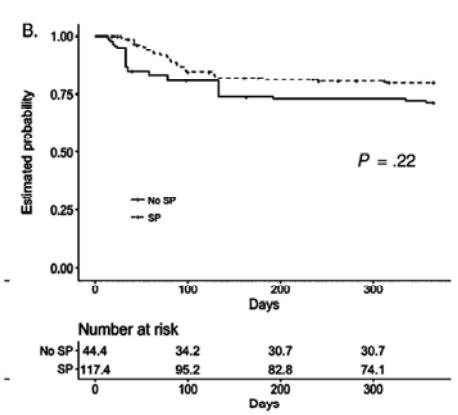
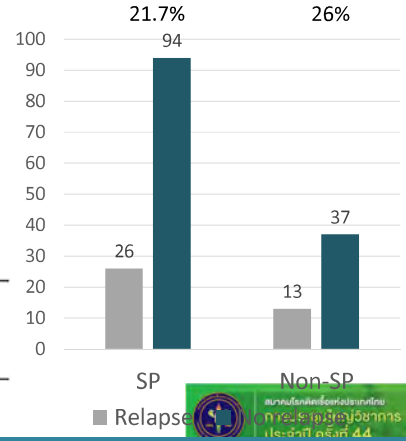
CMV Load Conversion (IU/mL)

CMV Realtime-PCR	Linear range (IU/mL)	1 copies/mL	e.g. 20,000 copies/mL
RealTimeCMV (Abbott)	31.2 to 156 million	**1.56 IU/mL**	31,2000 IU/mL
COBAS AmpliPrep/COBAS Taqman (Roche)	137 to 9.1 million	**0.91 IU/mL**	18,200 IU/mL
Artus CMV RGQ MDx (Qiagen)	159 to 7.94 million	**1.64 IU/mL**	32,800 IU/mL

WHO 2010 International Standard Calibration

Role of Secondary Prophylaxis (SP)

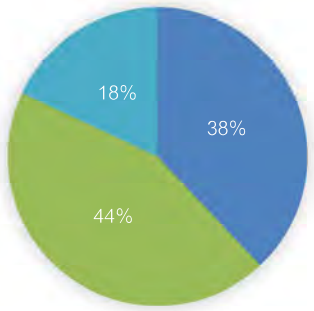




SP was protective against relapse from 0-6 weeks (HR 0.19) but not after 6 weeks

Gardiner BJ. Clin Infect Dis. 2017 Nov 29;65(12):2000-2007.

Low level CMV Viremia in SOT

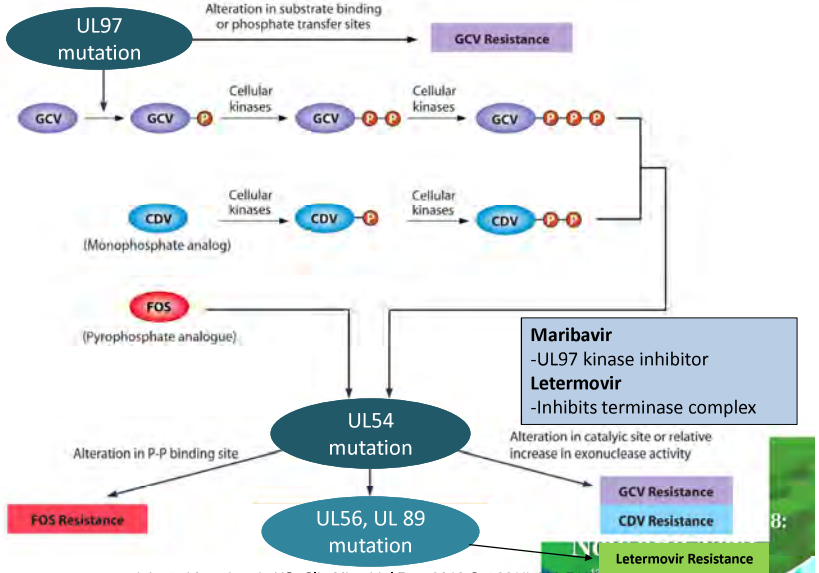


- Progresssion to high CMV load > 1,000 IU/mL or +symptoms
- Spontaneous CMV viral clearance
- Persistently low CMV viremia

Progression
Risk factors: lung transplantation (OR 2.9)
Protective factor: CMV infection Rx anytime post-tx (OR 0.09)

Natori Y. et al. Poster C355 at American Transplant Congress 2018

Drug-resistant CMV



Adapted from Lurain NS. Clin Microbiol Rev. 2010 Oct;23(4):689-712

Anti-CMV Drug Resistance

New

Term	Definition
Refractory CMV infection	CMV viremia that increases* after at least 2 weeks of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load** after at least 2 weeks of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 weeks of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs

** >1 log10 increase in CMV DNA levels in blood or serum and determined by log10 change betw... first week to the peak viral load at 2 weeks or more as measured in the same laboratory with the same assay*
*** CMV viral load at the same level or higher than the peak viral load within 1 week but < 1 log10 ... in the same laboratory and with the same assay*

Chemaly RF. Clin Infect Dis. 2018 Aug 22.

Ganciclovir Resistance Levels

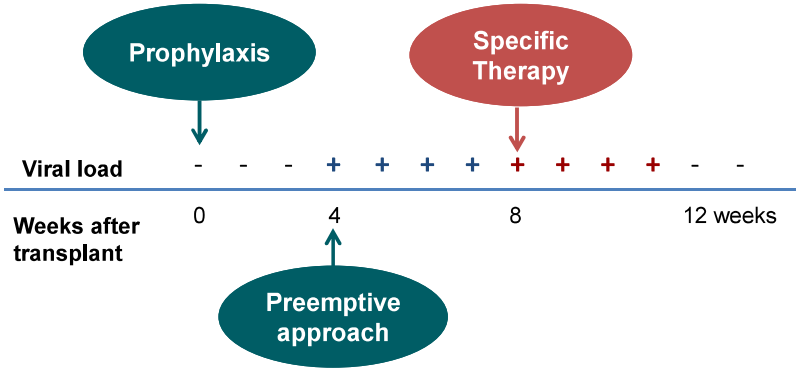
TABLE 8.
GCV resistance levels associated with selected UL97 genotypes

Genotype frequency	Fold change in GCV EC50[a]		
	5-15×	2-5×	<2×
Most common	M460V/I, H520Q, A594V, L595S, C603W	C592G	
Less common at codons 460, 590-607	M460T, A594G, 595del[b], L595F/W, E596Y, 597del2[b], 599del, K599T, 600del, 601del, 601del2, C603R, C607Y, del(≥3)[c]	A591V, A594E/T, E596G, C603S, 596del[b], 600del2, C607F	E596D, N597D, K599E/R, L600I, T601M, D605E[d]
Atypical loci	F342S[e], K355M[e],V356G[e], V466G[e], C480R[e], C518Y, P521L[e]	L405P, I610T, A613V	M615V, Y617H, A619V, L634Q, E655K, A674T

[a] Moderate resistance (5-15×), low-grade resistance (2-5×), or insignificant resistance (<2×).
[b] del = in frame deletion of codon.
[c] In frame deletion of ≥3 codons in the 590-607 range can be assumed to confer moderate GCV resistance (eightfold to 15-fold). Deletion of less than 3 codons may confer varying degrees of GCV resistance (fourfold to 10-fold).[102]
[d] D605E is a baseline sequence polymorphism common in east Asia, unrelated to drug resistance.
[e] Maribavir cross-resistance documented; all except F342S are markedly growth-inhibited.

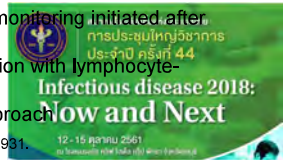
Kotton CN. et al. Transplantation. 2018 Jun;102(6):900-931.

CMV Prevention in SOT



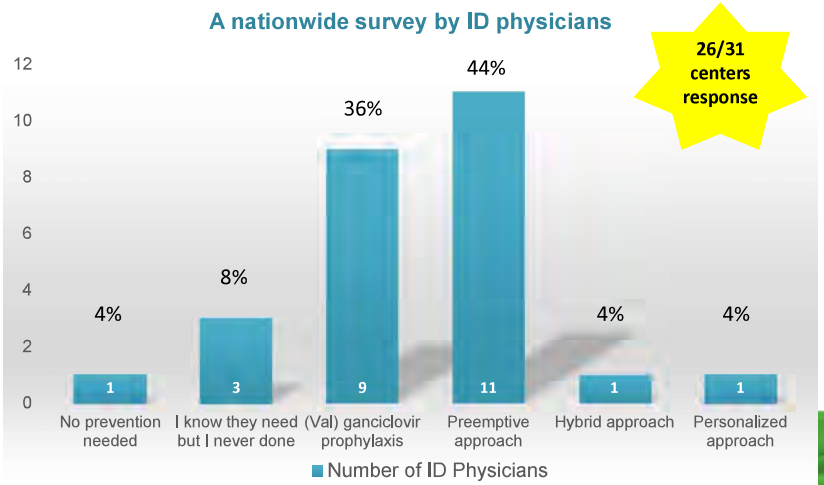
Hybrid approach (surveillance after prophylaxis): preemptive monitoring initiated after completing prophylaxis
Targeted prophylaxis: after induction or treatment of acute rejection with lymphocyte-depleting agents
Personalized approach: CMV-specific T cell immunity guided approach

Kotton CN. et al. Transplantation. 2018 Jun;102(6):900-931.



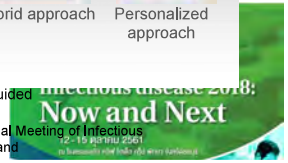
CMV Prevention Strategies in Thailand

A nationwide survey by ID physicians



Hybrid = surveillance after prophylaxis, personalized=CMV-specific T-cell immunity-guided

Bushyakanist A. Bruminhent J. presenting as poster presentation at the 44th Annual Meeting of Infectious Disease Association of Thailand, 12–15 October 2018, Thailand



Prevention of CMV Infection in SOT

Organ	Risk category	Recommendation/options	Months(mo) (Evidence)
Kidney	**D+/R-**	Prophylaxis for 6 mo preferred over preemptive Rx	I (Impact trial)
	R+	Either prophylaxis for 3 mo or preemptive Rx* is acceptable	I
Liver	**D+/R-**	Prophylaxis for 3-6 mo preferred over preemptive Rx *Valganciclovir was not US-FDA approved for CMV prophylaxis	3 mo (I) 6 mo (II)
	R+	Either prophylaxis for 3 mo or preemptive Rx* is acceptable	I

For R- use acyclovir 400 mg twice a day for 30 days (HSV & VZV seropositive recipients), use leukocyte-depleted blood products
Prophylaxis: Valganciclovir 900 mg daily (renal adjusted dose needed)
Preemptive therapy: Weekly CMV PCR for 12 weeks after transplant, and if threshold is reached, treat with valganciclovir 900 mg PO or IV ganciclovir 5 mg/kg IV BID until negative test

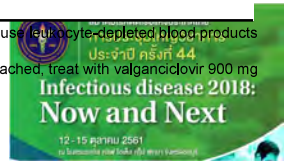
Razonable RR. Am J Transplant. 2013

Prevention of CMV Infection in SOT (2)

Organ	Risk category	Recommendation/options	Months(mo) (Evidence)
Heart	**D+/R-**	Prophylaxis for 3-6 mo preferred over preemptive Rx Some centers add CMV immunoglobulin	3 mo (I) 6 mo (III) CMV Ig (II-2)
	R+	Either prophylaxis for 3 mo or preemptive Rx is acceptable	II-2
Lung/heart -lung	**D+/R-**	Prophylaxis for 12 months Some centers prolong prophylaxis > 12 months Some centers add CMV Immunoglobulin	12 mo (I) >12 mo (II-2) CMV Ig (II-2)
	R+	Prophylaxis for 6-12 months	II-2

For R- use acyclovir 400 mg twice a day for 30 days (HSV & VZV seropositive recipients), use leukocyte-depleted blood products
Prophylaxis: Valganciclovir 900 mg daily (renal adjusted dose needed)
Preemptive therapy: Weekly CMV PCR for 12 weeks after transplant, and if threshold is reached, treat with valganciclovir 900 mg PO or IV ganciclovir 5 mg/kg IV BID until negative test

Razonable RR. Am J Transplant. 2013



Renal-adjusted Dose

Dosage recommendations for ganciclovir and valganciclovir and valacyclovir for adult patients with impaired renal function (using Cockcroft-Gault formula)

Intravenous ganciclovir (adapted from[265])

CrCl, mL/min	Treatment dose	Maintenance/prevention dose
≥70	5.0 mg/kg q12 h	5.0 mg/kg q24 h
50-69	2.5 mg/kg q12 h	2.5 mg/kg q24 h
25-49	2.5 mg/kg q24 h	1.25 mg/kg q24 h
10-24	1.25 mg/kg q24 h	0.625 mg/kg q24 h
<10	1.25 mg/kg 3 times a week after hemodialysis	0.625 mg/kg 3 times a week after hemodialysis

Valganciclovir (adapted from[263,264])

CrCl, mL/min	Treatment dose	Maintenance/prevention dose
≥60	900 mg every 12 h	900 mg once daily
40-59	450 mg every 12 h	450 mg once daily
25-39	450 mg once daily	450 mg every 2 d
10-24	450 mg every 2 d	450 mg twice weekly
<10	200 mg 3 times a week after hemodialysis[a]	100 mg 3 times a week after hemodialysis[a]

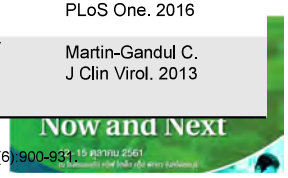
[a] Oral solution must be used in this instance (as VGCV tablets cannot be split)
Cockcroft-Gault formula

Kotton CN. et al. Transplantation. 2018 Jun;102(6):900-931.

CMV Load Cut-off Value

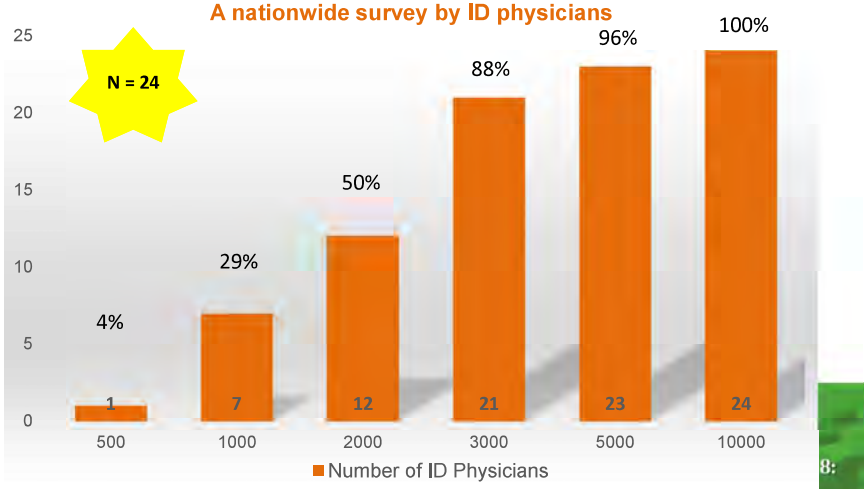
Population	Threshold (IU/mL)	Comments	Ref.
High risk 39 D+/R- SOTR	1,500 IU/mL	No symptomatic CMV disease in patients with < 1,500 IU/mL	Martin-Gandul C. Transpl Int. 2014
Mixed risk D+/R- (11%), R+ (71%) SOTR	2,520 IU/mL in whole blood, 2x/wk (3,000 cps/mL)	More of a study of preemptive Rx	Atabani SF. Am J Transplant. 2012
D+/R- (7%), R+ (93%) SOTR	2,275 IU/mL in plasma (2,500 cps/mL)	< 2,275 IU/mL → self clearance > 2,275 IU/mL → requiring Rx	Boaretti M. J Clin Virol. 2013
SOTR + HSCTR	2,520 IU/mL in whole blood	More of a study of preemptive Rx	Griffiths PD. PLoS One. 2016
Lower risk R+	3,983 IU/mL	NPV 99.6% for CMV disease	Martin-Gandul C. J Clin Virol. 2013

Adapted from Kotton CN. et al. Transplantation. 2018 Jun;102(6):900-931.



Plasma CMV Cut-off Value to Initiate Preemptive Therapy in KT

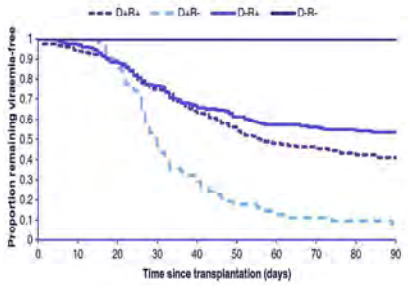
A nationwide survey by ID physicians



Bushyakanist A. Bruminhent J. presenting as poster presentation at the 44th Annual Meeting of Infectious Disease Association of Thailand, 12–15 October 2018, Thailand

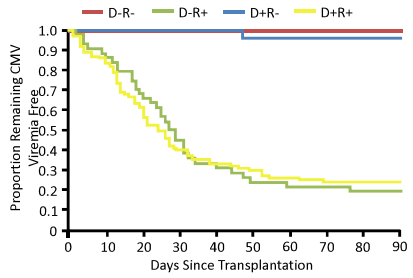
CMV Serostatus & Risk of CMV Infection

Solid organ transplant



Highest risk in D+/R-

Hematopoietic stem cell transplant



Highest risk in R+

Atabani SF. Am J Transplant. 2012 Sep;12(9):2457-64.
Panagou E, et al. Transpl Infect Dis. 2016;18:405-414. Slide credit: clinicaloptions.com

New

The NEW ENGLAND JOURNAL of MEDICINE

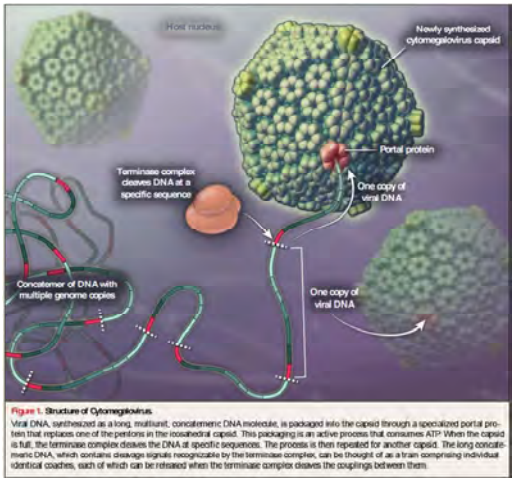
ORIGINAL ARTICLE

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

F.M. Marty, P. Ljungman, R.F. Chemaly, J. Maertens, S.S. Dadwal, R.F. Duarte, S. Haider, A.J. Ullmann, Y. Katayama, J. Brown, K.M. Mullane, M. Boeckh, E.A. Blumberg, H. Einsele, D.R. Snydman, Y. Kanda, M.J. DiNubile, V.L. Teal, H. Wan, Y. Murata, N.A. Kartsonis, R.Y. Leavitt, and C. Badshah

N ENGL J MED 377;25 NEJM.ORG DECEMBER 21, 2017

Letermovir



PREVYMIS™ (letermovir)
240 mg, 480 mg tablets
Injection 20 mg/mL

-Not covered HSV & VZV, need acyclovir prophylaxis

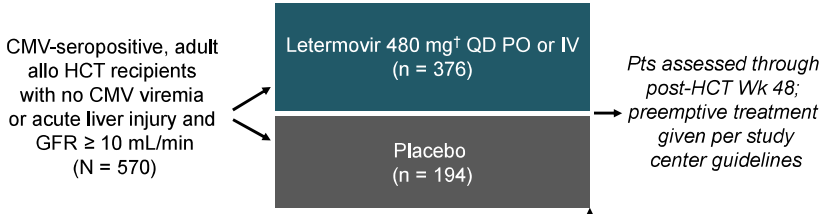
-No BMS or nephrotoxicity

-50% dose in cyclosporine user

-No cross-resistance with drugs currently used in treatment of CMV

Letermovir for Post-HSCT CMV Prophylaxis

- Randomized, MCT, double-blind, placebo-controlled phase III trial
- Primary endpoint: pts with clinically significant CMV infection* through post-HCT Wk 24, 37.5 vs. 60.6% (P<0.001)
- Side effects and All-cause mortality at week 48 were not different

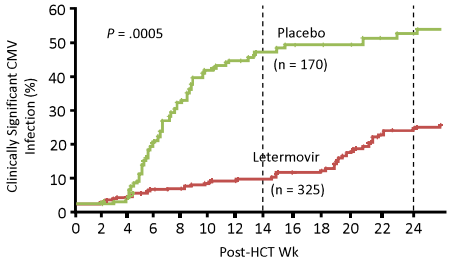


Pts required to begin treatment before post-HCT Day 28.
*CMV disease occurrence or treatment with anti-CMV preemptive therapy (occurred if confirmed CMV viremia and CMV disease risk).
†240 mg if concomitantly receiving cyclosporine.

N Engl J Med. 2017 Dec 21;377(25):2433-2444.

Clinically Significant CMV Infection and Mortality Through Wk 24

Clinically Significant CMV Infection, Full Analysis Set

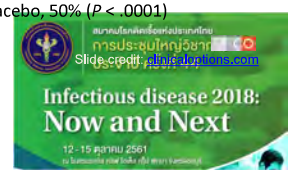


Outcome at Wk 24,* %	Letermovir (n = 325)	Placebo (n = 170)
Failure of therapy	37.5	60.6
Clinically significant CMV	17.5†	41.8
▪ Started preemptive therapy	16.0	37.6
▪ CMV diagnosis	1.5	1.8
All-cause mortality	9.8‡	15.9
Nonrelapse mortality	6.5	10.6

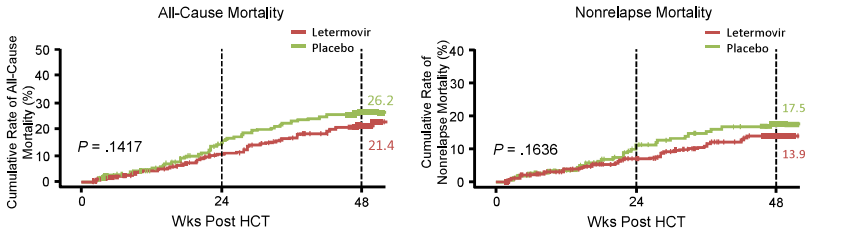
*Full analysis set. †Adjusted treatment difference: -23.5% (95% CI: -32.5% to -14.6%; P < .0001). ‡P = .0317 vs placebo.

Failure of therapy at Wk 14 (end of treatment): letermovir, 19.1%; placebo, 50% (P < .0001)

Marty FM, et al. BMT Tandem 2017. Abstract LBA2.

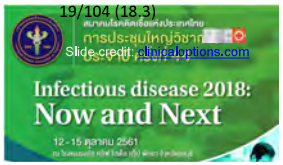


Mortality Through Wk 48



Deaths, n/N (%)	Letermovir (n = 373)	Placebo (n = 192)
Pts with clinically significant CMV infection	14/79 (17.7)	26/88 (29.5)
Pts without clinically significant CMV infection	58/294 (19.7)	19/104 (18.3)

Maertens J, et al. IDWeek 2017. Abstract 1029.



CMV Immunology