



Decisions About Antiviral Therapy in Babies Identified by Universal Screening

Whom, When, How Long to Treat and What to Watch Out For!

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CMV Public Health and Policy Meeting

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Member – Pfizer, Endpoint Adjudication Committee, 2020-23, Maternal RSV Vaccine Trial
- Stock – Pfizer, Bristol Myers Squibb, Zimmer Biomet

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Valcyte (valganciclovir)

LEARNING OBJECTIVES

- Discuss the findings of key research studies evaluating antiviral treatment of infants with cCMV
- Apply these findings to a treatment approach for infants with cCMV
- Describe safety monitoring for infants receiving antiviral treatment for cCMV

Mayo cCMV Evaluation & Treatment Team

- **Pediatric Infectious Diseases**

- Annette Dauner-Olson, RN
- Holly Snyder, RN
- James Gaensbauer, MD
- Emily Levy, MD
- Theresa Madigan, MD
- Nipunie Rajapakse, MD, MPH
- Elizabeth Ristagno, MD, MPH
- Guyu Li, MD
- Mohamad Shieb, MD

- **Community Pediatrics & Family Medicine**

- Kara Fine, MD
- Jay Homme, MD
- Marla DeWitt, MD

- **Audiology** - Joscelyn Martin, AuD, MA + team

- **Ophthalmology** - Eric Bothun, MD + team

- **Radiology** - Amy Kolbe, MD + team

- **Scheduling** - Travis Jones, Damian Paulson

- **Minnesota Department of Health**

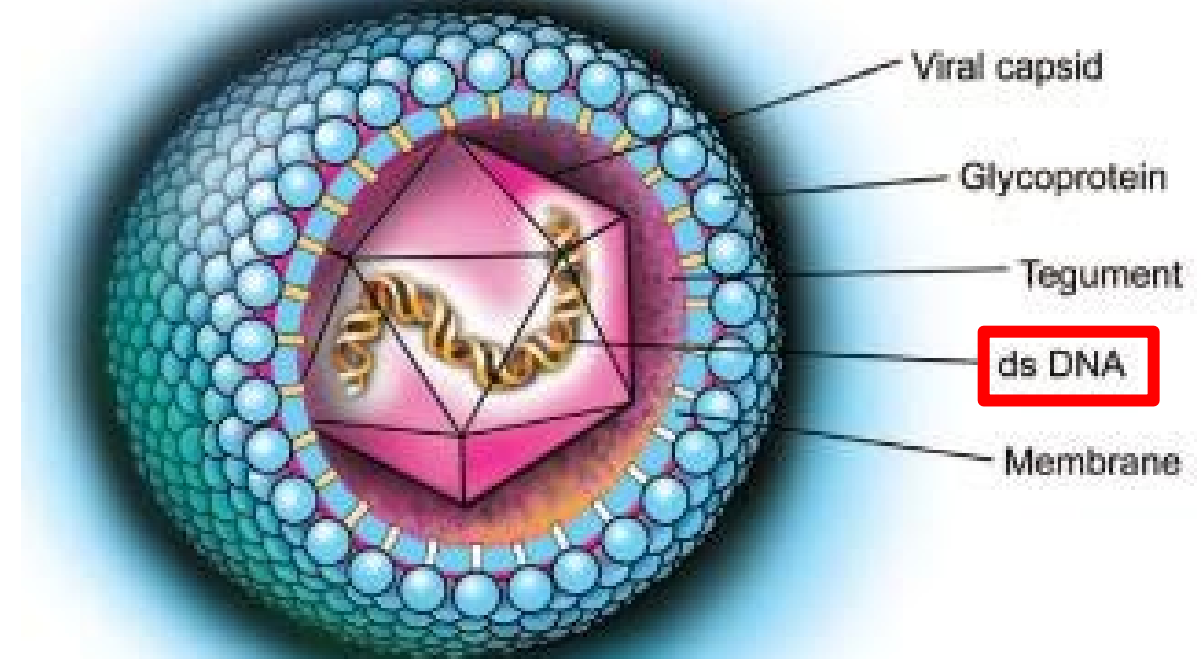
- Ruth Lynfield, MD, MPH
- Tory Kaye, MPH
- Jenna Hullerman Umar, MPH
- Gina Liverseed, DNP, APRN, PHN

- **Academic Partners at Minnesota's Children's Hospitals**

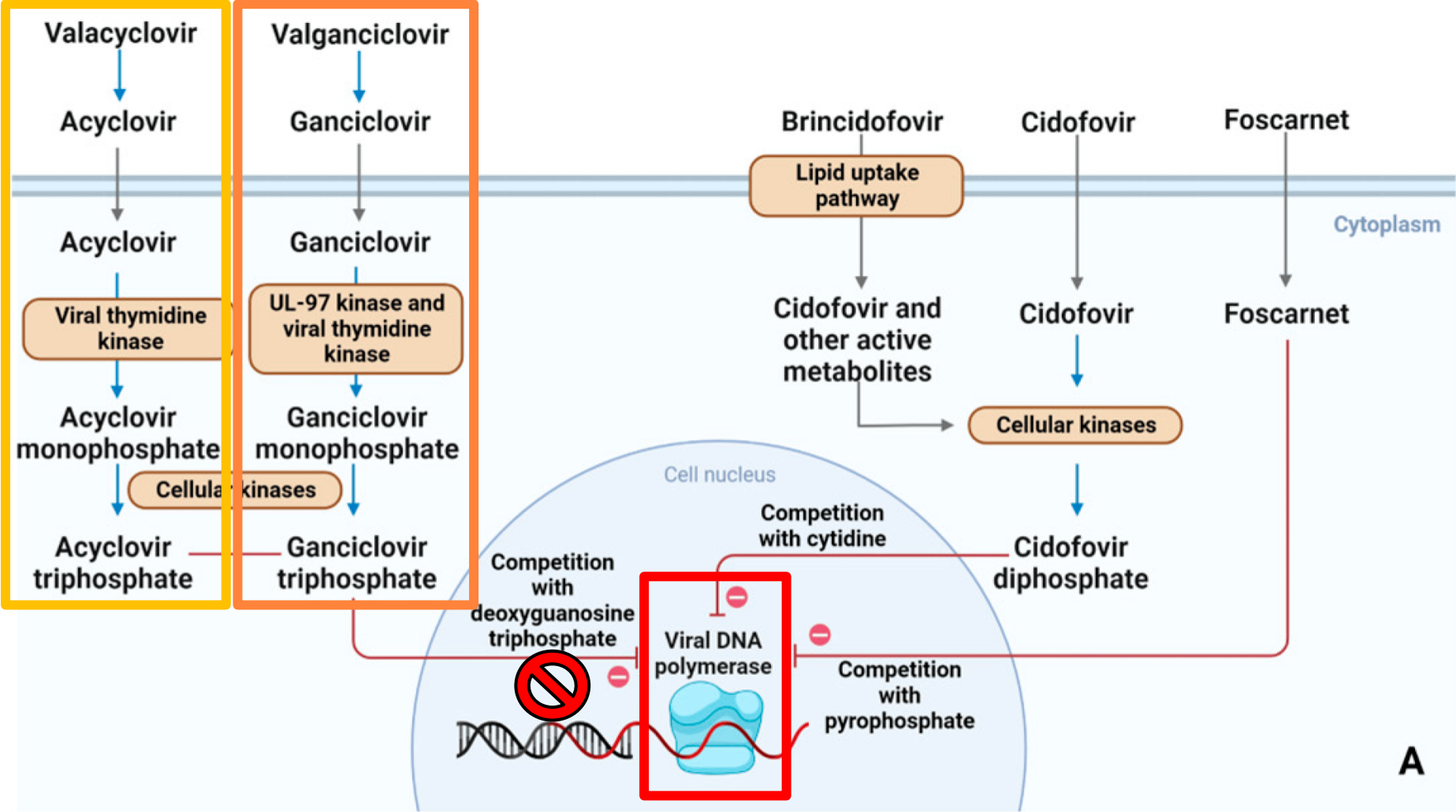
- Mark Schleiss, MD
- Emily Harrison, MD

Human Cytomegalovirus

- Member of Herpesvirus family – CMV, EBV, HSV 1/2, VZV, HSV 6, 7, & 8
- Double-stranded linear DNA
- Viral envelope glycoproteins facilitate cell attachment
- Biologic properties of latency & reactivation
- No distinct serotypes, but different genotypic strains identified by DNA analysis



Nucleoside Analogues to Inhibit Viral Replication



Huntjens DW, et al. Optimizing Antiviral Dosing for HSV and CMV Treatment in Immunocompromised Patients. *Pharmaceutics* 2023;15:163; <https://doi.org/10.3390/pharmaceutics15010163>



Whom to Treat, What With, When, & For How Long

Severity Categorization of Congenital CMV (cCMV) Infection

International Congenital CMV Recommendations Group

- **Asymptomatic infection (\pm 80%)** – no apparent abnormalities & normal hearing
- **Mildly symptomatic disease (\pm 5-10%)** – 1-2 isolated mild or transient manifestations
 - Elevated ALT
 - Thrombocytopenia
 - Mild hepatomegaly
- **Sensorineural hearing loss (SNHL) w/o other clinically apparent abnormalities (\pm 5-10%)** – Hearing loss \geq 21 decibels without other identified abnormalities
- **Moderately to severely symptomatic disease (\pm 5-10%)** – multiple manifestations
 - Skin – petechiae, extramedullary hematopoiesis (50-75%)
 - Thrombocytopenia, elevated ALT or bilirubin (40-70%)
 - Intrauterine growth restriction (40-50%)
 - Microcephaly (35-50%)
 - Hepatomegaly or splenomegaly (40-60%)
 - Sensorineural hearing loss (35-50%)
 - CNS involvement – microcephaly, radiographic abnormalities, abnormal CSF
 - Chorioretinitis

Major Sequelae of cCMV Infection

- **Sensorineural hearing loss (SNHL)**

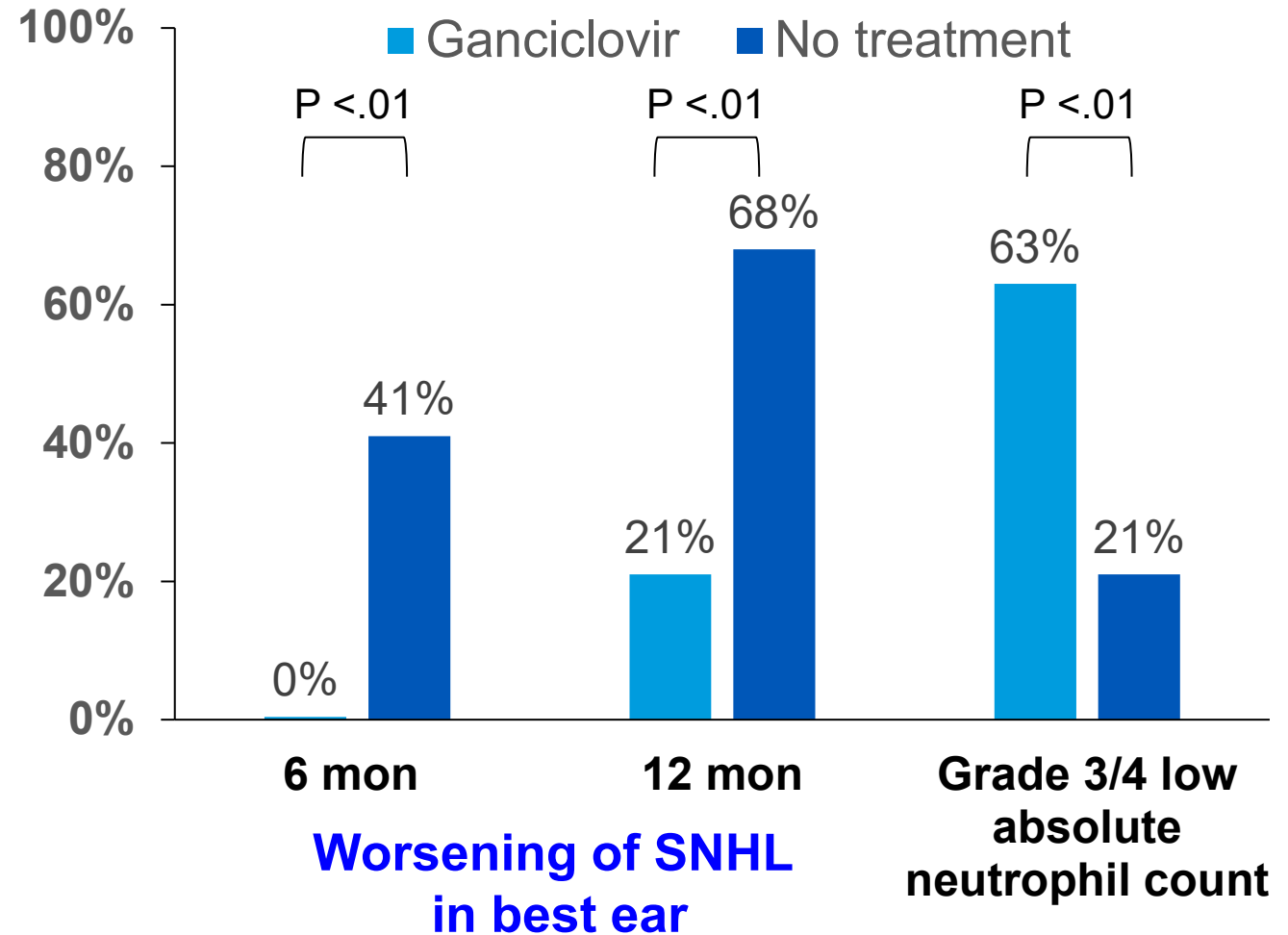
- Common in moderate to severe cCMV, especially with CNS involvement
- May progress or develop in 10-15% of infants with no hearing loss initially
- Evaluation – sequential testing of Auditory Brainstem Response (ABR)
 - “best” ear – functional assessment of effect on hearing most relevant for daily living
 - “total” ears – biological assessment of effect on cumulative hearing in both ears

- **Neurodevelopmental abnormalities**

- Cerebral palsy
- Intellectual disability
- Vision impairment
- Seizures
- Autism spectrum disorder
- Evaluation – Bayley Scales of Infant & Toddler Development (Bayley-III)

6-weeks of IV Ganciclovir Administered via CVC vs. No Treatment of cCMV with CNS Involvement

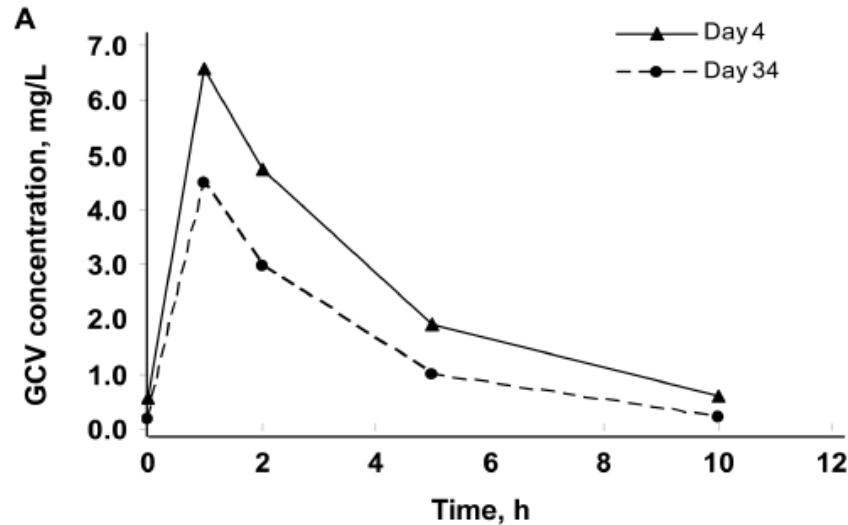
- 1991-1999
- 18 sites in the NIH-funded Collaborative Antiviral Study Group (CASG)
- 100 infants
 - 42 met all study criteria w/baseline & 6 mon ABR
 - 25 ganciclovir started w/in 1 month of life
 - 17 no treatment
 - 53 nonevaluable
 - more likely to be born prematurely or racial identification as black



Kimberlin DW, et al. J Pediatr 2003;143:16-25

Pharmacokinetic & Pharmacodynamic Evaluation of IV Ganciclovir vs. Oral Valganciclovir Treatment for cCMV

IV ganciclovir
5 mg/kg/dose



Oral valganciclovir
16 mg/kg/dose

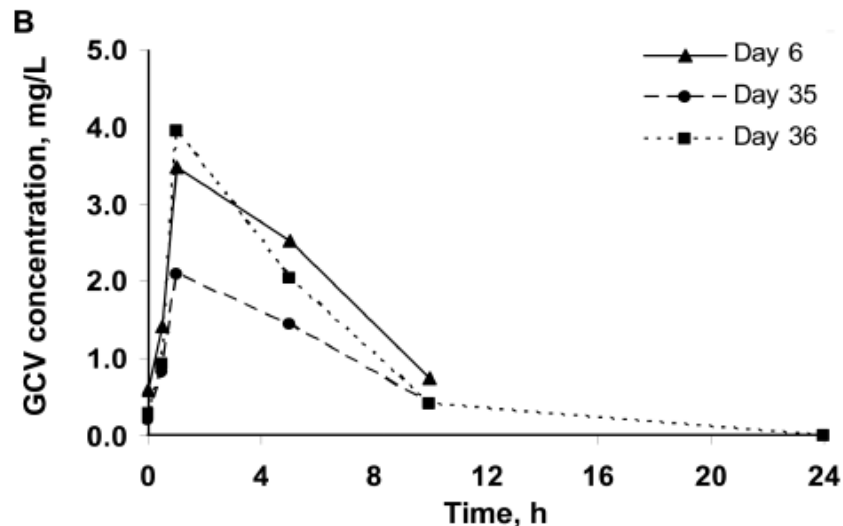


Table 4. Development of grade 3 or 4 toxicities during therapy (from baseline grades of 0, 1, or 2).

Laboratory determination	Subjects, no. (%) (n = 24)
Hemoglobin	3 (13)
Platelet count	0 (0)
White blood cell count	0 (0)
Absolute neutrophil count	9 (38)
Serum creatinine level	0 (0)
ALT level	1 (4)
AST level	0 (0)
Total bilirubin	1 (4)

Kimberlin DW, et al. J Infect Dis 2008; 197:836-45

6 Months vs. 6 Weeks of Valganciclovir for Treatment of Moderate to Severe cCMV Disease

Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, N. Ashouri, J.A. Englund, B. Estrada, R.F. Jacobs, J.R. Romero, S.K. Sood, M.S. Whitworth, M.J. Abzug, M.T. Caserta, S. Fowler, J. Lujan-Zilbermann, G.A. Storch, R.L. DeBiasi, J.-Y. Han, A. Palmer, L.B. Weiner, J.A. Bocchini, P.H. Dennehy, A. Finn, P.D. Griffiths, S. Luck, K. Gutierrez, N. Halasa, J. Homans, A.L. Shane, M. Sharland, K. Simonsen, J.A. Vanchiere, C.R. Woods, D.L. Sabo, I. Aban, H. Kuo, S.H. James, M.N. Prichard, J. Griffin, D. Giles, E.P. Acosta, and R.J. Whitley, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

6 Months vs. 6 Weeks of Valganciclovir for Moderate to Severe cCMV Disease

- Randomized controlled blinded trial
- Dose: 16 mg/kg/dose twice a day, started w/in 1 month of age
- Relatively small study
 - 6 weeks – 49 subjects
 - 6 months – 47 subjects
- 48% of infants were premature
- Extent of cCMV disease
 - 66% CNS involvement
 - 34% SNHL
 - 41% IUGR
 - 32% microcephaly
 - hepatosplenomegaly, hepatitis, thrombocytopenia were common

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	6 Mo of Therapy (N=47)	6 Wk of Therapy (N=49)	P Value
Gestational age — no. (%)			0.68
32 to ≤37 wk	24 (51)	22 (45)	
>37 wk	23 (49)	27 (55)	
Age at enrollment — no. (%)			0.08
<7 days	6 (13)	7 (14)	
7–14 days	19 (40)	12 (24)	
15–21 days	10 (21)	6 (12)	
22–29 days	12 (26)	24 (49)	
Extent of CMV disease — no. (%)†			
Thrombocytopenia	38 (81)	34 (69)	0.24
Petechiae	22 (47)	20 (41)	0.68
Hepatomegaly	26 (55)	21 (43)	0.31
Splenomegaly	23 (49)	22 (45)	0.84
Intrauterine growth restriction	17 (36)	22 (45)	0.41
Hepatitis	21 (45)	25 (51)	0.55
Central nervous system involvement	34 (72)	29 (59)	0.20
Microcephaly — no. (%)	14 (30)	17 (35)	0.19
Chorioretinitis — no. (%)	2 (4)	1 (2)	1.00
Neuroimaging results — no./total no. (%)‡			0.62
Normal	9/45 (20)	12/47 (26)	
Abnormal	36/45 (80)	35/47 (74)	
Baseline BSER of the best ear in participants with 6-mo follow-up data — no./total no. (%)§			0.17
Normal	32/43 (74)	25/43 (58)	
Mild	5/43 (12)	8/43 (19)	
Moderate	3/43 (7)	2/43 (5)	
Severe	3/43 (7)	8/43 (19)	

6 Months vs. 6 Weeks of Valganciclovir for Moderate to Severe cCMV Disease

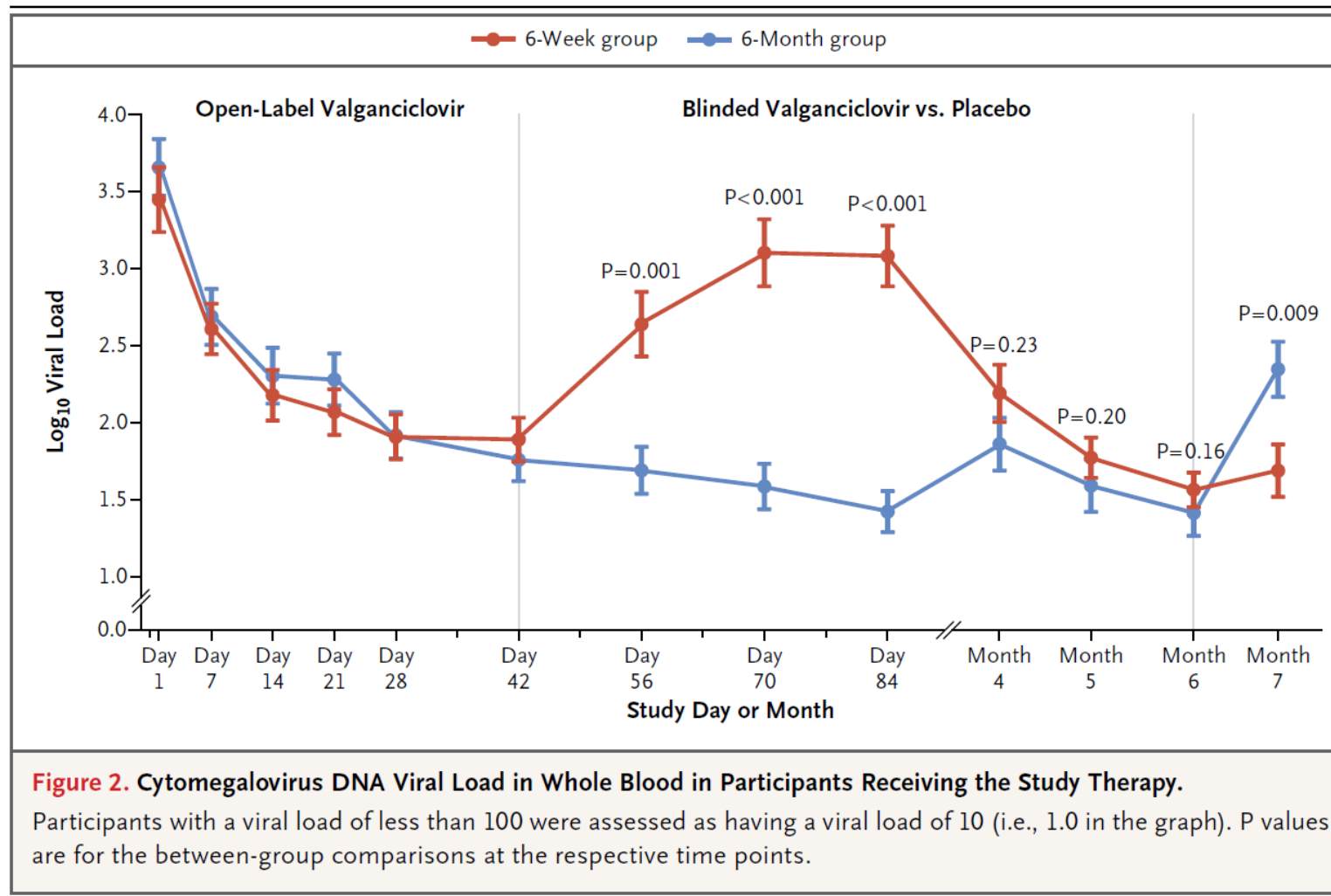


Figure 2. Cytomegalovirus DNA Viral Load in Whole Blood in Participants Receiving the Study Therapy.

Participants with a viral load of less than 100 were assessed as having a viral load of 10 (i.e., 1.0 in the graph). P values are for the between-group comparisons at the respective time points.

6 Months vs. 6 Weeks of Valganciclovir for Treatment of Moderate to Severe cCMV Disease

Hearing outcomes, 6 m vs 6 w

Neurodevelopmental outcomes, 6 m vs 6 w

1°
outcome


	Adjusted OR* (95% CI)	P value
6 months		
Best ear	1.75 (0.69-4.43)	0.24
Total ears	1.69 (0.76-3.73)	0.20
12 months		
Best ear	2.81 (0.99-7.99)	0.05
Total ears	3.04 (1.26-7.35)	0.01
24 months		
Best ear	3.28 (0.91-11.9)	0.07
Total ears	2.61 (1.05-6.43)	0.04

Bayley-III	12 month P value	24 month P value
Cognitive composite*	0.01	0.02
Language composite*	0.009	0.004
Receptive communication*	0.05	0.003
Expressive communication*	0.02	0.02
Motor composite*	0.03	0.01
Fine motor*	0.11	0.06
Gross motor*	0.07	0.02

*Odds ratio of improved, normal or no change in 6-month group, w/adjustment for baseline CNS disease

*Treatment effects all favor 6 months, but effect size is modest

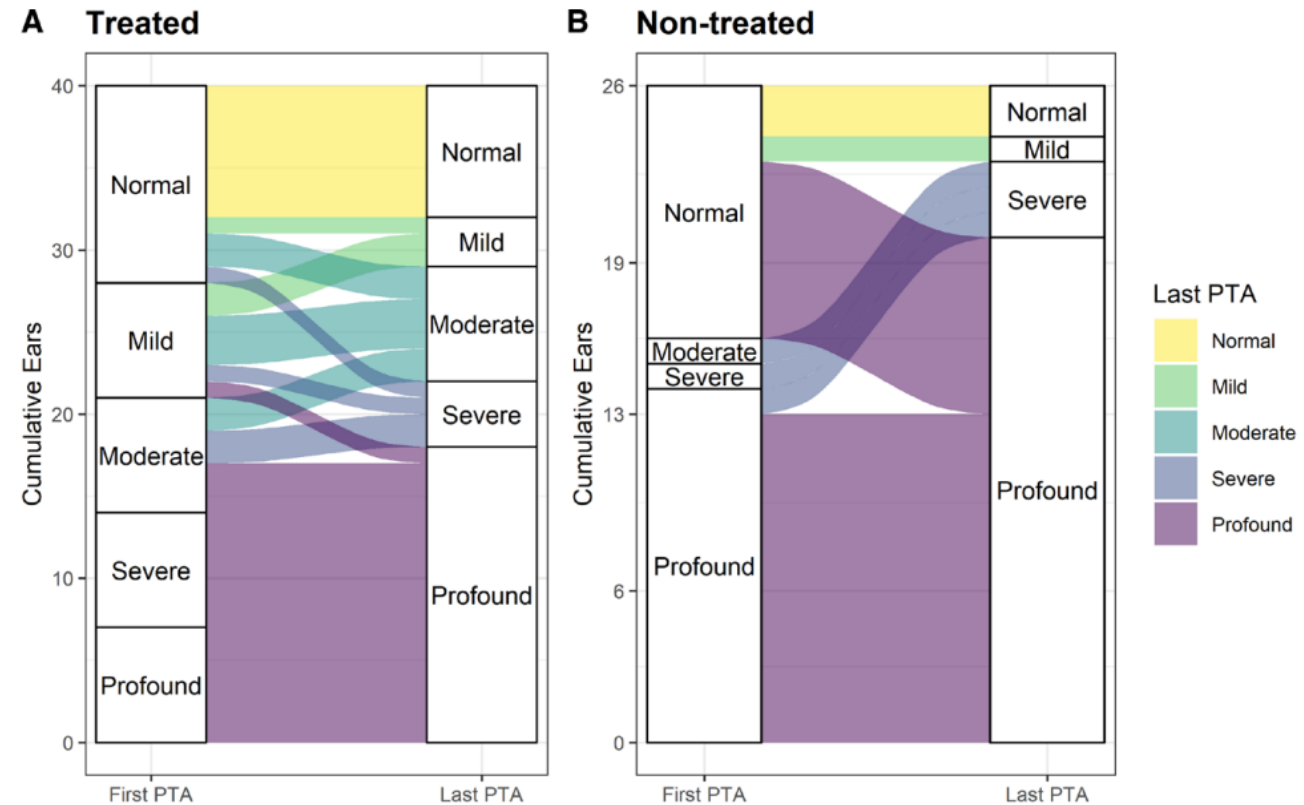
Conclusion: Rx for 6 months **did not improve short term hearing outcomes**, but **did improve long-term hearing outcomes after adjustment for baseline CNS involvement & improved long-term neurodevelopmental outcomes**

6 Months vs. 6 Weeks of Valganciclovir for Treatment of Moderate to Severe cCMV Disease

- Likelihood of improved, normal, or no change in long-term hearing was 3 times higher in infants receiving 6 months vs. 6 weeks of valganciclovir
 - With CNS involvement
 - 65% at 12 months, 46% at 24 months
 - Without CNS involvement
 - 22% at 12 months, 19% at 24 months
- Safety – no differences between 6 months vs. 6 weeks
 - Grade 3 or 4 neutropenia
 - 1st 6 weeks – 19%, 3 infants with drug temporarily stopped due to ANC <0.5
 - Week 6 to Month 6
 - 21% with valganciclovir
 - 29% with placebo

What About Treatment of Infants with SNHL?

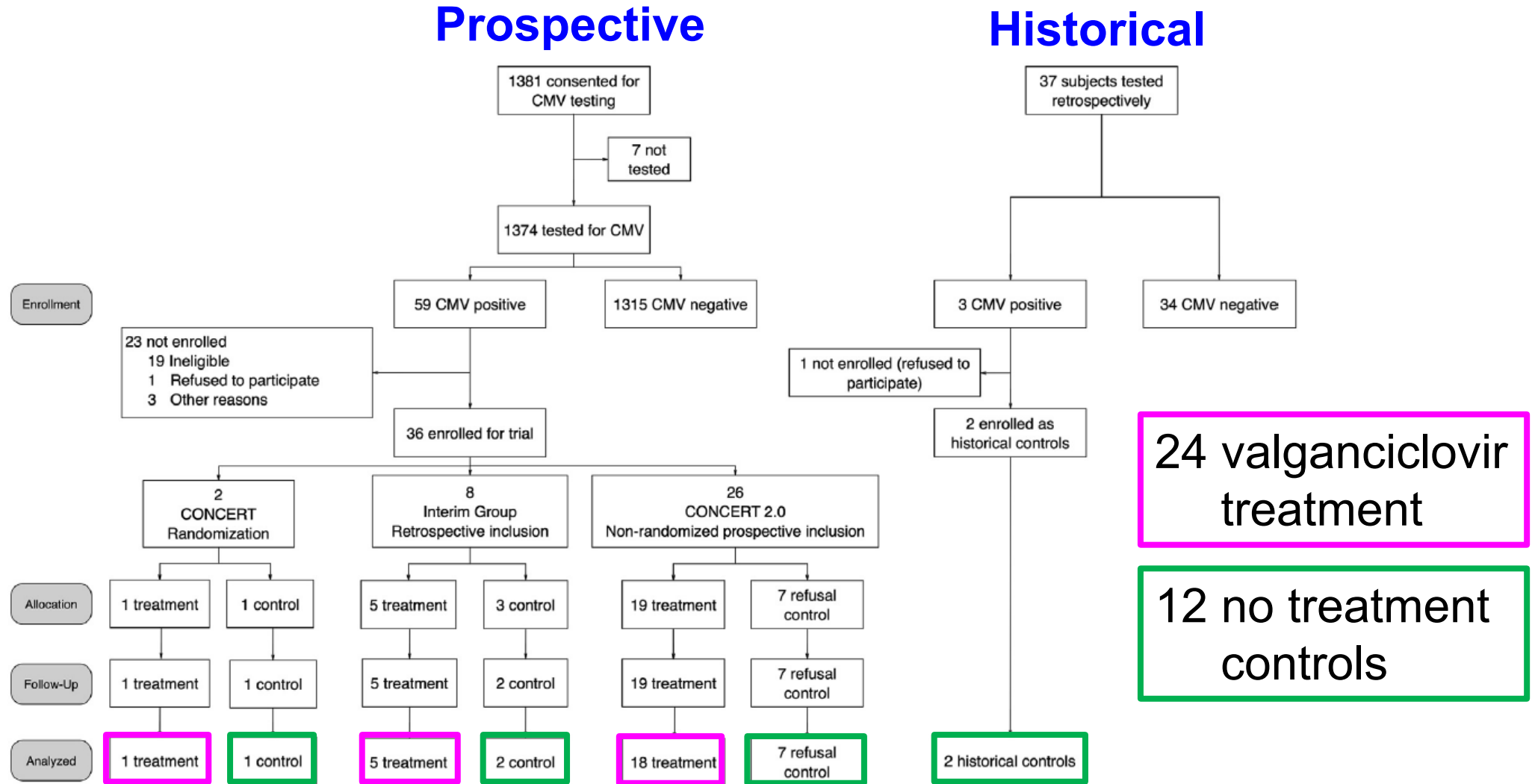
- Retrospective review of infants with cCMV followed at Lions Children's Hearing Center, Univ. of MN since 2005
- Followed progression of hearing loss
- 75% had SNHL at baseline with varying degrees of severity
- 50% with SNHL in 1 ear developed SNHL in other ear
- Children treated with valganciclovir had less progression of SNHL



Clinical Trials of Valganciclovir Rx to Prevent Occurrence or Progression of Hearing Loss in Asymptomatic Infants or Infants with SNHL only

- Phase II, open label study of 4 months of valganciclovir on **occurrence of SNHL in asymptomatic neonates**
=> study **stopped** due to low accrual, safety concerns
NCT03301415
- Phase II RCT of 6 weeks of valganciclovir vs. placebo on **progression of SNHL in children 1 month to 4 years of age with SNHL**
=> Rx with valganciclovir **did not improve hearing outcomes**
Kimberlin DW, et al. Pediatr 2024;268:113934
- Phase II RCT of 6 months of valganciclovir vs. placebo on **progression of SNHL in neonates with SNHL only (ValEAR)**
=> study **stopped** due to recruitment difficulty
NCT03107871

6 Weeks of Valganciclovir vs. No Treatment for Infants with Hearing Loss & Clinically Inapparent cCMV



6 Weeks of Valganciclovir vs. No Treatment for Infants with Hearing Loss and Clinically Inapparent cCMV

- Valganciclovir 16 mg/kg/dose twice a day started by parental choice in first 13 weeks of life
 - Age in days at start of treatment – median 61 (range, 19-88)
- Neuroimaging findings common, overall mild

Table II. Audiological outcome, categorical data analysis

Analysis	Best-ear		Total-ear	
	Control	Treatment	Control	Treatment
Number of participants or ears	12	24	24	49
Improved at follow-up	0	3 (13)	1 (4)	6 (12)
Normal hearing at baseline and follow-up	2 (17)	12 (50)	2 (8)	13 (27)
Same hearing loss at baseline and follow-up	4 (33)	7 (29)	11 (46)	26 (53)
Deteriorated hearing at follow-up	6 (50)	2 (8)	10 (42)	4 (8)
Common OR (95%CI)*	0.10 (0.02-0.45)		0.16 (0.05-0.47)	
P value	0.003		0.001	

Data are n (%) unless stated otherwise.

*Best ear analysis: proportional odds model, total ear analysis: proportional odds model, via General Estimating Equations.

Table III. Audiological outcome, continuous data analysis

Analysis	Best-ear		Total-ear	
	Control	Treatment	Control	Treatment
Number of participants or ears	12	24	24	49
Change in dB HL threshold (dB)	13.7	-3.3	13.9	-1.3
Difference (95% CI)	17 (2.6-31.4)		15.2 (4.2-26.1)	
P value*	0.02		0.007	

dB HL, decibels Hearing Level; *dB*, decibel.

Data are n (%) unless stated otherwise.

*Best ear analysis: linear regression, total ear analysis: linear regression, via General Estimating Equations.

Table IV. Developmental outcome (BSID-III)

BSID-III component	Control, n = 12 (mean ± SD)	Treatment, n = 25 (mean ± SD)	P Value
Cognitive composite score	95.5 ± 10.2	97.0 ± 17.0	.79
Language composite score	74.6 ± 13.1	83.2 ± 16.4	.12
Expressive scaled score	6.6 ± 3.2	8.0 ± 3.2	.22
Receptive scaled score	4.0 ± 2.3	5.7 ± 3.9	.16
Motor composite score	96.2 ± 9.4	96.6 ± 18	.93
Fine motor scaled score	11.7 ± 1.7	10.6 ± 3.4	.33
Gross motor scaled score	6.8 ± 2.8	7.8 ± 3.2	.34

BSID-III, Bayley Scales of Infant and Toddler Development Third Edition.

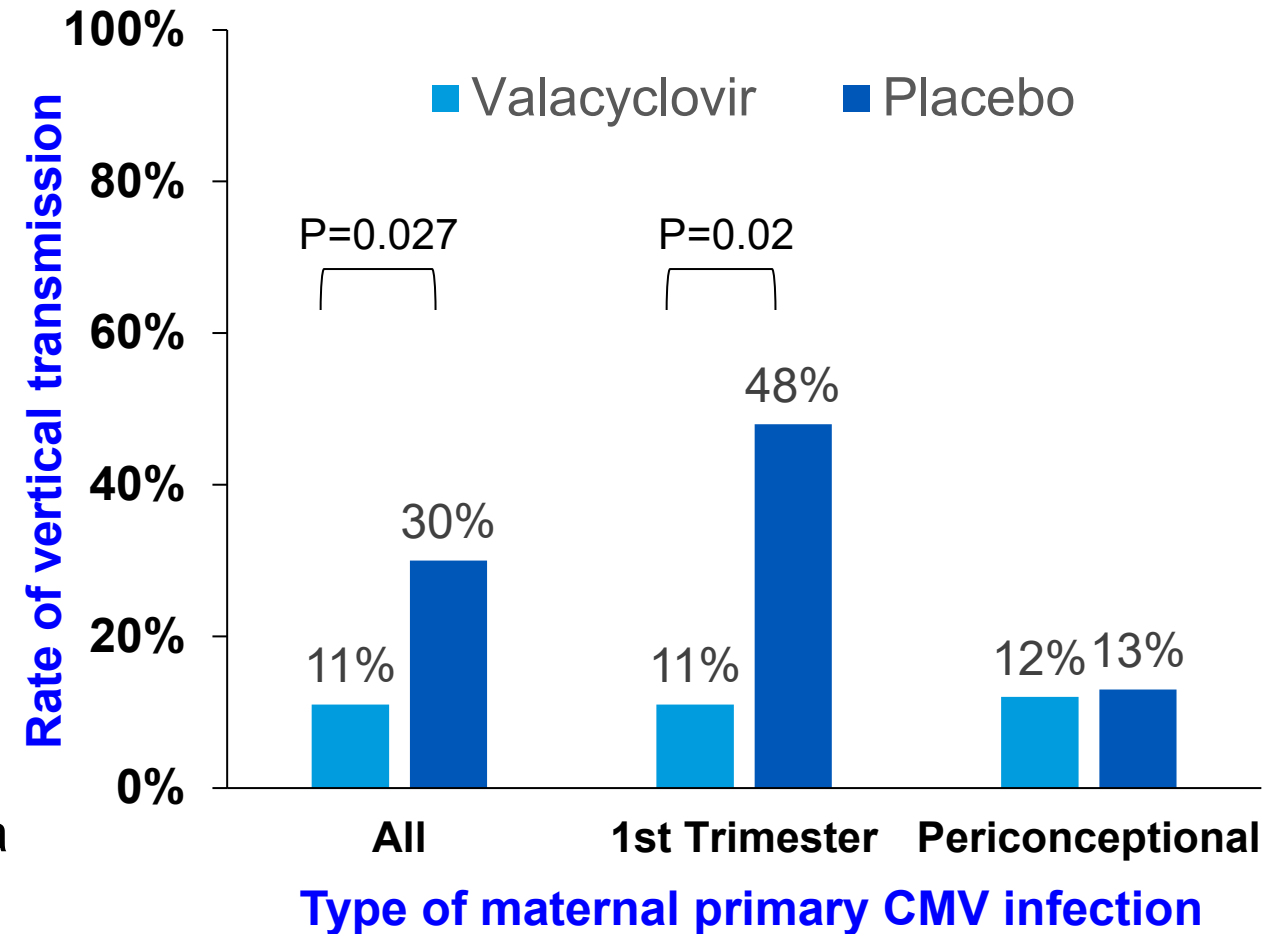
Treatment Considerations

American Academy of Pediatrics Red Book

- **Whom to treat**
 - Neonates with moderately to severely symptomatic cCMV disease – recommend treatment
 - SNHL only – offer treatment based on shared decision-making of benefit/risk
- **When to treat:** As soon as dx confirmed & evaluation complete but within 13 weeks of birth
- **What to treat with:** Valganciclovir 16 mg/kg/dose by mouth, twice a day
- **How long to treat:**
 - 6 months for moderate/severe disease
 - 6 weeks for SNHL only (*? consider MR to exclude cCMV CNS findings*)
- **What to monitor during treatment**
 - CBC w/diff weekly x 6 weeks, then at week 8, then monthly
 - ALT monitoring monthly
- **How to followup**
 - Audiology: 3-6 month intervals for 3 years then yearly through adolescence
 - Ophthalmology: If normal, repeat 3-6 months or MD recommendation
 - Development: Regular assessment at well-child care, refer to Early Intervention

Treatment of Maternal Primary CMV Infection to Prevent Vertical Transmission

- Randomized controlled trial in Israel
- Serologic evidence of maternal primary CMV infection
 - Periconceptional – w/in 4 weeks before LMP & <3 weeks gestation
 - 1st trimester
- Estimated time of infection
 - Clinical symptoms & signs
 - If asymptomatic, midway between - & + tests
 - <6 weeks if IgM value >10 x cut-off, IgG avidity <15%, or pp65 antigenemia
- Valacyclovir 4 g by mouth twice a day
- Amniocentesis ≥7 weeks after estimated time of infection & after 21st week to evaluate for vertical transmission by PCR



QUESTIONS & ANSWERS

