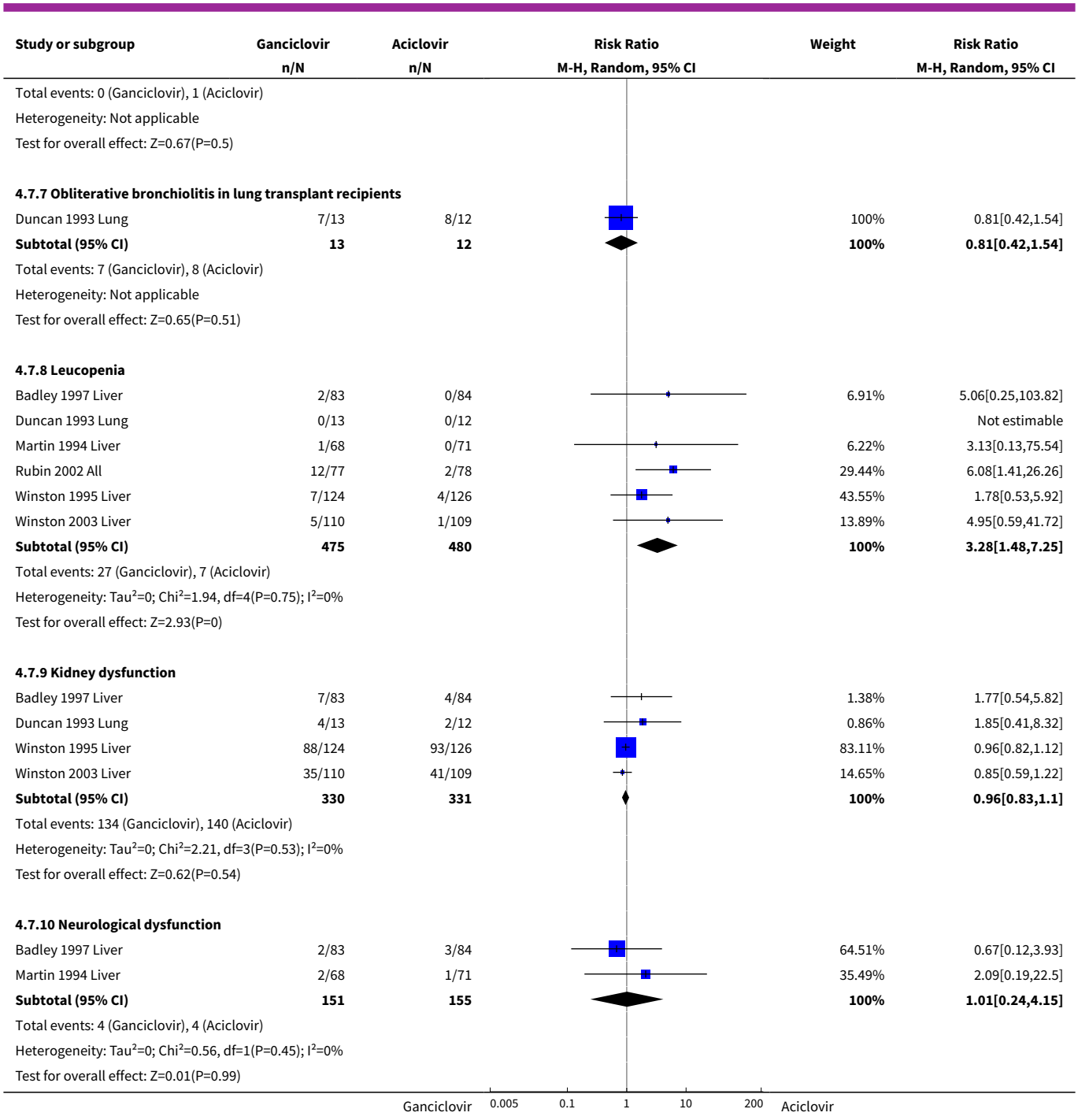
Analysis 4.6. Comparison 4 Ganciclovir versus aciclovir, Outcome 6 Death.



Analysis 4.7. Comparison 4 Ganciclovir versus aciclovir, Outcome 7 Additional outcomes.

Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Acute rejection					
Badley 1997 Liver	45/83	48/84		19.62%	0.95[0.72,1.24]
Flechner 1998 Kidney	13/40	7/39		2.22%	1.81[0.81,4.05]
Martin 1994 Liver	45/68	45/71		23.94%	1.04[0.82,1.33]
Rubin 2002 All	27/77	36/78		9.61%	0.76[0.52,1.12]
Winston 1995 Liver	72/124	76/126		33.93%	0.96[0.78,1.18]
Winston 2003 Liver	38/110	37/109		10.68%	1.02[0.71,1.47]
Subtotal (95% CI)	**502**	**507**		**100%**	**0.98[0.87,1.1]**
Total events: 240 (Ganciclovir), 249 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=4.27, df=5(P=0.51); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
4.7.2 Graft loss					
Duncan 1993 Lung	0/13	2/12		5.93%	0.19[0.01,3.52]
Martin 1994 Liver	3/68	9/71		32.12%	0.35[0.1,1.23]
Nakazato 1993 Liver	7/52	9/52		61.95%	0.78[0.31,1.93]
Subtotal (95% CI)	**133**	**135**		**100%**	**0.55[0.27,1.13]**
Total events: 10 (Ganciclovir), 20 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=1.62, df=2(P=0.45); I^2=0%					
Test for overall effect: Z=1.63(P=0.1)					
4.7.3 Other viral infections					
Badley 1997 Liver	3/83	6/84		36.07%	0.51[0.13,1.96]
Nakazato 1993 Liver	3/52	5/52		34.98%	0.6[0.15,2.38]
Winston 1995 Liver	2/124	2/126		19.6%	1.02[0.15,7.1]
Winston 2003 Liver	4/110	0/109		9.35%	8.92[0.49,163.69]
Subtotal (95% CI)	**369**	**371**		**100%**	**0.81[0.32,2.01]**
Total events: 12 (Ganciclovir), 13 (Aciclovir)					
Heterogeneity: Tau^2=0.13; Chi^2=3.49, df=3(P=0.32); I^2=14.13%					
Test for overall effect: Z=0.46(P=0.64)					
4.7.4 Invasive fungal infections					
Badley 1997 Liver	18/83	26/84		92.78%	0.7[0.42,1.18]
Flechner 1998 Kidney	1/40	2/39		4.48%	0.49[0.05,5.16]
Rubin 2002 All	0/77	2/78		2.74%	0.2[0.01,4.15]
Subtotal (95% CI)	**200**	**201**		**100%**	**0.67[0.4,1.1]**
Total events: 19 (Ganciclovir), 30 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.72, df=2(P=0.7); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					
4.7.5 Bacterial infections					
Badley 1997 Liver	39/83	36/84		100%	1.1[0.78,1.53]
Subtotal (95% CI)	**83**	**84**		**100%**	**1.1[0.78,1.53]**
Total events: 39 (Ganciclovir), 36 (Aciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
4.7.6 Protozoal infections					
Badley 1997 Liver	0/83	1/84		100%	0.34[0.01,8.16]
Subtotal (95% CI)	**83**	**84**		**100%**	**0.34[0.01,8.16]**





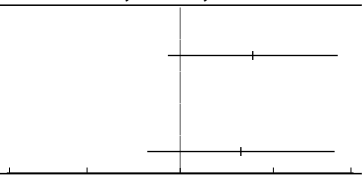
Comparison 5. Ganciclovir / aciclovir versus ganciclovir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 CMV infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Additional outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 EBV infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

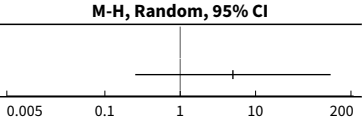
Analysis 5.1. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

Study or subgroup	GCV/ACV n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.1.1 CMV disease				
Green 1997 Liver	7/24	2/24		3.5[0.81,15.16]
5.1.2 CMV infection				
Green 1997 Liver	3/10	2/19		2.85[0.57,14.36]



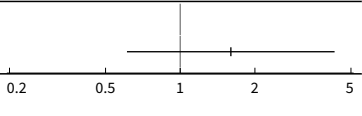
Analysis 5.2. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 2 Death.

Study or subgroup	GCV/ACV n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.2.1 All-cause mortality				
Green 1997 Liver	2/24	0/24		5[0.25,98.96]



Analysis 5.3. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 3 Additional outcomes.

Study or subgroup	GCV/ACV n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 EBV infection				
Green 1997 Liver	8/24	5/24		1.6[0.61,4.19]



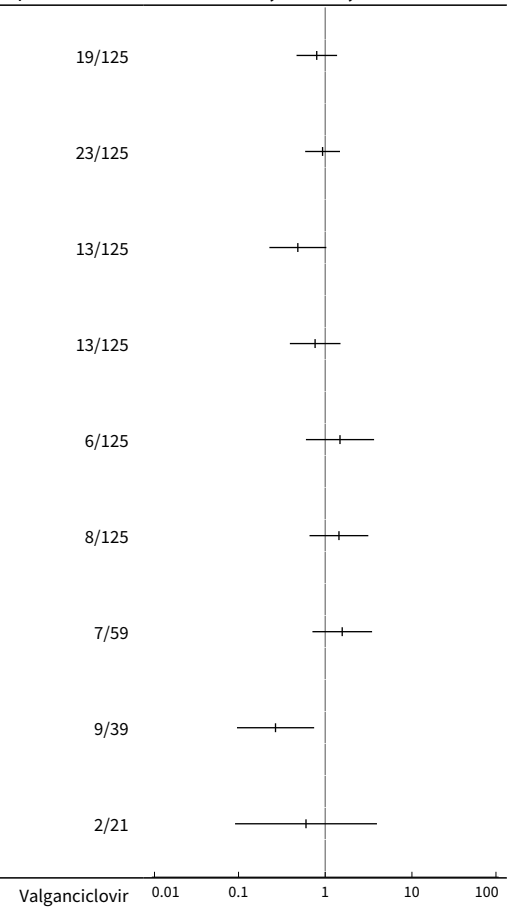
Comparison 6. Valganciclovir versus ganciclovir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease or infection in CMV donor +ve / recipient -ve	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 CMV disease by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 CMV disease by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 CMV syndrome by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 CMV syndrome by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Tissue invasive CMV disease by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Tissue invasive CMV disease by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 CMV disease in liver transplant recipients by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.8 CMV disease in renal transplant recipients by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.9 CMV disease in heart transplant recipients by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.10 CMV disease in renal-pancreas transplant recipients by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.11 CMV infection by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.12 CMV infection by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Death due to CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Additional outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Acute rejection in all recipients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Graft loss	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Opportunistic infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Neutrophil count < 1000/mm^3	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Medications ceased because of neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Anaemia (< 80 g/L)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Thrombocytopenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Tremor	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Valganciclovir versus ganciclovir, Outcome 1 CMV disease or infection in CMV donor +ve / recipient -ve.

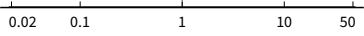
Study or subgroup	Valganciclovir n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 CMV disease by 6 months				
Paya 2004 All	29/239	19/125		0.8[0.47,1.37]
6.1.2 CMV disease by 1 year				
Paya 2004 All	41/239	23/125		0.93[0.59,1.48]
6.1.3 CMV syndrome by 6 months				
Paya 2004 All	12/239	13/125		0.48[0.23,1.03]
6.1.4 CMV syndrome by 1 year				
Paya 2004 All	19/239	13/125		0.76[0.39,1.5]
6.1.5 Tissue invasive CMV disease by 6 months				
Paya 2004 All	17/239	6/125		1.48[0.6,3.66]
6.1.6 Tissue invasive CMV disease by 1 year				
Paya 2004 All	22/239	8/125		1.44[0.66,3.14]
6.1.7 CMV disease in liver transplant recipients by 6 months				
Paya 2004 All	22/118	7/59		1.57[0.71,3.47]
6.1.8 CMV disease in renal transplant recipients by 6 months				
Paya 2004 All	5/81	9/39		0.27[0.1,0.74]
6.1.9 CMV disease in heart transplant recipients by 6 months				
Paya 2004 All	2/35	2/21		0.6[0.09,3.95]



Study or subgroup	Valganciclovir n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.10 CMV disease in renal-pancreas transplant recipients by 6 months				
Paya 2004 All	0/5	1/6		0.39[0.02,7.88]
6.1.11 CMV infection by 6 months				
Paya 2004 All	95/239	54/125		0.92[0.71,1.19]
6.1.12 CMV infection by 1 year				
Paya 2004 All	116/239	61/125		0.99[0.8,1.24]

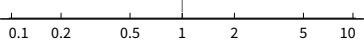
Analysis 6.2. Comparison 6 Valganciclovir versus ganciclovir, Outcome 2 Death.

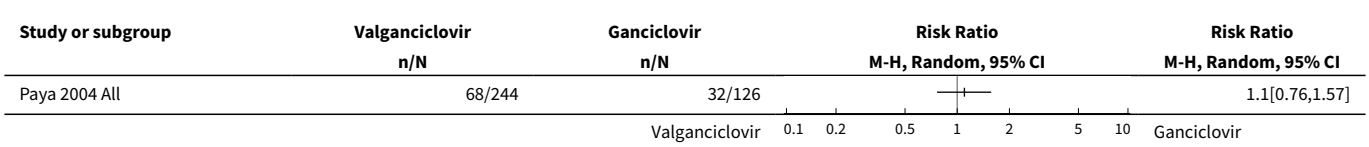
Study or subgroup	Valganciclovir n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.2.1 Death due to CMV disease				
Paya 2004 All	1/239	1/125		0.52[0.03,8.29]
6.2.2 All-cause mortality				
Paya 2004 All	15/239	8/125		0.98[0.43,2.25]



Analysis 6.3. Comparison 6 Valganciclovir versus ganciclovir, Outcome 3 Additional outcomes.

Study or subgroup	Valganciclovir n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.3.1 Acute rejection in all recipients				
Paya 2004 All	78/239	45/125		0.91[0.67,1.22]
6.3.2 Graft loss				
Paya 2004 All	3/239	2/125		0.78[0.13,4.63]
6.3.3 Opportunistic infections				
Paya 2004 All	18/239	11/125		0.86[0.42,1.76]
6.3.4 Neutrophil count < 1000/mm^3				
Paya 2004 All	31/244	10/126		1.6[0.81,3.16]
6.3.5 Medications ceased because of neutropenia				
Paya 2004 All	5/244	3/126		0.86[0.21,3.54]
6.3.6 Anaemia (< 80 g/L)				
Paya 2004 All	21/244	7/126		1.55[0.68,3.55]
6.3.7 Thrombocytopenia				
Paya 2004 All	62/244	24/126		1.33[0.88,2.03]
6.3.8 Tremor				





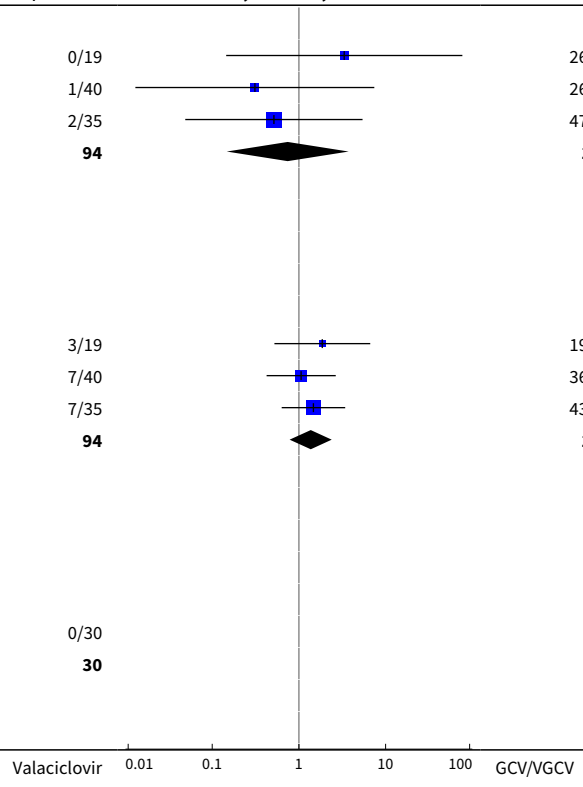
Comparison 7. Valaciclovir versus ganciclovir or valganciclovir

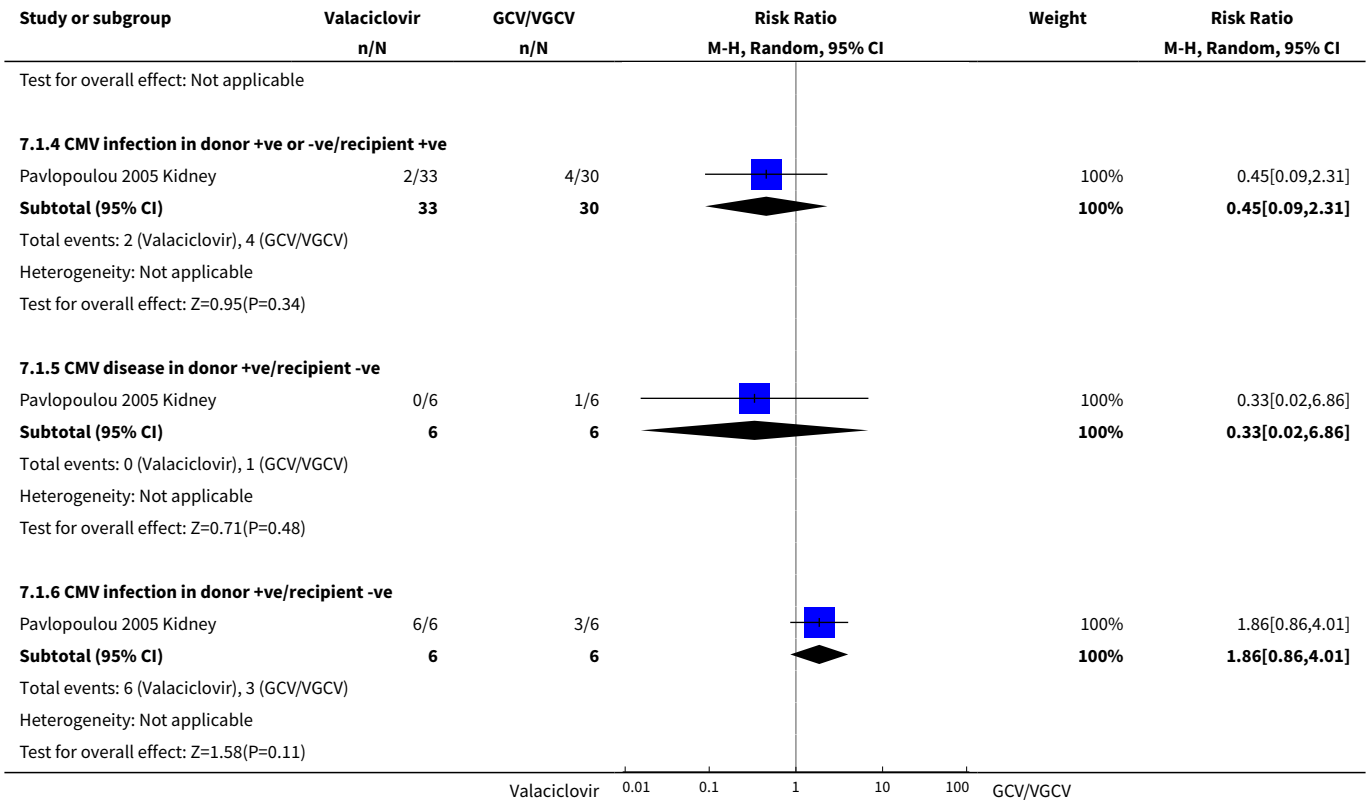
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease	3	188	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.15, 3.75]
1.2 CMV infection	3	188	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.78, 2.39]
1.3 CMV disease in donor +ve or -ve/recipient +ve	1	63	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 CMV infection in donor +ve or -ve/recipient +ve	1	63	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.09, 2.31]
1.5 CMV disease in donor +ve/recipient -ve	1	12	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 6.86]
1.6 CMV infection in donor +ve/recipient -ve	1	12	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.86, 4.01]
2 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All-cause mortality	2	154	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.15, 6.90]
3 Additional outcomes	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Acute rejection	3	188	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.22, 3.73]
3.2 Graft loss	2	107	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.23, 7.86]
3.3 Leucopenia	1	69	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.40, 2.62]
3.4 Thrombocytopenia	1	69	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
3.5 Anaemia	1	68	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.19, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 Neurological dysfunction	1	69	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.62, 3.87]
3.7 Dose reduction or cessation for adverse effects	1	69	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.25, 1.51]
3.8 Other herpes virus infections	1	83	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.18, 19.73]
3.9 Non-viral infections	1	83	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.44, 0.80]
4 Renal function at end of study	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Serum creatinine	3	188	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.51, 0.06]
4.2 Calculated GFR	1	69	Std. Mean Difference (IV, Random, 95% CI)	0.41 [-0.06, 0.89]

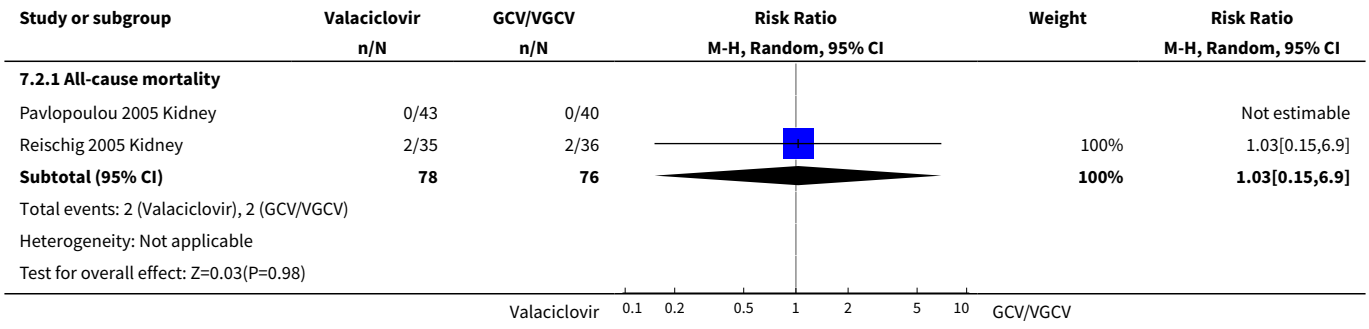
Analysis 7.1. Comparison 7 Valaciclovir versus ganciclovir or valganciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

Study or subgroup	Valaciclovir n/N	GCV/VGCV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 CMV disease					
2VAL Study 2010 Kidney	1/17	0/19		26.64%	3.33[0.14,76.75]
Pavlopoulou 2005 Kidney	0/43	1/40		26.05%	0.31[0.01,7.41]
Reischig 2005 Kidney	1/34	2/35		47.31%	0.51[0.05,5.42]
Subtotal (95% CI)	**94**	**94**		**100%**	**0.74[0.15,3.75]**
Total events: 2 (Valaciclovir), 3 (GCV/VGCV)					
Heterogeneity: Tau^2=0; Chi^2=1.27, df=2(P=0.53); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					
7.1.2 CMV infection					
2VAL Study 2010 Kidney	5/17	3/19		19.22%	1.86[0.52,6.65]
Pavlopoulou 2005 Kidney	8/43	7/40		36.92%	1.06[0.42,2.66]
Reischig 2005 Kidney	10/34	7/35		43.86%	1.47[0.63,3.42]
Subtotal (95% CI)	**94**	**94**		**100%**	**1.37[0.78,2.39]**
Total events: 23 (Valaciclovir), 17 (GCV/VGCV)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=1.09(P=0.27)					
7.1.3 CMV disease in donor +ve or -ve/recipient +ve					
Pavlopoulou 2005 Kidney	0/33	0/30			Not estimable
Subtotal (95% CI)	**33**	**30**			**Not estimable**
Total events: 0 (Valaciclovir), 0 (GCV/VGCV)					
Heterogeneity: Not applicable					

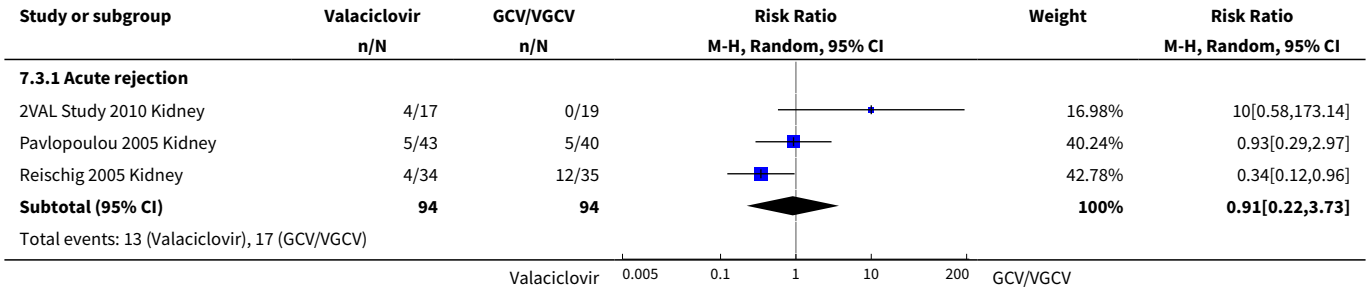


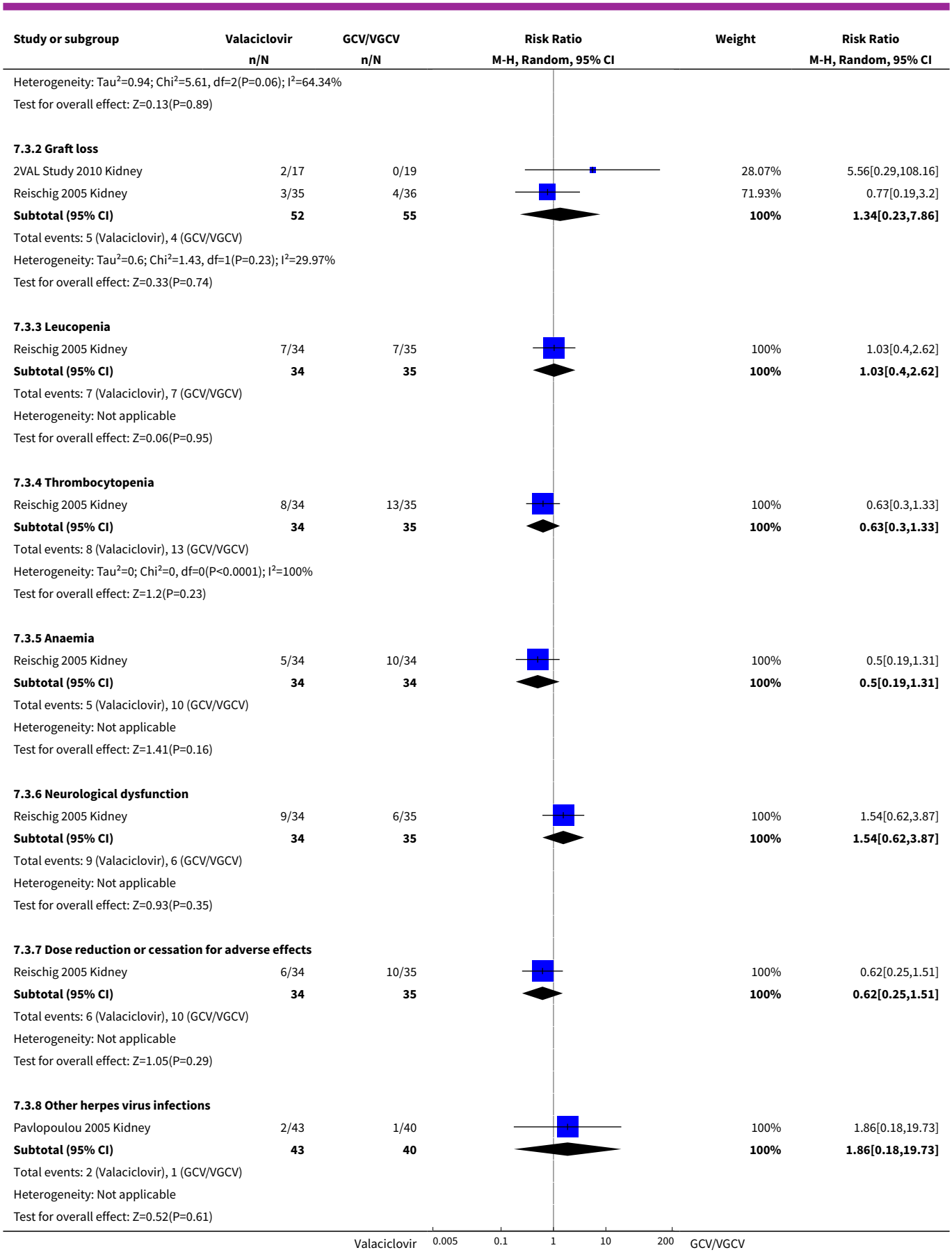


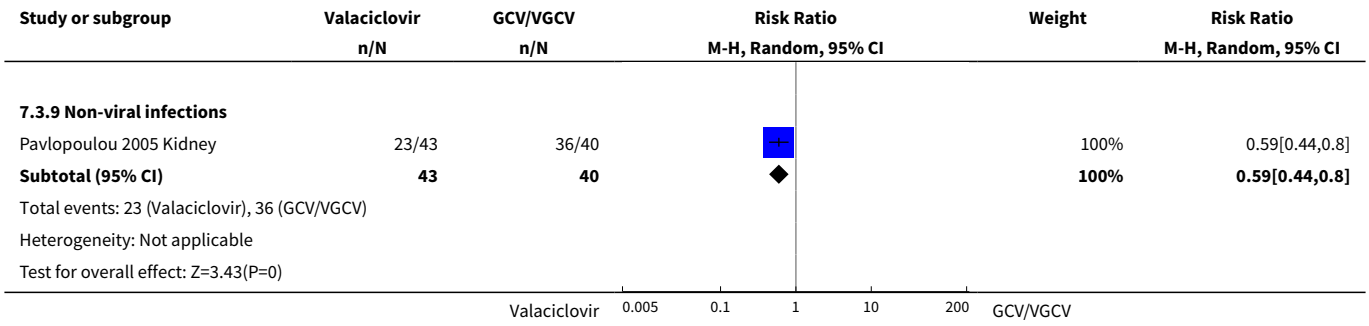
Analysis 7.2. Comparison 7 Valaciclovir versus ganciclovir or valganciclovir, Outcome 2 Death.



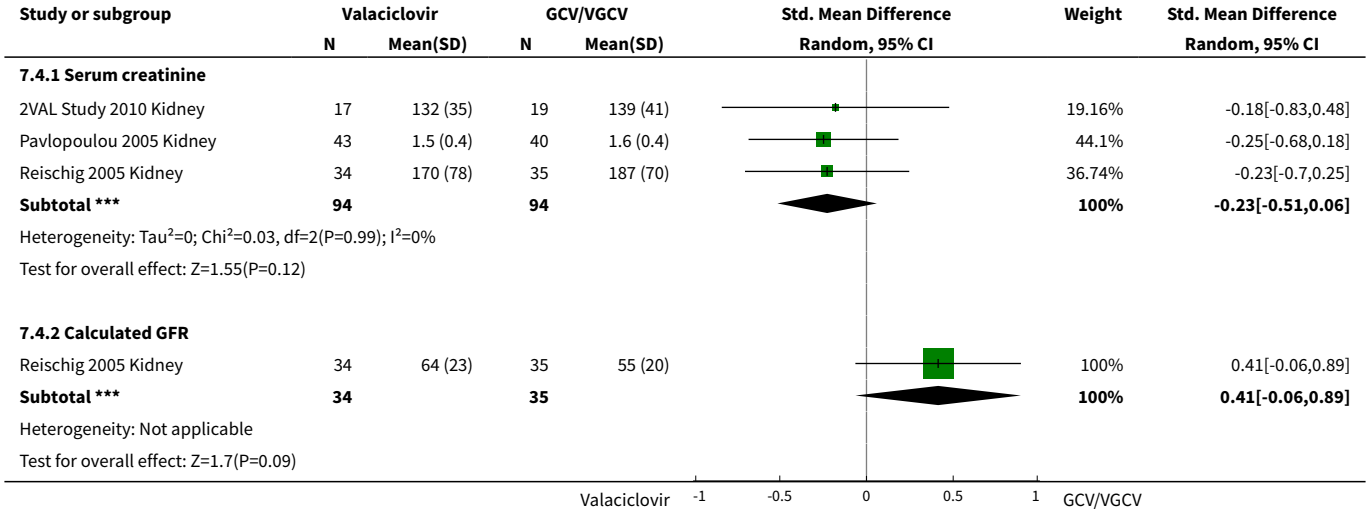
Analysis 7.3. Comparison 7 Valaciclovir versus ganciclovir or valganciclovir, Outcome 3 Additional outcomes.







Analysis 7.4. Comparison 7 Valaciclovir versus ganciclovir or valganciclovir, Outcome 4 Renal function at end of study.



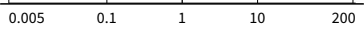
Comparison 8. Different ganciclovir regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IV doses given at different frequencies	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 CMV syndrome	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Invasive CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 CMV infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Death due to CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

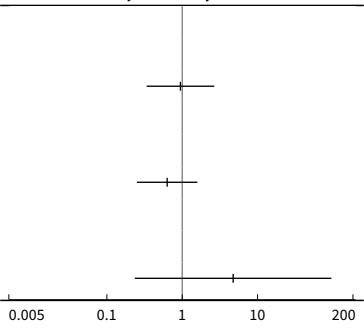
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Bacteraemia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.8 Bronchiolitis obliterans syndrome	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.9 Leucopenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Oral versus IV ganciclovir	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV disease	2	94	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.16, 2.05]
2.2 CMV syndrome	2	94	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.11, 2.11]
2.3 CMV invasive organ disease	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.30]
2.4 CMV infection	1	30	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.41, 2.70]
2.5 All-cause mortality	1	64	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.62, 40.44]
2.6 Acute rejection	2	94	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.59]
2.7 Graft loss	1	34	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.72]
2.8 Leucopenia due to ganciclovir	1	64	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.39]
2.9 Medications ceased due to leucopenia	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.66]

Analysis 8.1. Comparison 8 Different ganciclovir regimens, Outcome 1 IV doses given at different frequencies.

Study or subgroup	Thrice weekly doses n/N	Daily doses n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 CMV disease				
Hertz 1998 Heart/lung	11/37	18/35		0.58[0.32,1.04]
8.1.2 CMV syndrome				
Hertz 1998 Heart/lung	2/37	4/35		0.47[0.09,2.42]
8.1.3 Invasive CMV disease				
Hertz 1998 Heart/lung	9/37	14/35		0.61[0.3,1.22]
8.1.4 CMV infection				
Hertz 1998 Heart/lung	19/37	28/35		0.64[0.45,0.92]
8.1.5 All-cause mortality				
Hertz 1998 Heart/lung	9/37	2/35		4.26[0.99,18.34]
8.1.6 Death due to CMV disease				
Hertz 1998 Heart/lung	0/37	2/35		0.19[0.01,3.81]

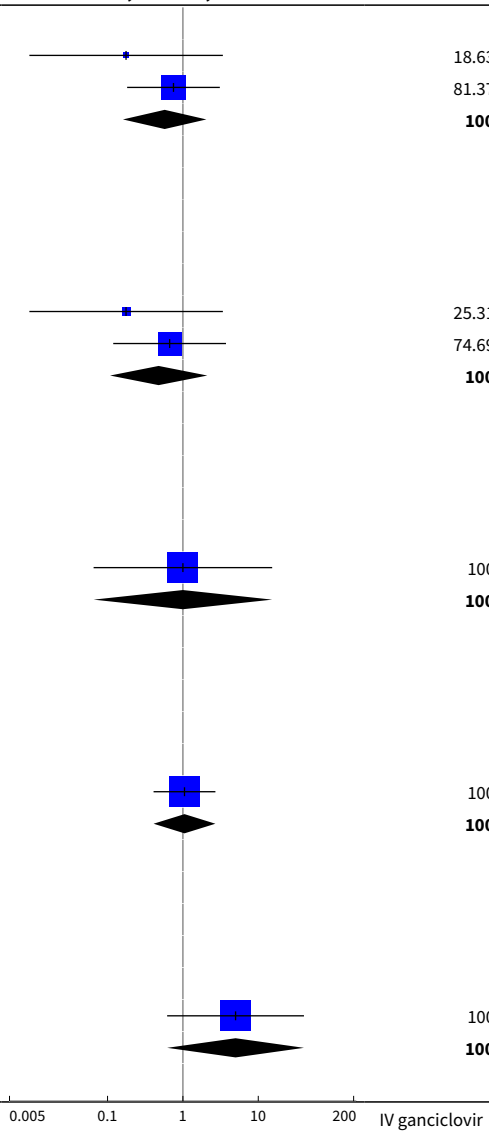


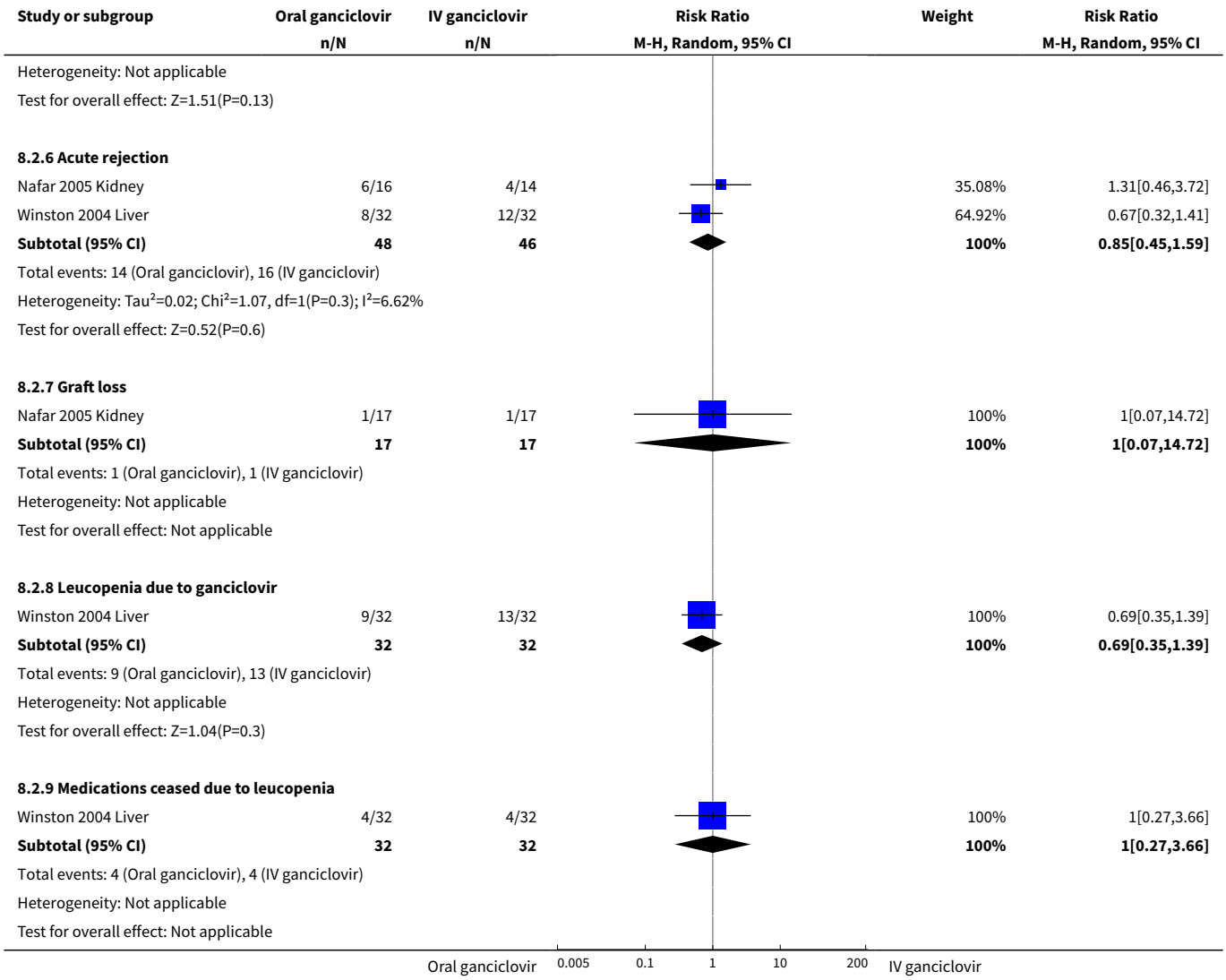
Study or subgroup	Thrice weekly doses n/N	Daily doses n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.7 Bacteraemia				
Hertz 1998 Heart/lung	6/37	6/35		0.95[0.34,2.66]
8.1.8 Bronchiolitis obliterans syndrome				
Hertz 1998 Heart/lung	6/37	9/35		0.63[0.25,1.59]
8.1.9 Leucopenia				
Hertz 1998 Heart/lung	2/37	0/35		4.74[0.24,95.33]



Analysis 8.2. Comparison 8 Different ganciclovir regimens, Outcome 2 Oral versus IV ganciclovir.

Study or subgroup	Oral ganciclovir n/N	IV ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 CMV disease					
Nafar 2005 Kidney	0/16	2/14		18.63%	0.18[0.01,3.39]
Winston 2004 Liver	3/32	4/32		81.37%	0.75[0.18,3.09]
Subtotal (95% CI)	**48**	**46**		**100%**	**0.57[0.16,2.05]**
Total events: 3 (Oral ganciclovir), 6 (IV ganciclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
8.2.2 CMV syndrome					
Nafar 2005 Kidney	0/16	2/14		25.31%	0.18[0.01,3.39]
Winston 2004 Liver	2/32	3/32		74.69%	0.67[0.12,3.73]
Subtotal (95% CI)	**48**	**46**		**100%**	**0.48[0.11,2.11]**
Total events: 2 (Oral ganciclovir), 5 (IV ganciclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					
8.2.3 CMV invasive organ disease					
Winston 2004 Liver	1/32	1/32		100%	1[0.07,15.3]
Subtotal (95% CI)	**32**	**32**		**100%**	**1[0.07,15.3]**
Total events: 1 (Oral ganciclovir), 1 (IV ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.2.4 CMV infection					
Nafar 2005 Kidney	6/16	5/14		100%	1.05[0.41,2.7]
Subtotal (95% CI)	**16**	**14**		**100%**	**1.05[0.41,2.7]**
Total events: 6 (Oral ganciclovir), 5 (IV ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)					
8.2.5 All-cause mortality					
Winston 2004 Liver	5/32	1/32		100%	5[0.62,40.44]
Subtotal (95% CI)	**32**	**32**		**100%**	**5[0.62,40.44]**
Total events: 5 (Oral ganciclovir), 1 (IV ganciclovir)					





Comparison 9. Extended duration compared with three months of valganciclovir

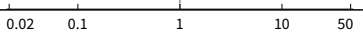
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease at end of treatment	2	454	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.12, 0.35]
1.2 CMV disease at 9 months	1	310	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.60]
1.3 CMV disease at 12 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.29, 0.66]

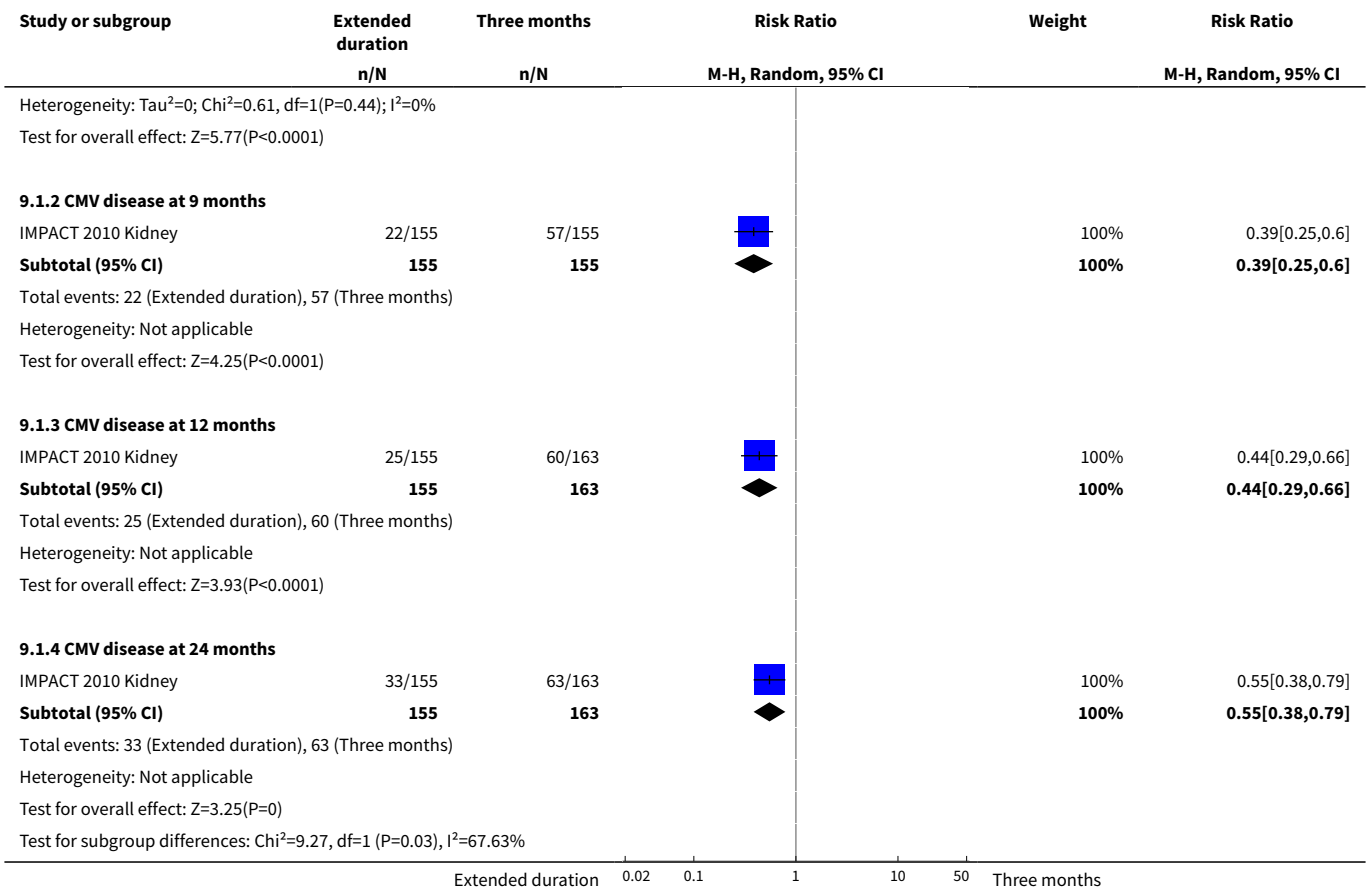
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 CMV disease at 24 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.38, 0.79]
2 CMV syndrome	2	454	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.24, 0.64]
3 CMV invasive disease	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Number at 12 months	2	454	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.34]
3.2 Number at 24 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.12, 4.14]
4 CMV infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 CMV infection at end of treatment	2	454	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.71]
4.2 CMV infection at 9 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.94]
4.3 CMV infection at 12 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.57, 0.95]
5 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Number at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Number at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Graft loss	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Number at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Number at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Acute rejection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Biopsy proved acute rejection < 100 days	1	318	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.32, 1.51]
7.2 Biopsy proven acute rejection at 12 months	2	454	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.43, 0.95]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.3 Biopsy proven acute rejection at 24 months	1	318	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.35, 1.08]
8 Other outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Opportunistic infections	2	456	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.57]
8.2 Post-transplant diabetes mellitus	1	244	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.58, 2.36]
9 Adverse effects	2		Risk Difference (M-H, Random, 95% CI)	Subtotals only
9.1 Total treatment related adverse effects	2	456	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.01, 0.16]
9.2 Treatment related serious adverse effects	2	456	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.07]
9.3 Leukopenia	1	320	Risk Difference (M-H, Random, 95% CI)	0.12 [0.01, 0.22]
9.4 Leucopenia leading to VGCV cessation	1	320	Risk Difference (M-H, Random, 95% CI)	0.04 [0.00, 0.07]
9.5 Termination due to treatment related adverse effects	1	136	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.04, 0.18]
9.6 Hospitalisations due to CMV disease	1	418	Risk Difference (M-H, Random, 95% CI)	-0.10 [-0.17, -0.04]
9.7 Hospitalisations due to adverse effects	1	418	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.05, 0.13]
9.8 CMV mutations known to confer ganciclovir resistance	2	208	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.08, 0.11]

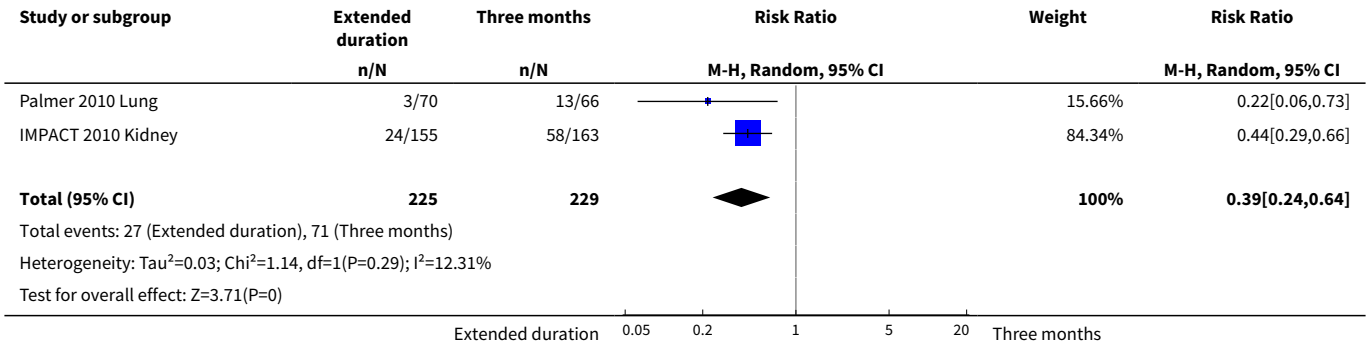
Analysis 9.1. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 1 CMV disease.

Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 CMV disease at end of treatment					
Palmer 2010 Lung	3/70	21/66		21.79%	0.13[0.04,0.43]
IMPACT 2010 Kidney	11/155	51/163		78.21%	0.23[0.12,0.42]
Subtotal (95% CI)	**225**	**229**		**100%**	**0.2[0.12,0.35]**
Total events: 14 (Extended duration), 72 (Three months)					





Analysis 9.2. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 2 CMV syndrome.



Analysis 9.3. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 3 CMV invasive disease.

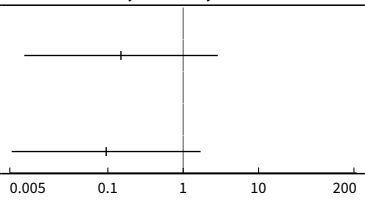
Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 Number at 12 months					
IMPACT 2010 Kidney	1/155	2/163		45.04%	0.53[0.05,5.74]
Palmer 2010 Lung	1/70	14/66		54.96%	0.07[0.01,0.5]
Subtotal (95% CI)	**225**	**229**		**100%**	**0.17[0.02,1.34]**
Total events: 2 (Extended duration), 16 (Three months)					
Heterogeneity: Tau^2=0.98; Chi^2=1.77, df=1(P=0.18); I^2=43.62%					
Test for overall effect: Z=1.68(P=0.09)					
9.3.2 Number at 24 months					
IMPACT 2010 Kidney	2/155	3/163		100%	0.7[0.12,4.14]
Subtotal (95% CI)	**155**	**163**		**100%**	**0.7[0.12,4.14]**
Total events: 2 (Extended duration), 3 (Three months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
Test for subgroup differences: Chi^2=1.04, df=1 (P=0.31), I^2=3.84%					

Analysis 9.4. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 4 CMV infection.

Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.4.1 CMV infection at end of treatment					
Palmer 2010 Lung	7/70	42/66		44.84%	0.16[0.08,0.32]
IMPACT 2010 Kidney	29/155	73/163		55.16%	0.42[0.29,0.6]
Subtotal (95% CI)	**225**	**229**		**100%**	**0.27[0.1,0.71]**
Total events: 36 (Extended duration), 115 (Three months)					
Heterogeneity: Tau^2=0.41; Chi^2=5.69, df=1(P=0.02); I^2=82.43%					
Test for overall effect: Z=2.66(P=0.01)					
9.4.2 CMV infection at 9 months					
IMPACT 2010 Kidney	55/155	80/163		100%	0.72[0.56,0.94]
Subtotal (95% CI)	**155**	**163**		**100%**	**0.72[0.56,0.94]**
Total events: 55 (Extended duration), 80 (Three months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.41(P=0.02)					
9.4.3 CMV infection at 12 months					
IMPACT 2010 Kidney	58/155	83/163		100%	0.73[0.57,0.95]
Subtotal (95% CI)	**155**	**163**		**100%**	**0.73[0.57,0.95]**
Total events: 58 (Extended duration), 83 (Three months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.38(P=0.02)					
Test for subgroup differences: Chi^2=3.94, df=1 (P=0.14), I^2=49.22%					

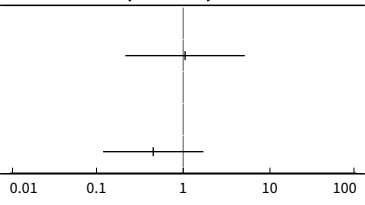
Analysis 9.5. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 5 All-cause mortality.

Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.5.1 Number at 12 months				
IMPACT 2010 Kidney	0/156	3/163		0.15[0.01,2.87]
9.5.2 Number at 2 years				
IMPACT 2010 Kidney	0/156	5/163		0.09[0.01,1.7]



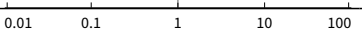
Analysis 9.6. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 6 Graft loss.

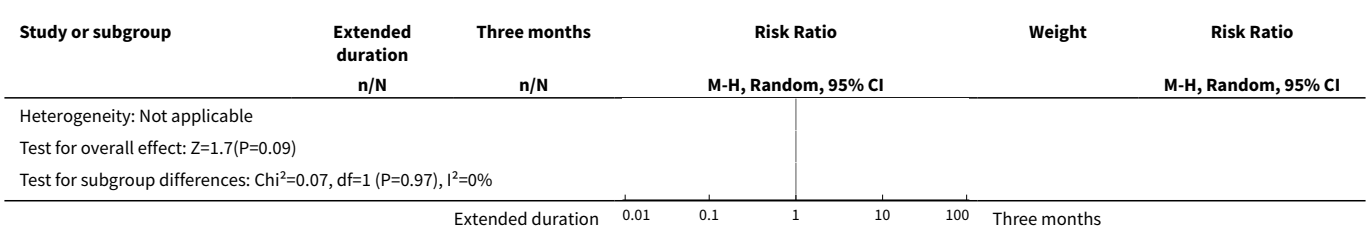
Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.6.1 Number at 12 months				
IMPACT 2010 Kidney	3/155	3/163		1.05[0.22,5.13]
9.6.2 Number at 24 months				
IMPACT 2010 Kidney	3/155	7/163		0.45[0.12,1.71]



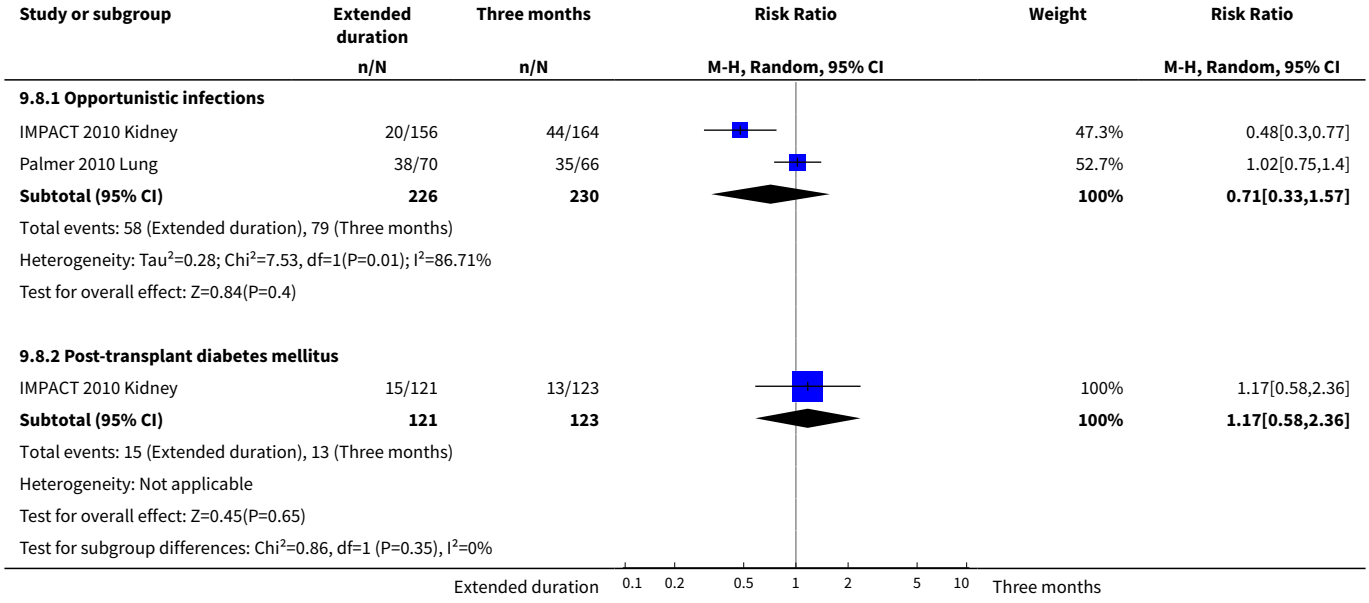
Analysis 9.7. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 7 Acute rejection.

Study or subgroup	Extended duration n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.7.1 Biopsy proved acute rejection < 100 days					
IMPACT 2010 Kidney	10/155	15/163		100%	0.7[0.32,1.51]
Subtotal (95% CI)	**155**	**163**		**100%**	**0.7[0.32,1.51]**
Total events: 10 (Extended duration), 15 (Three months)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.9(P=0.37)					
9.7.2 Biopsy proven acute rejection at 12 months					
Palmer 2010 Lung	15/70	22/66		49.78%	0.64[0.37,1.13]
IMPACT 2010 Kidney	17/155	28/163		50.22%	0.64[0.36,1.12]
Subtotal (95% CI)	**225**	**229**		**100%**	**0.64[0.43,0.95]**
Total events: 32 (Extended duration), 50 (Three months)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=2.19(P=0.03)					
9.7.3 Biopsy proven acute rejection at 24 months					
IMPACT 2010 Kidney	17/155	29/163		100%	0.62[0.35,1.08]
Subtotal (95% CI)	**155**	**163**		**100%**	**0.62[0.35,1.08]**
Total events: 17 (Extended duration), 29 (Three months)					

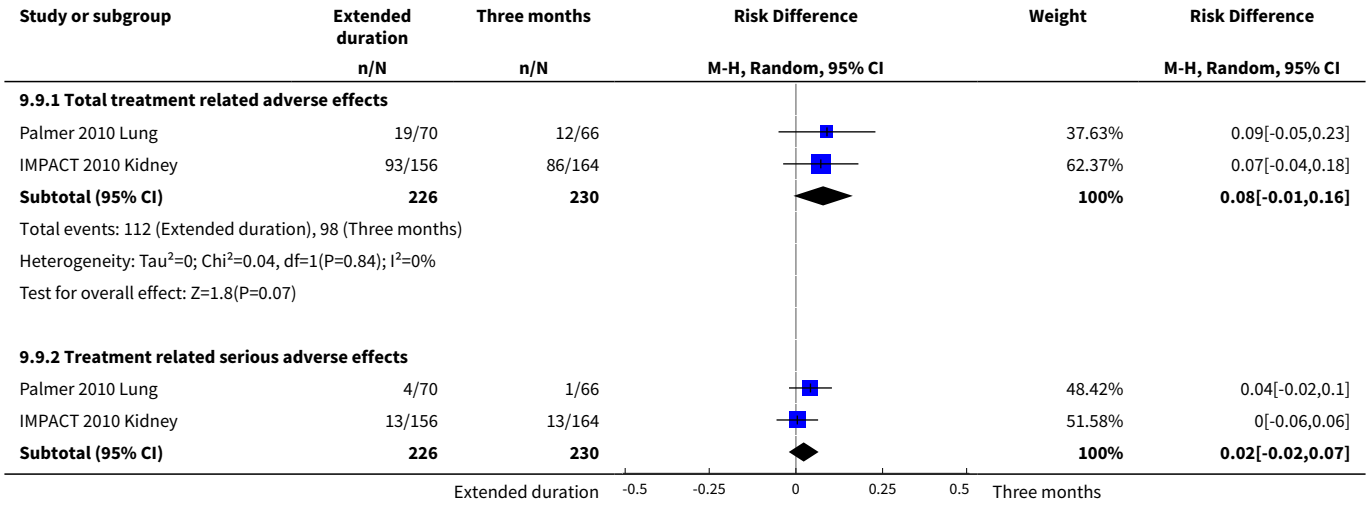


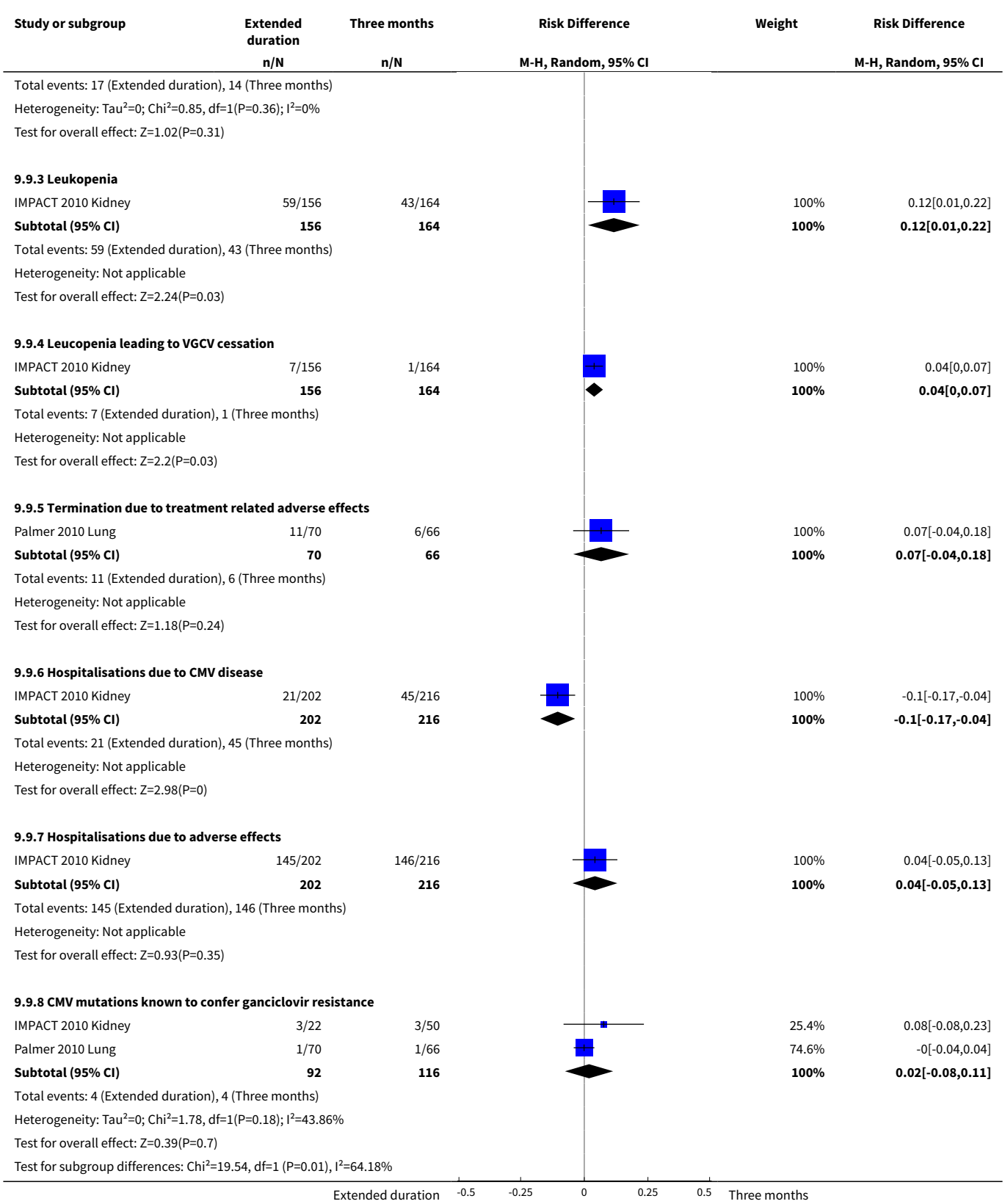


Analysis 9.8. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 8 Other outcomes.



Analysis 9.9. Comparison 9 Extended duration compared with three months of valganciclovir, Outcome 9 Adverse effects.





ADDITIONAL TABLES

Table 1. Potential sources of variability: CMV disease and all-cause mortality *(Continued)*

Variable	CMV disease			All-cause mortality		
	Number of studies	RR (95% CI)	P for interaction	Number of studies	RR (95% CI)	P for interaction
Antiviral medication 1. Aciclovir 2. Ganciclovir 3. Valaciclovir	1. 6 2. 11 3. 2	1. 0.45 (0.29 to 0.69) 2. 0.44 (0.34 to 0.58) 3. 0.30 (0.19 to 0.49)	0.43	1. 5 2. 10 3. 2	1. 0.67 (0.38 to 1.20) 2. 0.69 (0.29 to 1.65) 3. 0.50 (0.22 to 1.15)	0.85
Time to outcome assessment 1. 3 to 6 months 2. 9 to 12 months	1. 11 2. 8	1. 0.46 (0.36 to 0.58) 2. 0.36 (0.22 to 0.58)	0.37	1. 7 2. 10	1. 0.63 (0.40 to 0.97) 2. 0.64 (0.31 to 1.33)	0.83
Recipient CMV status 1. Positive (donor +ve or -ve)[1] 2. Negative	1. 13 2. 10	1. 0.34 (0.24 to 0.50) 2. 0.52 (0.37 to 0.74)	0.12	1. 7 2. 4	1. 0.59 (0.30 to 1.18) 2. 1.42 (0.44 to 4.66)	0.23

Table 1. Potential sources of variability: CMV disease and all-cause mortality *(Continued)*

(donor +ve)[2]						
Donor CMV status[3] 1. Positive (recipients all +ve) 2. Negative (recipients all +ve)	1. 5 2. 5	1. 0.18 (0.09 to 0.36) 2. 0.33 (0.11 to 0.95)	0.37	1. No data 2. No data	1. No data 2. No data	No data
Organ transplanted 1. Kidney 2. Liver 3. Heart	1. 11 2. 5 3. 3	1. 0.42 (0.31 to 0.57) 2. 0.49 (0.29 to 0.84) 3. 0.39 (0.25 to 0.63)	0.93	1. 10 2. 4 3. 3	1. 0.49 (0.24 to 1.00) 2. 0.64 (0.39 to 1.00) 3. 1.82 (0.39 to 8.51)	0.13
Antibody therapy 1. Yes 2. No	1. 11 2. 6	1. 0.43 (0.33 to 0.55) 2. 0.47 (0.29 to 0.76)	0.74	1. 10 2. 5	1. 0.81 (0.33 to 2.01) 2. 0.63 (0.39 to 1.00)	0.93
Treatment duration[a] 1. 6 weeks or less	1. 7 2. 4	1. 0.49 (0.36 to 0.68) 2. 0.33 (0.21 to 0.53)	0.72	1. 6 2. 4	1. 0.91 (0.17 to 4.92) 2. 0.62 (0.30 to 1.30)	0.15

Table 1. Potential sources of variability: CMV disease and all-cause mortality *(Continued)*

2. More than 6 weeks						
Allocation concealment 1. Adequate 2. Unclear or inadequate	1. 4 2. 15	1. 0.50 (0.31 to 0.79) 2. 0.41 (0.33 to 0.51)	0.64	1. 3 2. 14	1. 0.26 (0.06 to 1.20) 2. 0.67 (0.45 to 0.99)	0.88
Blinding 1. Yes 2. No	1. 5 2. 14	1. 0.35 (0.25 to 0.48) 2. 0.47 (0.37 to 0.59)	0.18	1. 5 2. 12	1. 0.62 (0.39 to 0.98) 2. 0.65 (0.33 to 1.27)	0.97
Intention to treat 1. Yes 2. No	1. 10 2. 9	1. 0.38 (0.30 to 0.48) 2. 0.47 (0.33 to 0.68)	0.37	1. 9 2. 8	1. 0.62 (0.40 to 0.98) 2. 0.65 (0.32 to 1.29)	0.57

[1]Studies in "positive" group included those in which recipients were positive for CMV with donor positive or negative for CMV.
[2]Studies in "negative" group included those in which CMV negative recipients received CMV positive organs.
[3]Studies in which recipients were CMV positive and the donors CMV positive (positive group) or negative (CMV negative group).
[a]Ganciclovir studies only.

Table 2. Summary of outcomes for antiviral medication versus placebo/no treatment

Outcome	Aciclovir Studies; RR (95% CI)	Ganciclovir Studies; RR (95% CI)	Valaciclovir Studies; RR (95% CI)	All medications Studies; RR (95% CI)
Acute rejection	4; 1.03 (0.78 to 1.36)	7; 0.92 (0.70 to 1.21)	2; 0.81 (0.51 to 1.28)^	13; 0.90 (0.78 to 1.17)
Graft loss	4; 0.77 (0.35 to 1.68)	6; 0.73 (0.41 to 1.28)	No data	10; 0.74 (0.47 to 1.17)
Herpes simplex or zoster infections	3; 0.30 (0.14 to 0.62)	4; 0.25 (0.08 to 0.78)	2; 0.28 (0.20 to 0.40)	9; 0.27 (0.19 to 0.40)

Table 2. Summary of outcomes for antiviral medication versus placebo/no treatment *(Continued)*

Post-transplant lymphoproliferative disease	1; 2.90 (0.12 to 68.2)	1; 0.34 (0.01 to 8.33)	No data	2; 1.01 (0.11 to 9.51)
Bacterial infections	1; 0.67 (0.33 to 1.38)	1; 0.72 (0.44 to 1.17)	1; 0.27 (0.07 to 1.05)	3; 0.65 (0.44 to 0.96)
Fungal infections	1; 1.30 (0.31 to 5.39)	2; 0.28 (0.07 to 1.12)	No data	3; 0.58 (0.19 to 1.73)
Protozoal infections	No data	2; 0.31 (0.01 to 0.99)	No data	2; 0.31 (0.01 to 0.99)
Leucopenia[a]	No data	3; 0.99 (0.37 to 2.65)	1; 1.05 (0.62 to 1.78)	
Creatinine > 200 µmol/L[a]	2; 1.14 (0.27 to 4.70)	3; 2.36 (0.91 to 6.15)	No data	
Hallucinations[a]	1; 10.6 (0.62 to 183.3)	1; 1.59 (0.98 to 2.58)	1; 8.78 (2.69 to 28.7)	

[a]Placebo-controlled RCTs only.
^Heterogeneity of study results present.

Table 3. Effects of antiviral medication on CMV disease and all-cause mortality

Recipient group	Without prophylaxis[1]	With prophylaxis[2]	Number prevented	Number with harms[3]
CMV disease 1. Kidney[a] 2. Kidney[a]; liver^; heart[a] 3. Liver, heart[a]; all^, antibody therapy included in immunosuppressive regimen	1. 7/100 2. 28/100 3. 59/100	1. 3/100 2. 12/100 3. 25/100	1. 4/100 2. 16/100 3. 39/100	1. 7/100 2. 7/100 3. 7/100
All-cause mortality 1. Kidney 2. Liver 3. Heart or lung	1. 6/100 2. 20/100 3. 24/100	1. 4/100 2. 13/100 3. 15/100	1. 2/100 2. 7/100 3. 9/100	1. 7/100 2. 7/100 3. 7/100

[1]Data from references.
[2]Calculated from summary estimates of RR (0.42 for prevention of CMV disease, 0.63 for all-cause mortality).
[3]Based on proportion of patients, treated with valaciclovir, who developed hallucinations.
[a]Donor positive or negative for CMV; recipient negative.
^Donor positive recipient negative for CMV.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Cytomegalovirus, this term only in MeSH products 2. MeSH descriptor Cytomegalovirus Infections explode all trees in MeSH products

(Continued)

	3. MeSH descriptor Cytomegalovirus Vaccines explode all trees 4. cytomegalovirus* in All Fields in CENTRAL 5. cmv* in All Fields in CENTRAL 6. (#1 OR #2 OR #3 OR #4 OR #5) 7. (organ or renal or kidney or heart or lung or liver or pancreas) adj transplant in All Fields in all products 8. MeSH descriptor Organ Transplantation, this term only 9. MeSH descriptor Heart Transplantation explode all trees 10. MeSH descriptor Lung Transplantation explode all trees 11. MeSH descriptor Kidney Transplantation, this term only 12. MeSH descriptor Liver Transplantation, this term only 13. MeSH descriptor Pancreas Transplantation, this term only 14. (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) 15. (#6 AND #14)
MEDLINE (OVID SP)	1. Cytomegalovirus/ 2. exp Cytomegalovirus Infections/ 3. Cytomegalovirus Vaccines/ 4. cytomegalovirus.tw. 5. cmv.tw. 6. or/1-5 7. Organ Transplantation/ 8. exp Heart Transplantation/ 9. exp Lung Transplantation/ 10. Kidney Transplantation/ 11. Liver Transplantation/ 12. Pancreas Transplantation/ 13. ((organ or renal or kidney or heart or lung or liver or pancreas) adj transplant$).tw. 14. or/8-13 15. 6 and 14
EMBASE (OVID SP)	1. exp CYTOMEGALOVIRUS/ 2. Cytomegalovirus Infection/ 3. Cytomegalovirus Antibody/ 4. Cytomegalovirus Vaccine/ 5. cytomegalovirus.tw. 6. CMV.tw. 7. or/1-6 8. exp organ transplantation/ 9. ((organ or renal or kidney or heart or lung or liver or pancreas) adj transplant$).tw. 10. or/8-9 11. 7 and 10

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
3 January 2013	New search has been performed	New studies included
3 January 2013	New citation required and conclusions have changed	Risk of bias assessment incorporated

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2005

Date	Event	Description
18 March 2010	Amended	Contact details updated.
13 May 2009	Amended	Contact details updated.
13 August 2008	Amended	Converted to new review format.

Date	Event	Description
7 January 2008	New citation required and conclusions have changed	Substantive amendment, 6 additional publications identified, 2 new studies included
16 October 2004	Amended	Title changed. Background, methods edited to reflect limitation of review to prophylaxis with antiviral medication. Quality assessment criteria added.

CONTRIBUTIONS OF AUTHORS

Review update in 2013

- EMH, ML, ACW and JCC contributed to the data extraction, quality assessment, data analysis and rewriting of the review update.

Review update in 2008

- EMH, ACW, JCC, GFMS contributed to the data extraction, quality assessment, data analysis and rewriting of the review update.

Original review 2005

- EMH identified and extracted data from included studies, contacted authors, analysed and interpreted the results and wrote the manuscript.
- CAJ conceived, designed and developed the protocol and search strategy for the review, identified and extracted data from included studies and participated in revision of the manuscript.
- ACW analysed and interpreted the results and participated in the revision of the manuscript.
- GFMS checked the analysis and interpretation of the results and participated in the revision of the manuscript.
- PGB and KK identified and extracted data from included studies and participated in revision of the manuscript.
- DV developed the protocol and search strategy for the review.
- JCC conceived, designed and developed the protocol, analysed and interpreted the results and edited the drafting and revision of the manuscript.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Organ Transplantation; Acyclovir [analogs & derivatives] [therapeutic use]; Antiviral Agents [adverse effects] [*therapeutic use]; Cytomegalovirus Infections [*prevention & control]; Ganciclovir [therapeutic use]; Randomized Controlled Trials as Topic; Valacyclovir; Valine [analogs & derivatives] [therapeutic use]

MeSH check words

Humans