# Analysis of Maribavir and Brincidofovir, Antibiotic Treatments, for Cytomegalovirus Infection in Postoperative Renal Transplant Patients

Lydia Sheppard AP Research STEM

# Introduction

# Cytomegalovirus (CMV)

- Cytomegalovirus infection (CMV) is a double stranded Deoxyribonucleic acid (DNA) virus
- Concern for those with a weakened immune system
- Requires antiviral treatment

# Cytomegalovirus (CMV)

Diseases caused by CMV:

- Retinitis
- Hepatitis
- Colitis
- Pneumonia
- Encephalitis

# Direct/Indirect Consequences from CMV

**Direct:**

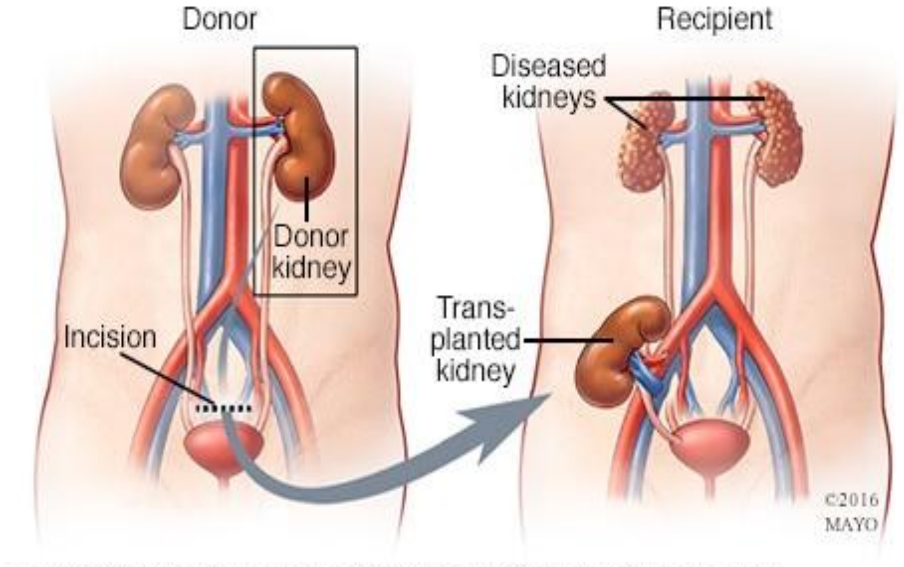
- CMV pneumonia
- Viral syndrome
- Organ involvement

**Indirect:**

- Risk of fungal and GNB infections
- Risk of acute rejection and graft injury
- Substantial healthcare expenses

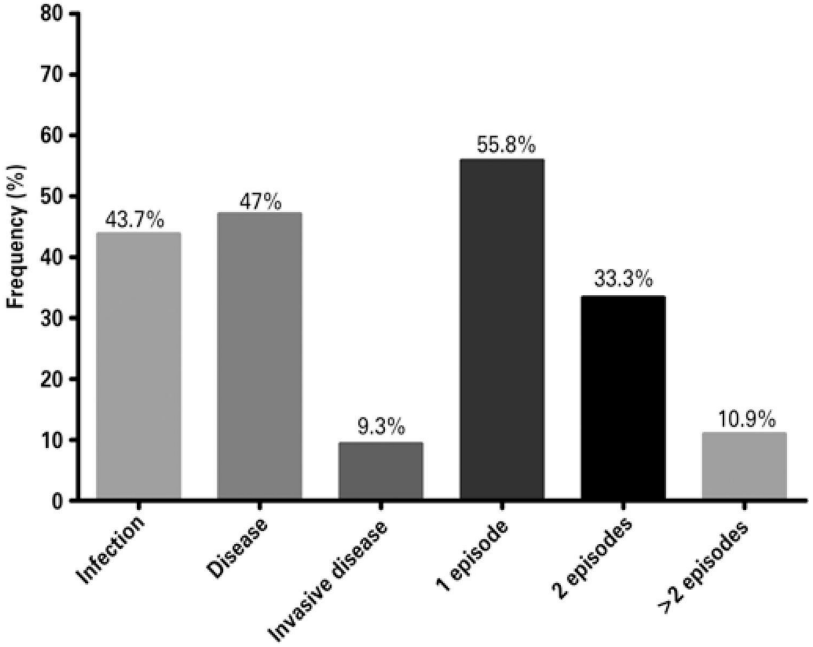
# Renal Transplant

- Approximately 17,878 each year in the U.S.
- Patients with end stage renal failure
- Donor can pass CMV to recipient



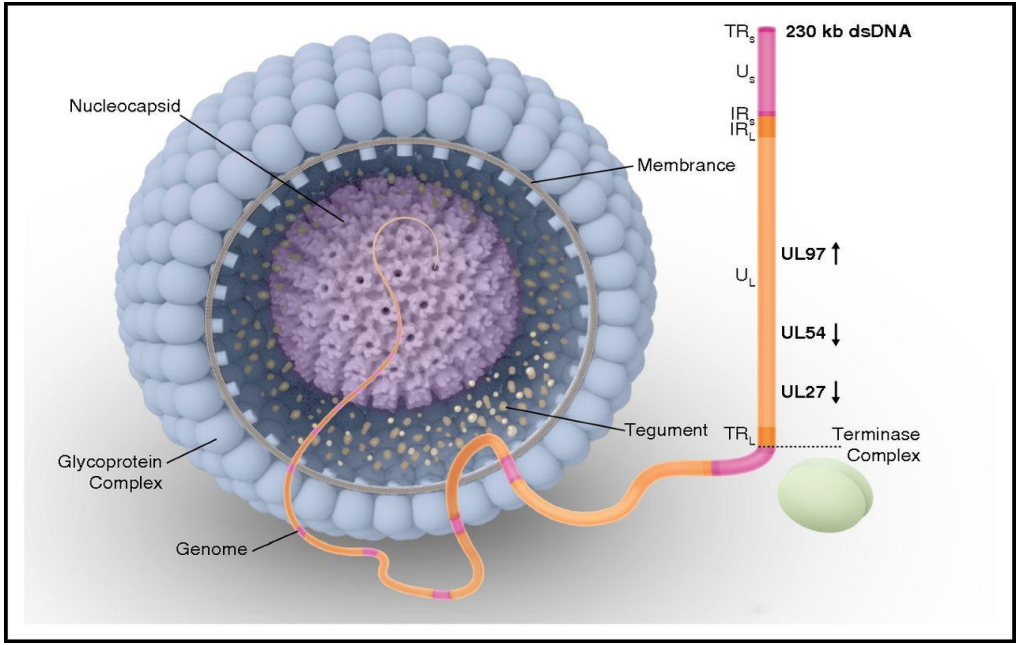
# Cytomegalovirus Infection

- CMV transmission from reactivation of latent infection or after a primary infection in seronegative patients
- CMV infection occurs between 30 and 90 days after transplantation



# CMV Within the Cell

- Virus infects certain segments of DNA
- CMV infection is the most common infection after a solid organ transplant
- Antigen resistant effects with treatments



# Substantial Risks of CMV

- Prolonged antiviral CMV drug exposure
- Inadequate antiviral absorption and bioavailability
- Rise in CMV viral load after initial decline with treatment
- Congenital immunodeficiency syndromes

# CMV Treatment Options

- Ganciclovir (GCV)
- Leflunomide (LEF)
- Foscarnet (FOS)
- Valganciclovir (ValGCV)

- Patients are or become resistant to the antigen within the treatment due to bacteria unable to survive and regenerate

| Patient No. | Age (years)/ Gender | CMV Serostatus | Months Post Transplantation | Months Since First CMV+ | CMV Organ Disease | Prior CMV Treatment | Known Genotypic Resistance (to) |
|---|---|---|---|---|---|---|---|
| 1 | 39/ Female | D+/R- | 12 | 11 | Glomerulitis, retinitis | ValGCV, FOS, CMVIg, CDV, LEF | Yes (GCV) |
| 2 | 65/Male | D+/R- | 16 | 11 | Pneumonia | ValGCV, GVC, FOS, LEF, CMVIg | Yes (GCV) |
| 3 | 68/ Female | D+/R- | 33 | 30 | Duodenitis, retinitis | ValGCV, GCV, FOS, IVIg, CDV | Yes (GCV, FOS, CDV) |
| 4 | 44/Male | D+/R- | 17 | 8 | - | GCV, FOS, CMVIg, ValGCV | Yes (GCV, FOS) |
| 5 | 47/Male | D+/R- | 5 | 1.5 | Enteritis | GCV, ValGCV, FOS, LEF, CMVIg | No |
| 6 | 68/ Female | D+/R- | 26 | 6 | CMV Retinitis | ValGCV, GCV, FOS, CDV | Yes (GCV, FOS, CDV) |
| 7 | 44/ Male | D+/R- | 9 | 6 | Early rejection of Transplant | ValGCV, CMVIg, GCV, FOS | Yes (GCV, FOS) |

# Purpose & Methods

# Purpose

- Evaluate different treatments for CMV
- Minimize resistance, thus minimizing recurrence

- Antigens:
  - Maribavir (MBV)
  - Brincidofovir

# Research Question

- **Is Maribavir more effective than Brincidofovir as cytomegalovirus treatment for postoperative renal transplant patients?**

- Investigate effect of treatments on the mortality and morbidity rate in patients, and differing mutation levels

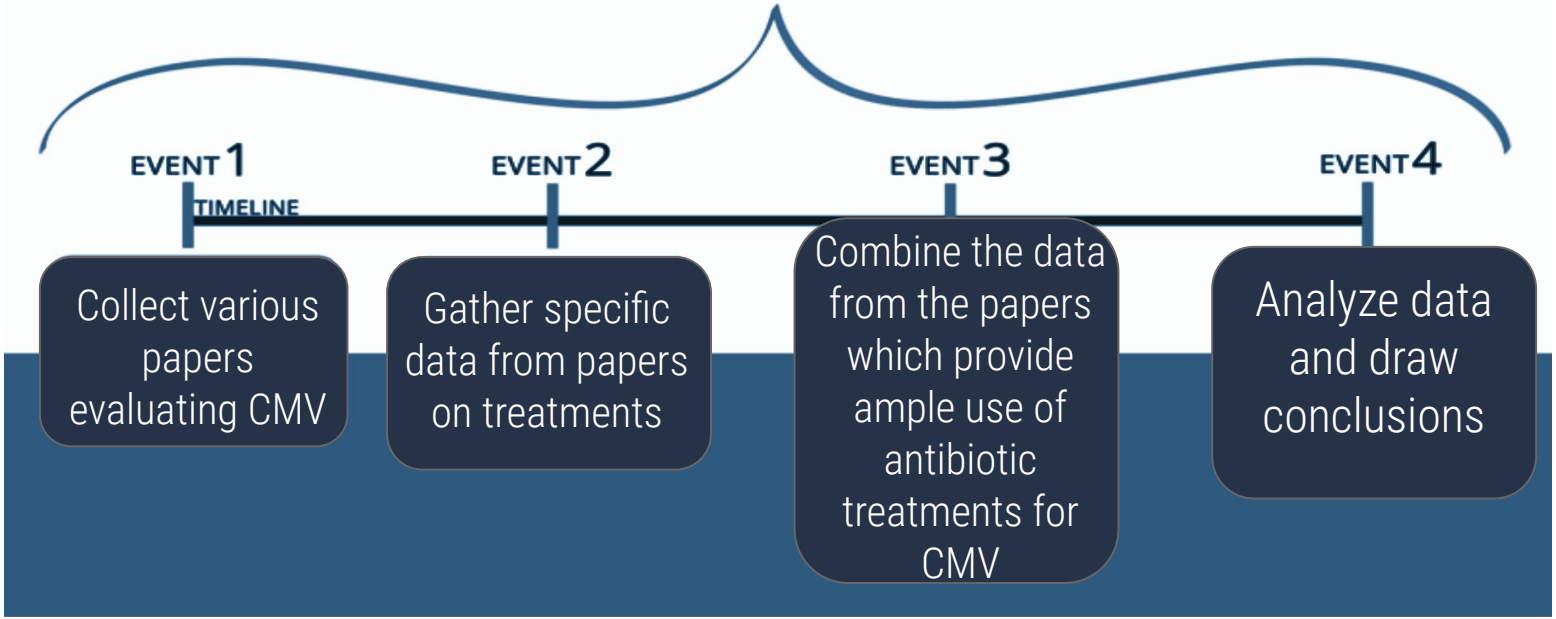
# Hypothesis

Alternative: Maribavir will provide postoperative renal transplant patients with a more successful overall outcome including lower recurrence rates and less drug resistance.

Null: Maribavir and brincidofovir treatment has no significant improvement providing patients with less recurrence of CMV.

# Methods

## Systematic Literature Review



# Results

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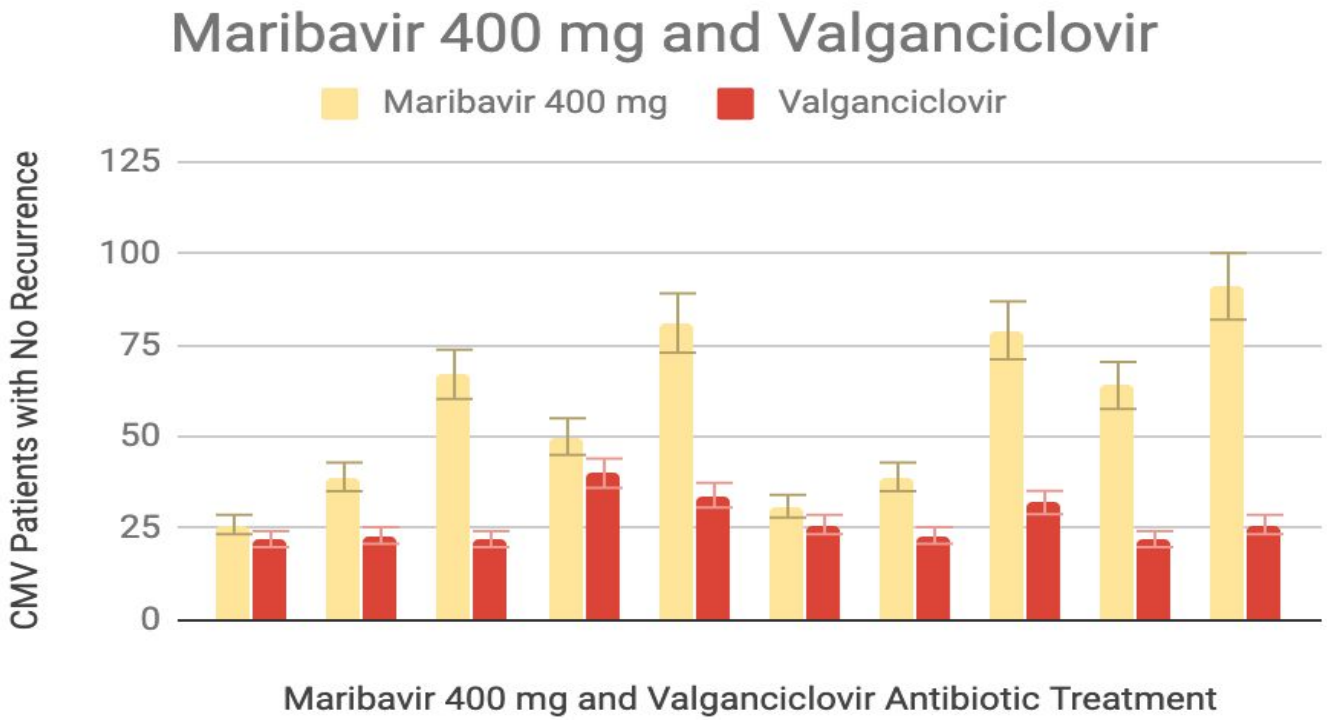
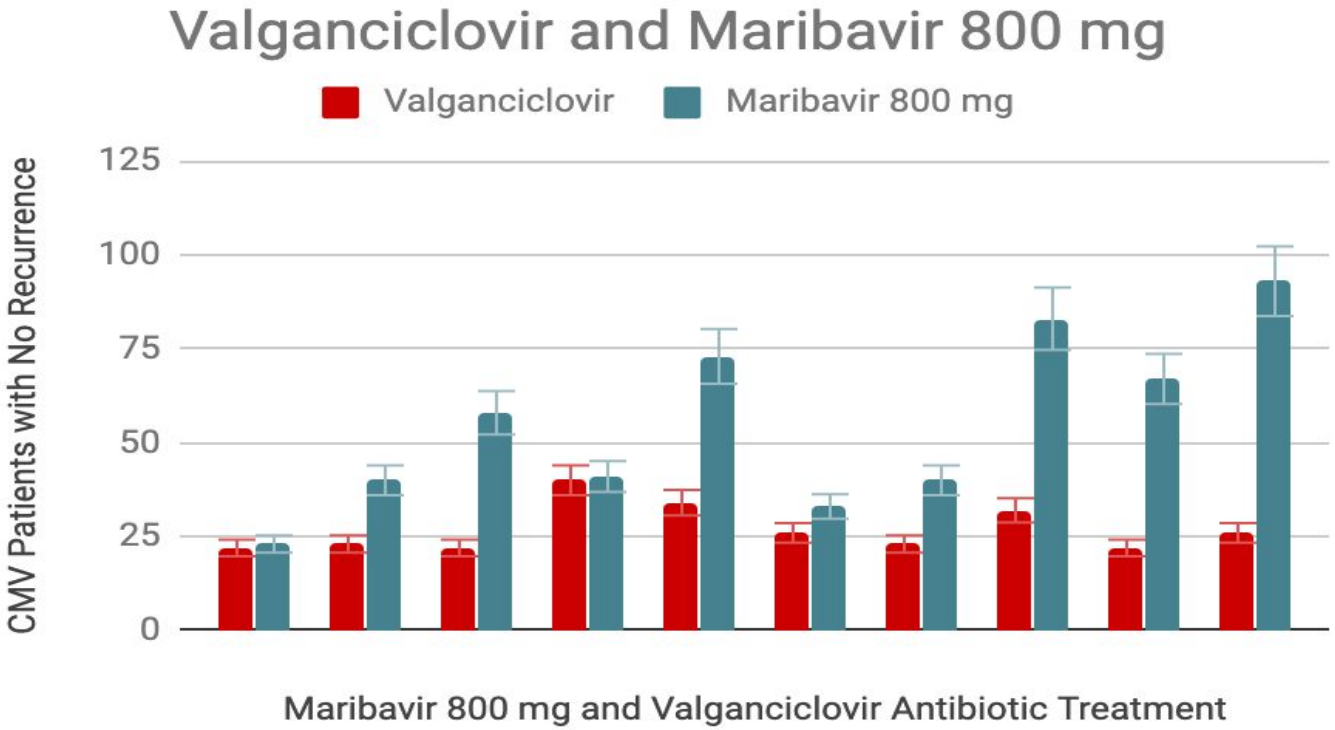


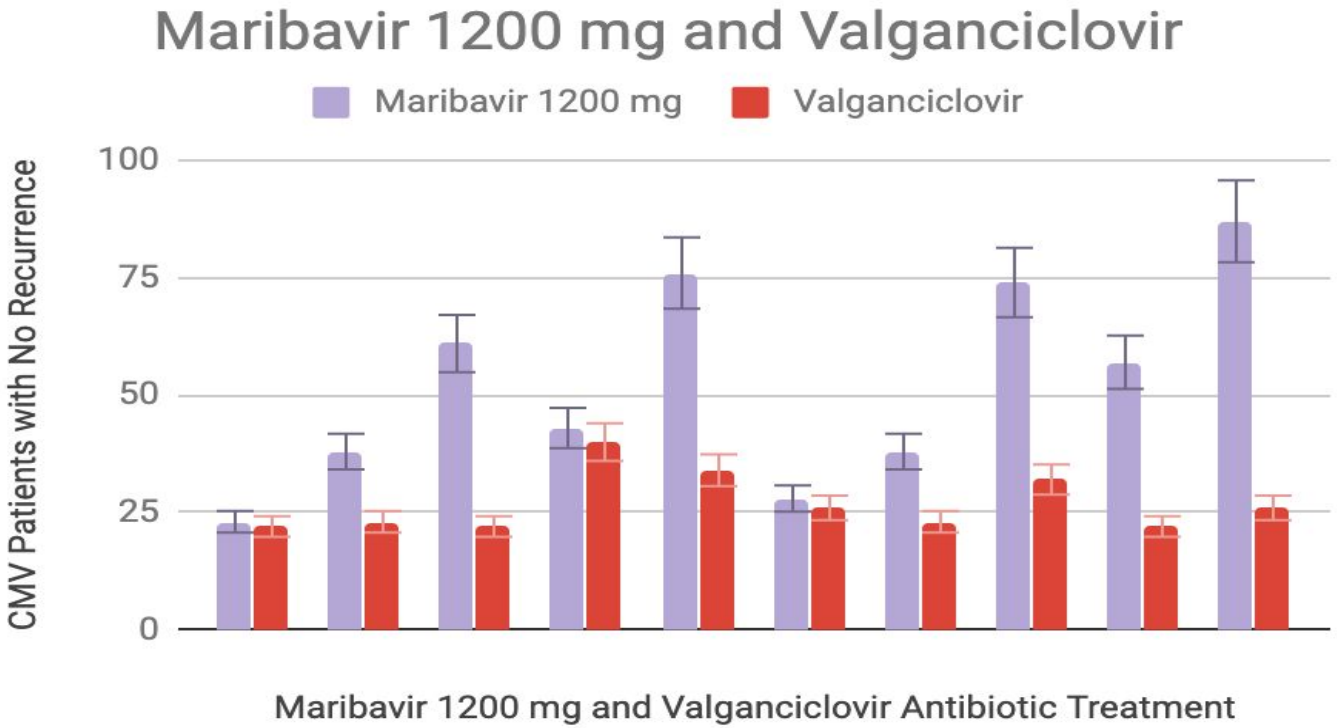

T-test result:
0.001< 0.05

# Results



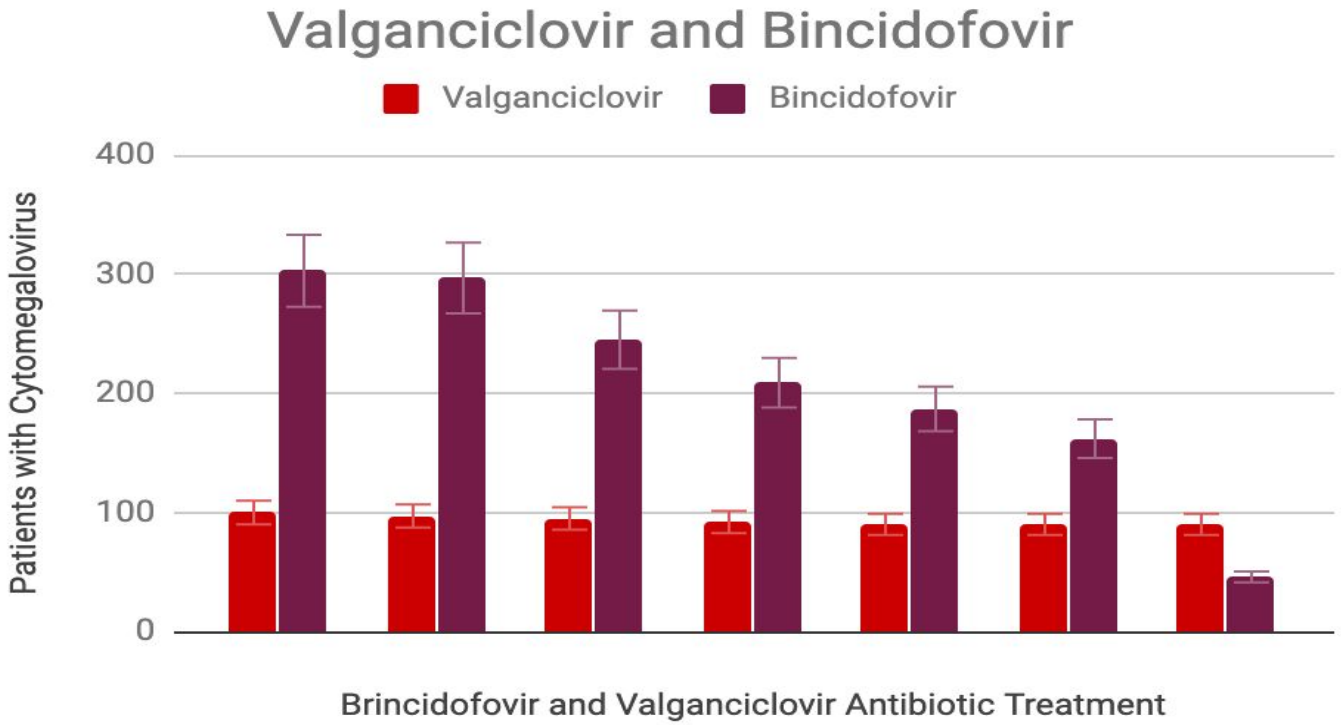

T-test result:
0.002<0.05

# Results



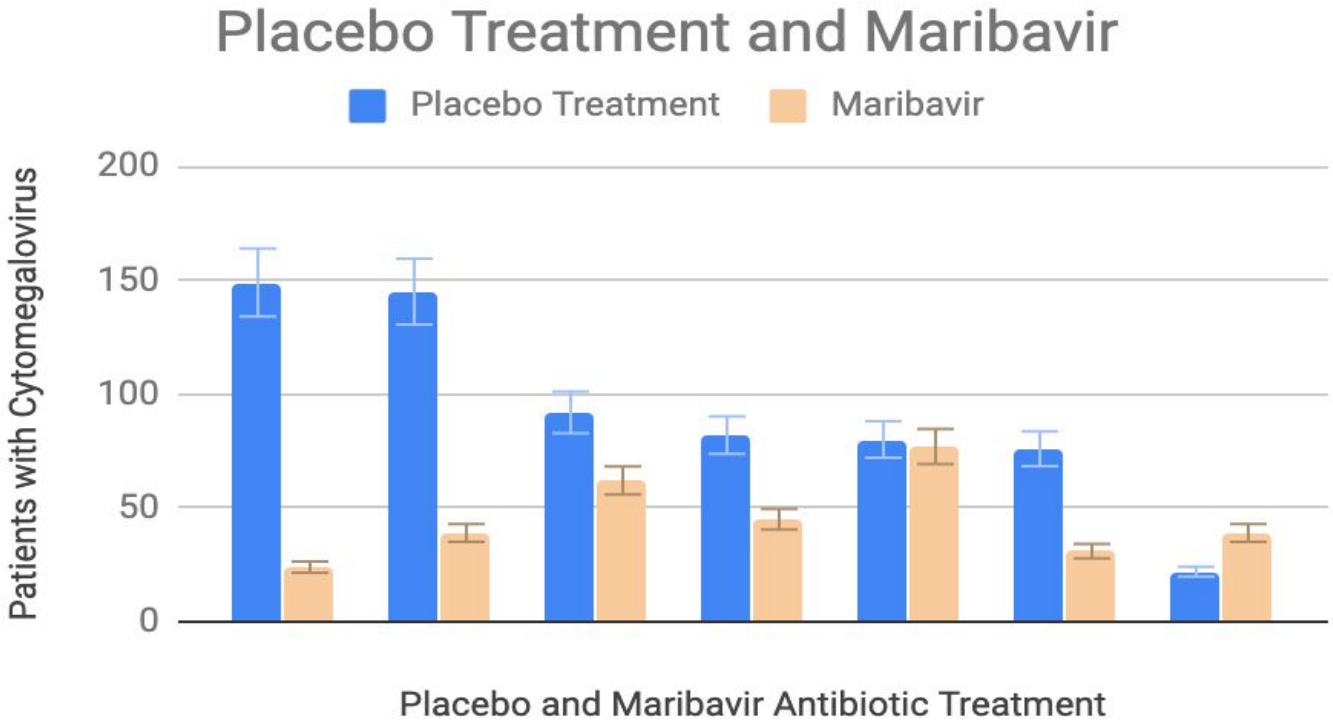

T-test result:
0.002<0.05

# Results



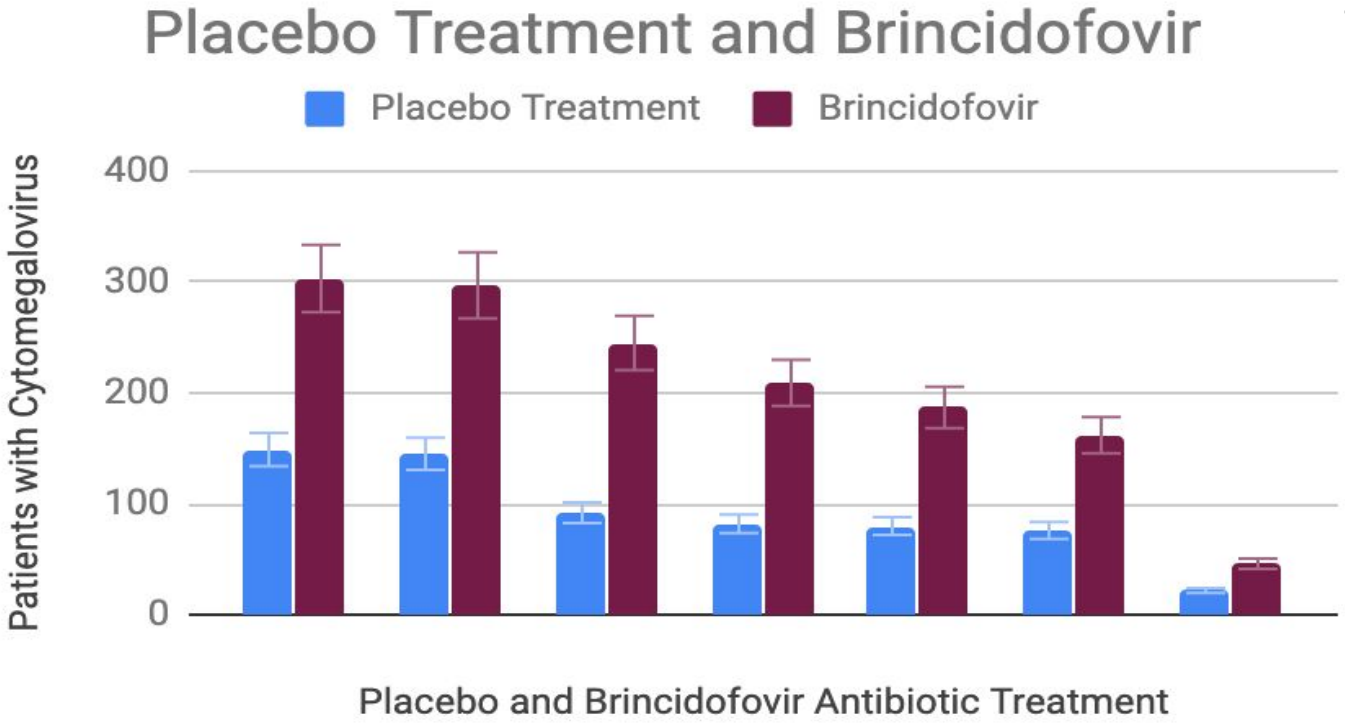

T-test result:
0.007<0.05

# Results




T-test result: 0.02<0.05

# Results




T-test result: 0.007<0.05

# Discussion

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- Accept alternative hypothesis with 95% confidence

With no clinically significant CMV:

- MBV 400 mg range: 26 to 91 patients
- ValGCV range: 22 to 40 patients

With clinically significant CMV:

- Brincidofovir range: 46 to 303 patients
- Placebo range: 22 to 149 patients

# Conclusion

# Conclusions

- MBV is most effective antibiotic for SOT CMV patients
- MBV resistance rates are far lower than treatment of Brincidofovir

# Conclusions

- MBV Inhibits the viral UL97 kinase, an antiviral mechanism which differs from ValGCV
- MBV eliminates resistance strains, while treating CMV

# Limitations

- Limited data with the MBV and brincidofovir antibodies
- Treatment procedures change between patients due to bodies reaction to CMV and the treatment

# Further Work

- Review more antibiotic treatments being proposed for CMV
- Focus on pretreatment, preventing CMV before transplant
- Using multiple treatments to find if a synthesis is more productive

# Acknowledgments

I would like to thank Dr. Camille Kotton, Dr. Maureen Metzger, as well as Dr. Nikki Malhotra for their support throughout the research process.

# References


- Ardalan, M. R., et al., (2009). Transplant renal artery stenosis associated with acute cytomegalovirus infection: Resolution following ganciclovir administration. *Renal Failure*, *31*(10), 982–984. Retrieved from https://doi.org/10.3109/08860220903288526
- Avery, R.k., et al., (2010). Oral maribavir for treatment of refractory or resistant cytomegalovirus infections in transplant recipients. *Transplant Infectious Disease, 12*(6), 489–496. doi:10.1111/j.1399-3062.2010.00550.x.
- Chon, W. J., et al., (2015). Use of leflunomide in renal transplant recipients with ganciclovir-resistant/refractory cytomegalovirus infection: A case series from the University of Chicago. *Case Reports in Nephrology & Dialysis*, *5*(1), 96–105. Retrieved from https://doi.org/10.1159/000381470
- Chou, Sunwen, et al., (2018). Antiviral activity of maribavir in combination with other drugs active against human cytomegalovirus. *Antiviral Research*, *157*, 128–133. doi:10.1016/j.antiviral.2018.07.013.
- Jones, D. C., et al. (2014). Killer immunoglobulin-like receptor gene repertoire influences viral load of primary human cytomegalovirus infection in renal transplant patients. *Genes & Immunity*, *15*(8), 562–568. Retrieved from https://doi.org/10.1038/gene.2014.53
- Kotton, Camille N., et al., (2018). The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation, 102*(6), 900–931. doi:10.1097/tp.0000000000002191.
- Kranz, B., et al., (2008). Acute rejection episodes in pediatric renal transplant recipients with cytomegalovirus infection. *Pediatric Transplantation*, *12*(4), 474–478. Retrieved from https://doi.org/10.1111/j.1399-3046.2007.00781.x
- Manuel, K. et al., (2014). Prevalence of cytomegalovirus and bk polyomavirus infections in post-renal transplant patients.: Abstract# D2427 *Wolters Kluwer Health, 98*(261), n.p. Retrieved from https://journals.lww.com/transplantjournal/Fulltext/2014/07151/Prevalence_of_Cytomegalovirus_and_BK_Polyoma_Virus.797.aspx

# References


- Marty, Francisco M., et al., (2013) CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. *New England Journal of Medicine, 369*(13), 1227–1236. doi:10.1056/nejmoa1303688.
- Marty, Francisco M., et al., (2017). Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation." *New England Journal of Medicine, 377*(25), 2433–2444. doi:10.1056/nejmoa1706640.
- Menghi, V., et al., (2016). Ganciclovir-resistant cytomegalovirus infection in a kidney transplant recipient successfully treated with foscarnet and everolimus. *Case Reports in Nephrology*, 1–4. Retrieved from https://doi.org/10.1155/2016/2736805
- Ozaki, K. S., et al., (2007). The use of sirolimus in ganciclovir-resistant cytomegalovirus infections in renal transplant recipients. *Clinical Transplantation*, *21*(5), 675–680. Retrieved from https://doi.org/10.1111/j.1399-0012.2007.00699.x
- Pavlopoulou, I. D., et al., (2005). A comparative randomised study of valacyclovir vs. oral ganciclovir for cytomegalovirus prophylaxis in renal transplant recipients. *Clinical Microbiology & Infection*, *11*(9), 736–743. Retrieved from https://doi.org/10.1111/j.1469-0691.2005.01215.x
- Strasfeld, Lynne, et al., (2010). Virologic characterization of multidrug-resistant cytomegalovirus infection in 2 transplant recipients treated with maribavir. *The Journal of Infectious Diseases*, *202*(1), 104–108. doi:10.1086/653122.
- Tornatore, K. M., et al., (2001). Ganciclovir pharmacokinetics and cytokine dynamics in renal transplant recipients with cytomegalovirus infection. *Clinical Transplantation*, *15*(5), 297–308. Retrieved from https://doi.org/10.1034/j.1399-0012.2001.150501.x
- Turgeon, N., Fishman, J. A., Doran, M., Basgoz, N., Tolkoff-Rubin, N. E., Cosimi, A. B., & Rubin, R. H. (2000). Prevention of recurrent cytomegalovirus disease in renal and liver transplant recipients: Effect of oral ganciclovir. *Transplant Infectious Disease*, *2*(1), 2–10. Retrieved from https://doi.org/10.1034/j.1399-3062.2000.020102.x

# References


- Winston, D. J., et al., (2012). Efficacy and safety of maribavir dosed at 100 mg orally twice daily for the prevention of cytomegalovirus disease in liver transplant recipients: A randomized, double-blind, multicenter controlled trial. *American Journal of Transplantation, 12*(11), 3021–3030. doi:10.1111/j.1600-6143.2012.04231.x.
- Witzke, O., et al. (2012). Valganciclovir prophylaxis versus preemptive therapy in cytomegalovirus-positive renal allograft recipients: 1-year results of a randomized clinical trial. *Ovid, 93*(1), 61-68. doi: 10.1097?TP.0b013e318238dab3Ardalan, M. R., et al., (2009). Transplant renal artery stenosis associated with acute cytomegalovirus infection: Resolution following ganciclovir administration. *Renal Failure*, *31*(10), 982–984. Retrieved from https://doi.org/10.3109/08860220903288526

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