

General comments:

The reviewer appreciates that in the revised manuscript the authors tried to address the concerns raised during the first reviewing process, e.g. Figure 2 improved greatly. However, there are still a number of points, which should be addressed before the review is suitable for publication in Viruses. The reviewer is still of the opinion that many sections could be presented in a more structured manner. Also, several references are still missing/incorrect (see specific comments).

Specific comments:

Line 18: should read “chronic state of infection” → delete “a”

Line 28: should read “Human cytomegalovirus” → delete “the”

Line 28: should read “virus **either** existing”

Line 29: should read “**in** immunocompromised patients → add “in”

Line 71: should read “particle **with a** diameter” → add “with a”

Lines 76-77: what is meant by “and to its replication” – viral replication? – please clarify

Line 77: reference [13] doesn’t seem appropriate as it summarizes HCMV tegument proteins but not glycoproteins

Line 81: should read “UL131” → without hyphen

Figure 1: Why are there two identical viral particles → delete the upper one and keep the larger version at the bottom. The glycoprotein complexes should be drawn outside of the lipid envelope (anchored to the outer lipid membrane). Abbreviations like gC-II, TC, gC-I and PC should be explained in the figure legend.

Line 95: should read “HCMV” → delete “the”

Line 96: Exchange the term “cells” by virions or virus particles

Lines 160-161: what is meant by “Viral DNA replication is mediated by ganciclovir-5’-triphosphate (ganciclovir-TP).” → please clarify

Lines 166-169: Citations are missing

Lines 177-179: Citation is missing

Line 217: delete one “in”

Lines 217-218: what is meant by “in early haematopoietic stem cell transplant” → please clarify

Line 238: should read “plays a critical role”

Line 239: should read “packaging **of**” → add “of”

Lines 239-240: what is meant by “which are transported to the nucleus of the host cell for replication”
→ please clarify

Line 242: should read “prevents”

Lines 244-245: should read “binding **of**” → exchange “with” by “of”

Line 245: exchange “Pul56” by “pUL56”

Line 245: should read “reduces”

Line 250: should read: “humans”

Line 251: should read: “without **significant** side”

Line 254: what is meant by “capsids are transported to the nucleus of the host cell for replication” → please clarify

Lines 266-267: what do the abbreviations VPD and VCD stand for

Line 271: should read “unreported” → without hyphen

Line 272: should read “**HCMV**” → abbreviations should be consistent throughout the manuscript

Lines 273-275: The last sentence of this passage does not provide novel information and is identical to the preceding sentence → please delete

Line 280: reference [47] is incorrect!! → This publication is a case report where leflunomide **failed** to control recurrent HCMV infection in the setting of renal failure after **allogeneic stem cell transplantation** and not after renal transplantation. Effective leflunomide therapy for HCMV disease has been reported in the following publications: <https://pubmed.ncbi.nlm.nih.gov/15489872/> and <https://pubmed.ncbi.nlm.nih.gov/15167608/>.

Line 284: should read „stem cell **transplant** recipients” → without “s”

Lines 289-293: First sentence of this passage needs to be revised.

Table 1: In the major toxicity column of ganciclovir it should read “bone marrow **suppression**” and bone marrow **suppression** of letermovir is missing a “p”

Line 349: should read: “polyadenylation” → delete one “yl”

Line 351: should read “shuts down”

Lines 351-352: should read “proteins”

Line 358: *in vitro* and *in vivo* should be written in *italics* throughout the text

Lines 372-374: First sentence of this passage needs to be revised.

Line 384: should read “and **a** multiplex” → add “a”

Line 402 should read “antivirals” → add “s”

Lines 427-429: TALEN-based antiviral strategies have shown promise in laboratory studies with MCMV... → reference is missing

Lines 434-437: What is meant by aptamers have been used for targeting viral envelopes? → please clarify

Lines 441-442: should read “(-550 to -750 **bp**) and (-750 to -1140 **bp**) → please add “bp”

Figure 2 is generally hard to read, please enlarge the text.

Line 446: should read “UL102” instead of UL1O2

Line 451: The reviewer would not call figure 2 a diagram but e.g. a schematic illustration.

Line 460: should read “reduction of viral plaque **formation/count/numbers**”

The reviewer thinks that paragraph “4. Cytomegalovirus vaccines” should be switched to 3. so that “Possible alternative strategies to combat HCMV infection” represents the last paragraph of the manuscript as this is the major focus of this review.

Line 492: should read “**neutralizing** antibodies”

Line 500: should read “RNA-based”

Lines 497-501: Reference is missing for the first sentence of this passage.

Lines 502-503: “Initially, gB seemed a perfect choice, but trials showed limited efficacy.” → reference is missing

Line 504: exchange “**the**” HCMV vaccine by “**an**” HCMV vaccine

Line 505: should read “**into** host cells”

Line 530: ensure uniform spelling of “*in vitro*” and “*in vivo*” throughout the manuscript