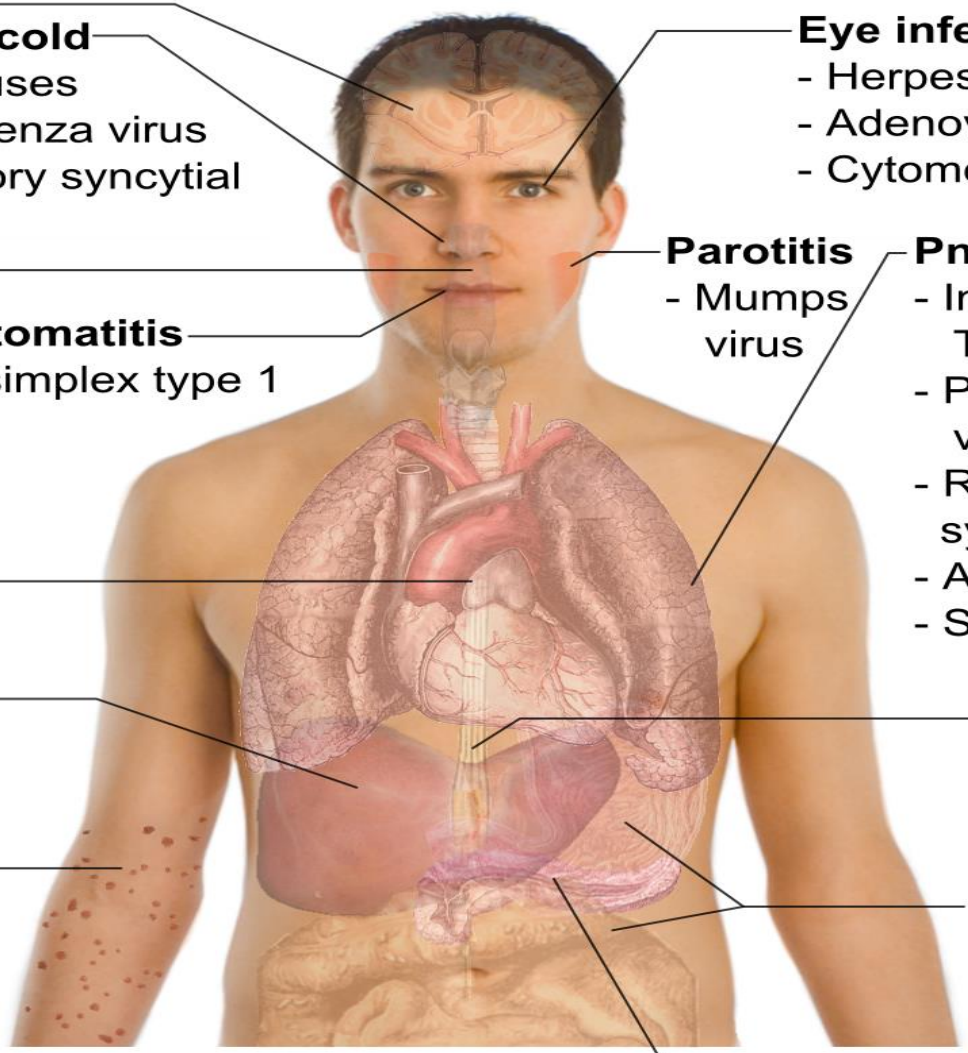
ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ
ΛΟΙΜΩΞΙΟΛΟΓΙΑ

ΑΝΤΙ-ΙΙΚΑ ΦΑΡΜΑΚΑ

Σ ΤΣΙΟΔΡΑΣ
Καθηγητής Παθολογίας-Λοιμώξεων
Ιατρική Σχολή ΕΚΠΑ

Overview of Viral infections



Encephalitis/ meningitis
- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

Common cold
- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

Eye infections
- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

Parotitis
- Mumps virus

Pneumonia
- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

Pharyngitis
- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

Gingivostomatitis
- Herpes simplex type 1

Cardiovascular
- Coxsackie B virus

Hepatitis
- Hepatitis virus types A, B, C, D, E

Myelitis
- Poliovirus
- HTLV-I

Skin infections
- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

Gastroenteritis
- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

Sexually transmitted diseases
- Herpes simplex type 2
- Human papillomavirus
- HIV

Pancreatitis
- Coxsackie B virus

Anti-Viral drugs

- Many antiviral drugs are *Purine or Pyrimidine analogs.*
- Many antiviral drugs are Prodrugs.
  - They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral agents inhibits active replication
  - so the viral growth resumes after drug removal.

Anti-viral drugs

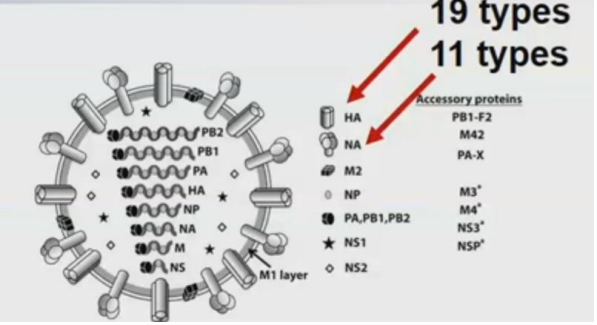
- Current anti-viral agents do not eliminate non-replicating or latent virus

- Effective host immune response remains essential for the recovery from the viral infection

Anti-viral drugs

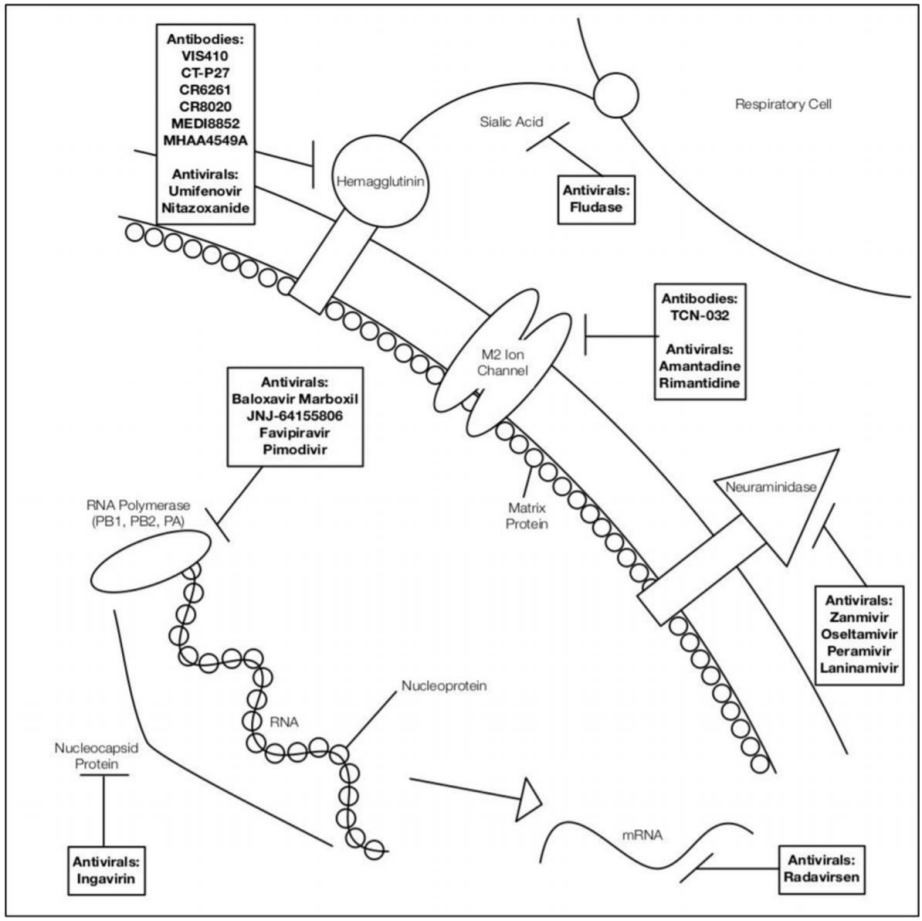
Stages of viral replication

- Cell entry – attachment
  - penetration
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release



Ιός της γρίπης

- Single stranded RNA Orthomyxovirus
- Influenza A and B have structural differences that influence therapeutic viral targets:
  - Capsule proteins
    - HA (fusion/uncoating), NA (release) shared
    - Flu A: M2 ion channel (uncoating and assembly)
    - Flu B: BM2 and NB Protein channels
  - Ribonucleoprotein complex (RNA segments coated with NP + RNA polymerase)
  - mRNA
  - Sialic Acid (enables HA binding to host cell)

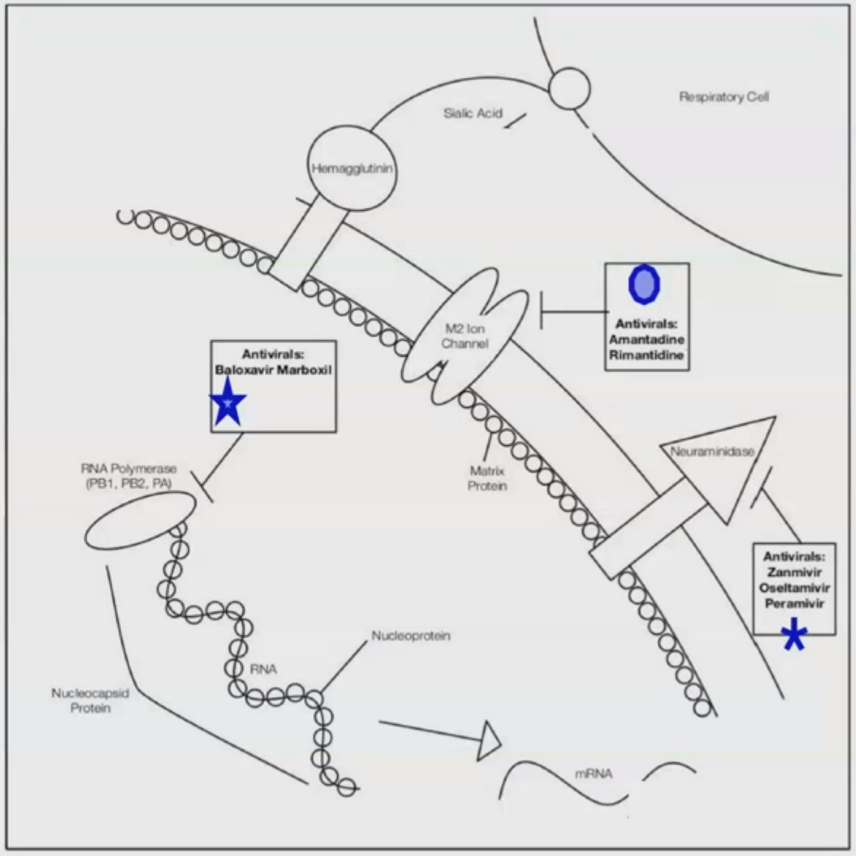


Nicholson 2018

Αντι-ιικά για γρίπη

Flu – FDA Approved

- M2-Ion Channel Blockers
  - Amantadine/Rimantadine
- Neuraminidase Inhibitors
  - Oseltamivir
  - Zanamivir
  - Peramivir
- Cap-dependent endonuclease inhibitor
  - Baloxavir Marboxil



Nicholson 2018

Πλειοψηφία=ήπια νόσος !!!

- Η πλειοψηφία όσων ασθενούν με γρίπη
  - νοσούν για 3 έως 7 ημέρες και
- η υγεία τους αποκαθίσταται πλήρως

Rx σε ΑΤΟΜΑ ↑↑ ΚΙΝΔΥΝΟΥ επιδείνωση χρονίων νόσων

- οι θάνατοι αφορούν κυρίως άτομα με υποκείμενα νοσήματα
- **ΕΜΒΟΛΙΑΣΜΟΣ = SOS**
  - Άσθμα κι άλλες αναπνευστικές ασθένειες, καρδιαγγειακά νοσήματα
  - Διαβήτη, νοσήματα του ήπατος
  - Νεφροπάθειες, νευρολογικά νοσήματα
  - Καρκινοπαθείς και άλλοι ασθενείς σε ανοσοκαταστολή
  - **Έγκυες & παχύσαρκοι**

ΚΕΕΛΠΝΟ
ΚΕΝΤΡΟ ΕΛΕΓΧΟΥ & ΠΡΟΛΗΨΗΣ ΝΟΣΗΜΑΤΩΝ (ΚΕΕΛΠΝΟ)
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ

Amantadine και Rimantadine

- Δραστικά έναντι γρίπης Α, αλλά **<u>όχι Β</u>**
- Πρόληψη & Rx
  - 50% για μόλυνση, 70-90% σε νόσησης από ιό Α

- **<u>ΔΕΝ ΧΡΗΣΙΜΟΠΟΙΟΥΝΤΑΙ ΛΟΓΩ ΑΝΤΟΧΗΣ</u>**
  - **Α Η3Ν2 από το 2003, παγκόσμια κατανομή**

- Ριμανταδίνη ΟΧΙ στην Ελλάδα

ΑΝΤΙ-ΙΪΚΑ ΦΑΡΜΑΚΑ-ΓΡΙΠΗ

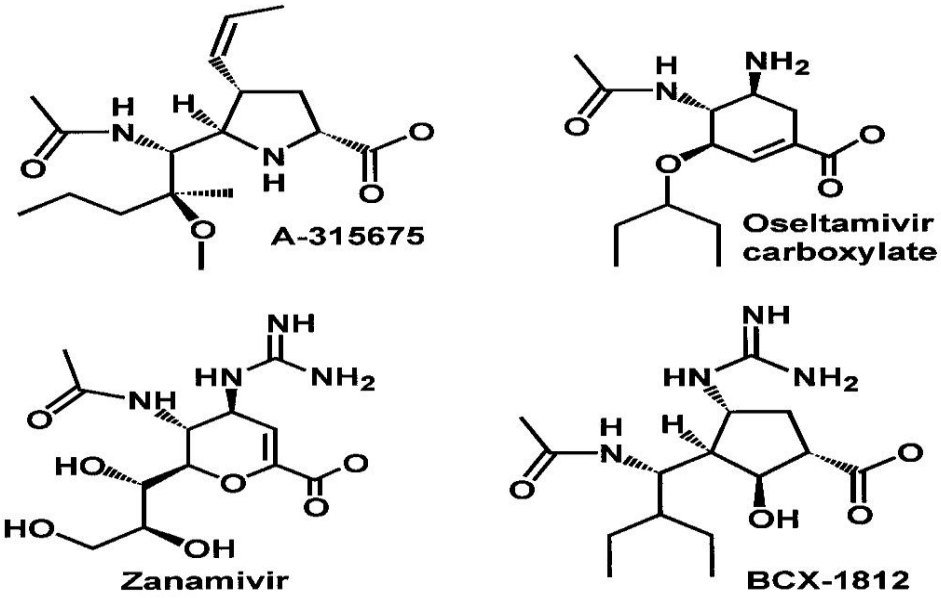
Drug (Trade Name)	Virus	Route	Treatment [a,b]	Chemopro-phylaxis [d]	Adverse Effects
Oseltamivir (Tamiflu)	A and B	PO	Birth or older[c]	≥ 3 mo	Nausea, vomiting Skin reactions Neuropsychiatric events
Zanamivir (Relenza)	A and B	Inhalation	≥ 7 y	≥ 5 y	Bronchospasm Allergic reactions Neuropsychiatric events
Peramivir* (Rapivab)	A and B	IV	≥ 2 y	NA	Diarrhea Skin reactions Neuropsychiatric events
Boloxavir* (Xofluza)	A and B	PO	≥ 12 yr	NA	Diarrhea Bronchitis, nasopharyngitis Nausea, Headache

a. Treatment within 48 hr of onset of illness has greatest effect in reduction of symptoms and duration of illness
b. No antiviral is specifically approved for severe influenza, but observational studies support effect on reduction of complications, and most experts support use
c. FDA approved for children 2 wk of age and older but AAP supports use from birth in term and preterm infants
d. Chemoprophylaxis: High risk children who cannot get vaccinated or may not respond to vaccine; within 2 weeks after vaccination if circulation of influenza, contacts of HR patients, control of outbreaks

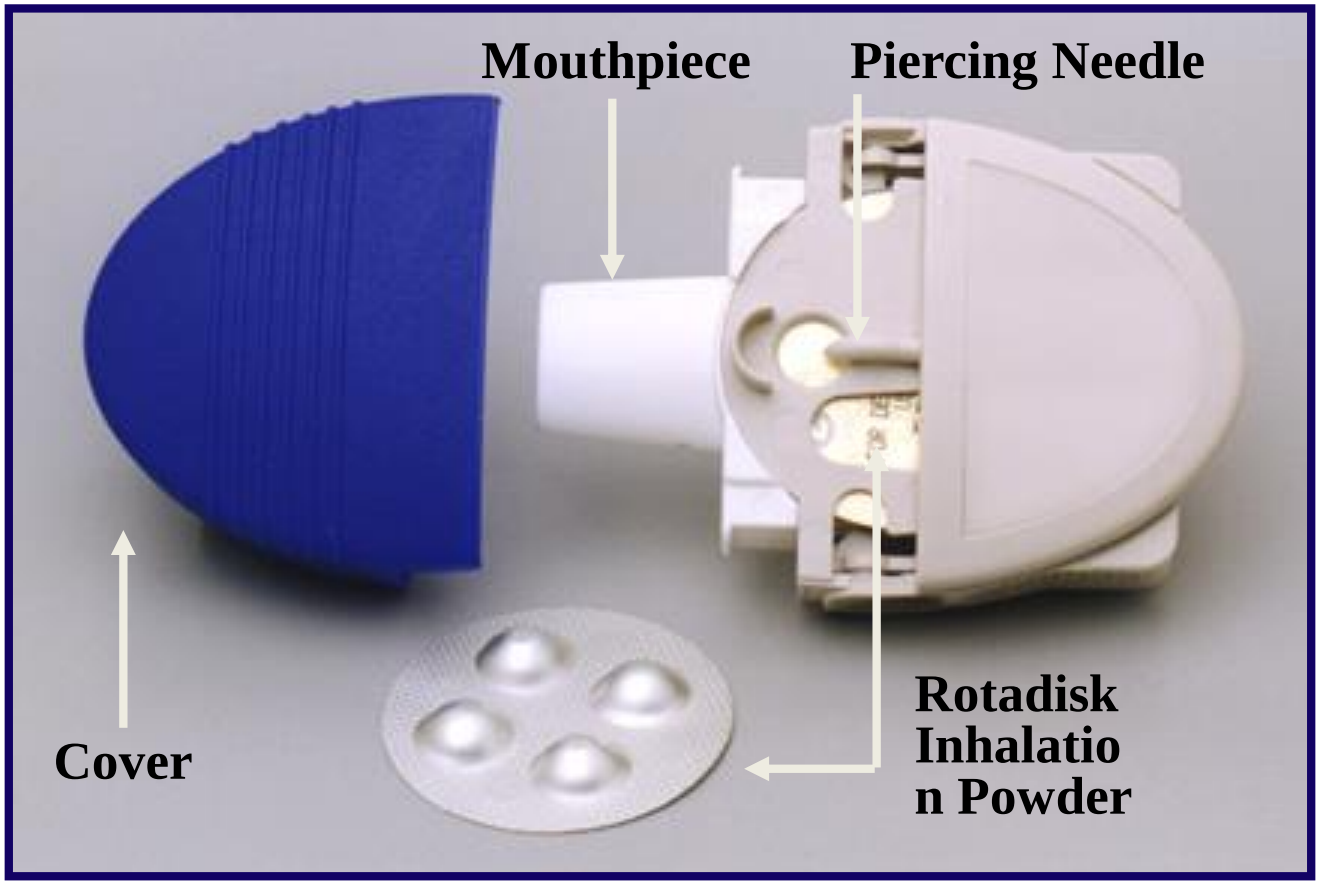
* Long Acting

ΑΝΤΙ-ΙΪΚΑ ΦΑΡΜΑΚΑ-ΓΡΙΠΗ

- Αναστολείς της Νευραμινιδάσης
  - Ζαναμιβίρη (Zanamivir-Relenza)
  - Οσελταμιβίρη (Oseltamivir-Tamiflu)



Relenza® (zanamivir for inhalation) Rotadisk® and Diskhaler®



Δίνουμε Αντιγριπικά & πότε;

- **Πυρετός + βήχας** σε περίοδο γρίπης = Rx

  σαν γρίπη σε high risk groups

- Χωρίς εργαστηριακή επιβεβαίωση

ΣΥΣΤΑΣΕΙΣ ΓΙΑ Rx

Ήπια γρίπη χωρίς επιπλοκές (ενήλικες και παιδιά)

Rx σε αυξημένου κινδύνου για την εμφάνιση επιπλοκών

Γρίπη με επιπλοκές ή προοδευτική επιδείνωση

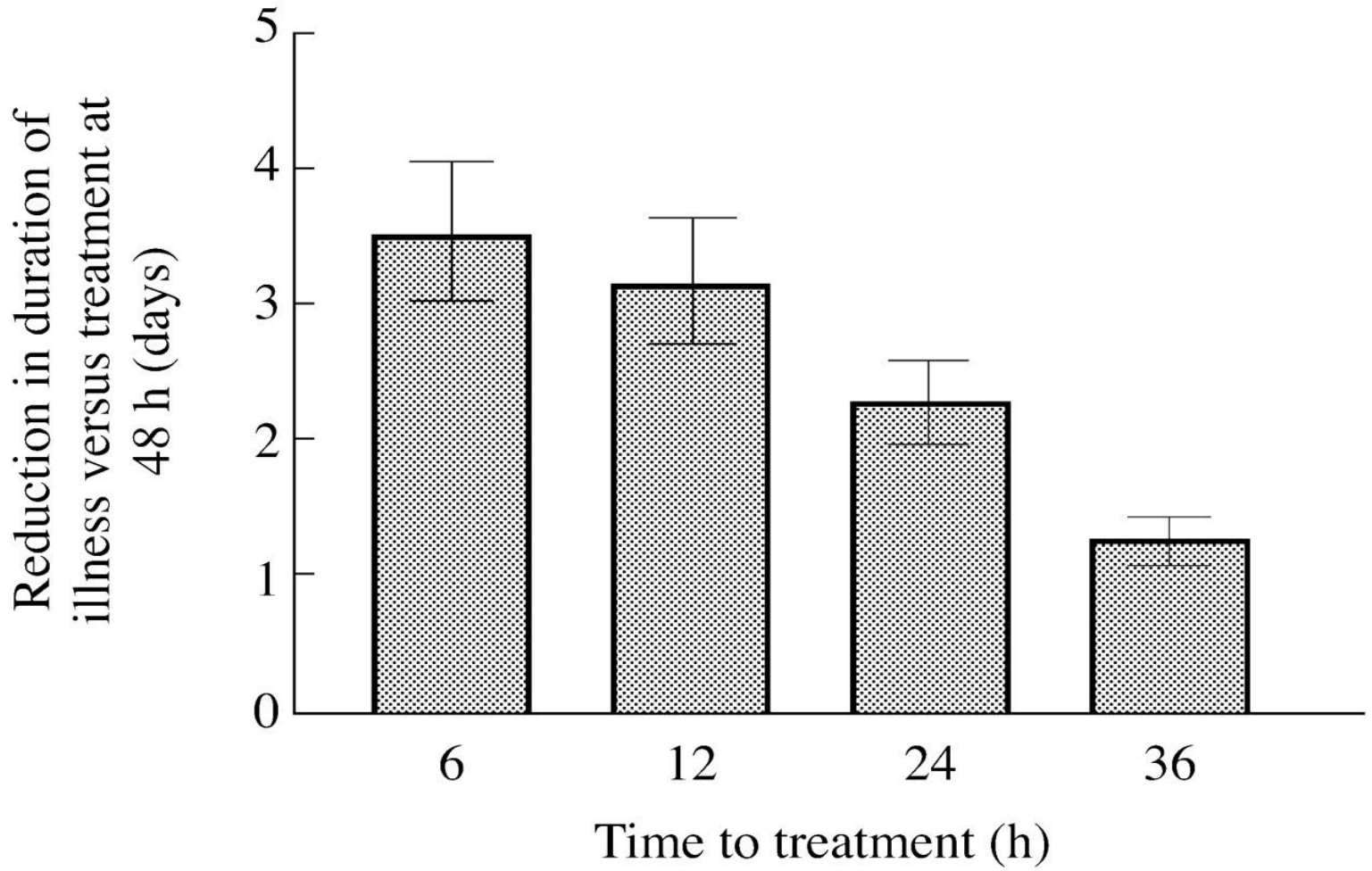
Rx σε όλους

ΟΦΕΛΗ ΘΕΡΑΠΕΙΑΣ-OSELTAMIVIR

- Όταν δοθεί εγκαίρως
  - πρώτες 24-30 ώρες
- ↓ διάρκειας νόσου ~ 0.5-3 ημέρες
- ↓ διάρκειας απέκκρισης ιού
- ↓ σοβαρότητας νόσου
- ↓ % επιπλοκών

MMWR 2008:57(RR-7):1;Cooper NJ etal. BMJ 2003;326; Aoki FY et al. J Clin Virol 2009;44:255; Nicholson KG et al. Lancet 2000;355:1845; Hayden FG et al. NEJM 1997;337:874; Lancet 1998;352:1877; Jefferson T et al. BMJ 2014;348:g2545
Treanor JJ et all JAMA 2000;283:1016; Kaiser L et al. Arch Intern Med 2003;163:1667

Figure 2. The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population).



Aoki F Y et al. J. Antimicrob. Chemother. 2003;51:123-129

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Journal of

ΟΦΕΛΗ ΘΕΡΑΠΕΙΑΣ

Comment

Optimum timing of oseltamivir: lessons from Bangladesh

Ison G et al. Lancet Inf Dis 2014

- Μόνο 13% των ασθενών καλούν ιατρό < 48 hrs!!!

Gaglia MA et al. Clin Infect Dis. 2007;45(9):1182.

ΟΦΕΛΗ ΘΕΡΑΠΕΙΑΣ-OSELTAMIVIR

- ↓ σοβαρότητας νόσου
- ↓ % επιπλοκών

Treanor JJ et all JAMA 2000;283:1016; Kaiser L et al. Arch Intern Med 2003;163:1667

- Αλλά…

- Μετα-αναλύσεις με αντικρουόμενες απόψεις

Heman MA et al. CID 2011;53:277; Jefferson T et al. BMJ 2014;348:g2545

ΜΕΤΑ-ΑΝΑΛΥΣΗ 2014 - Οσελταμιβίρη

BMJ

BMJ 2014;348:g2545 doi: 10.1136/bmj.g2545 (Published 9 April 2014)

RESEARCH

Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

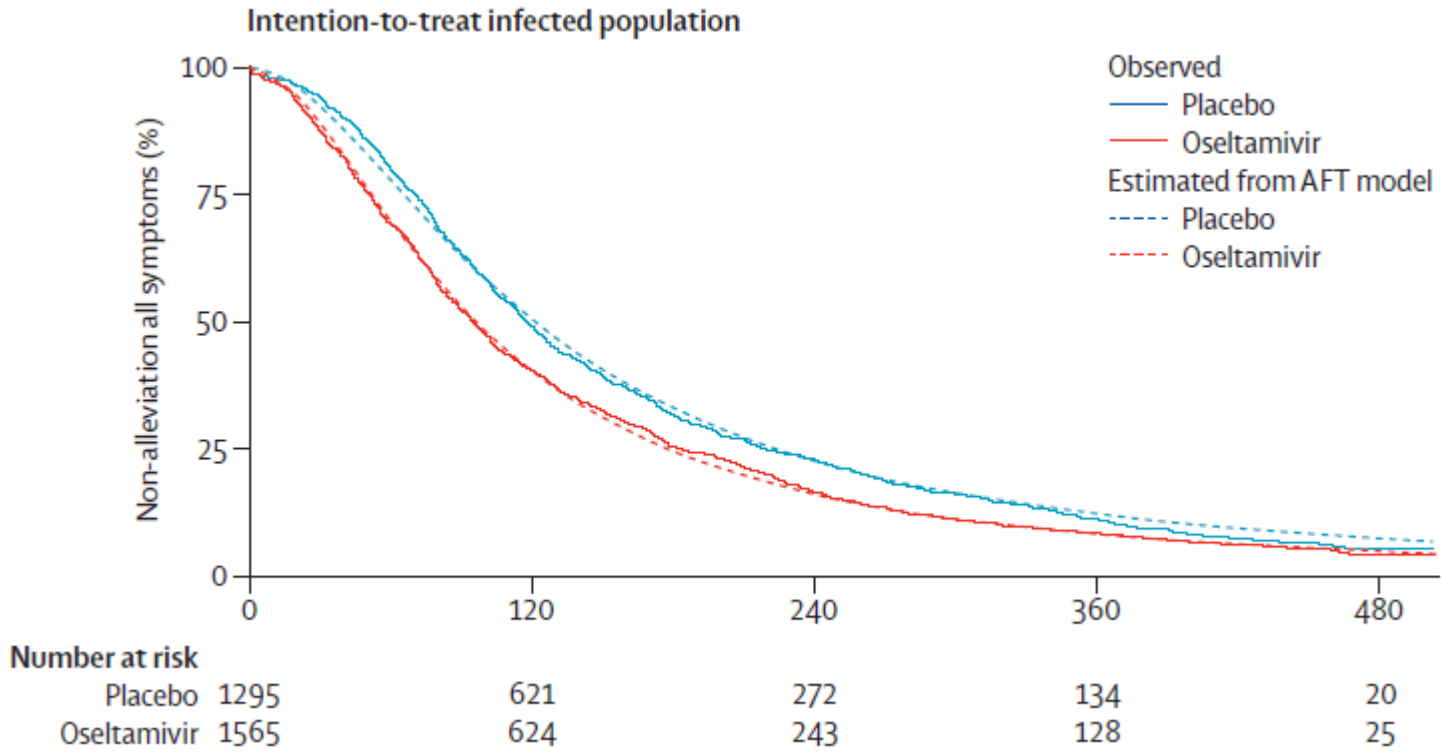
OPEN ACCESS

Tom Jefferson *reviewer*[1], Mark Jones *senior research fellow (biostatistics)*[2], Peter Doshi *assistant professor*[3], Elizabeth A Spencer *nutritional epidemiologist*[4], Igho Onakpoya *research fellow in evidence-based practice and pharmacovigilance*[4], Carl J Heneghan *professor*[4]

Jefferson T et al. BMJ 2014;348:g2545

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto



Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

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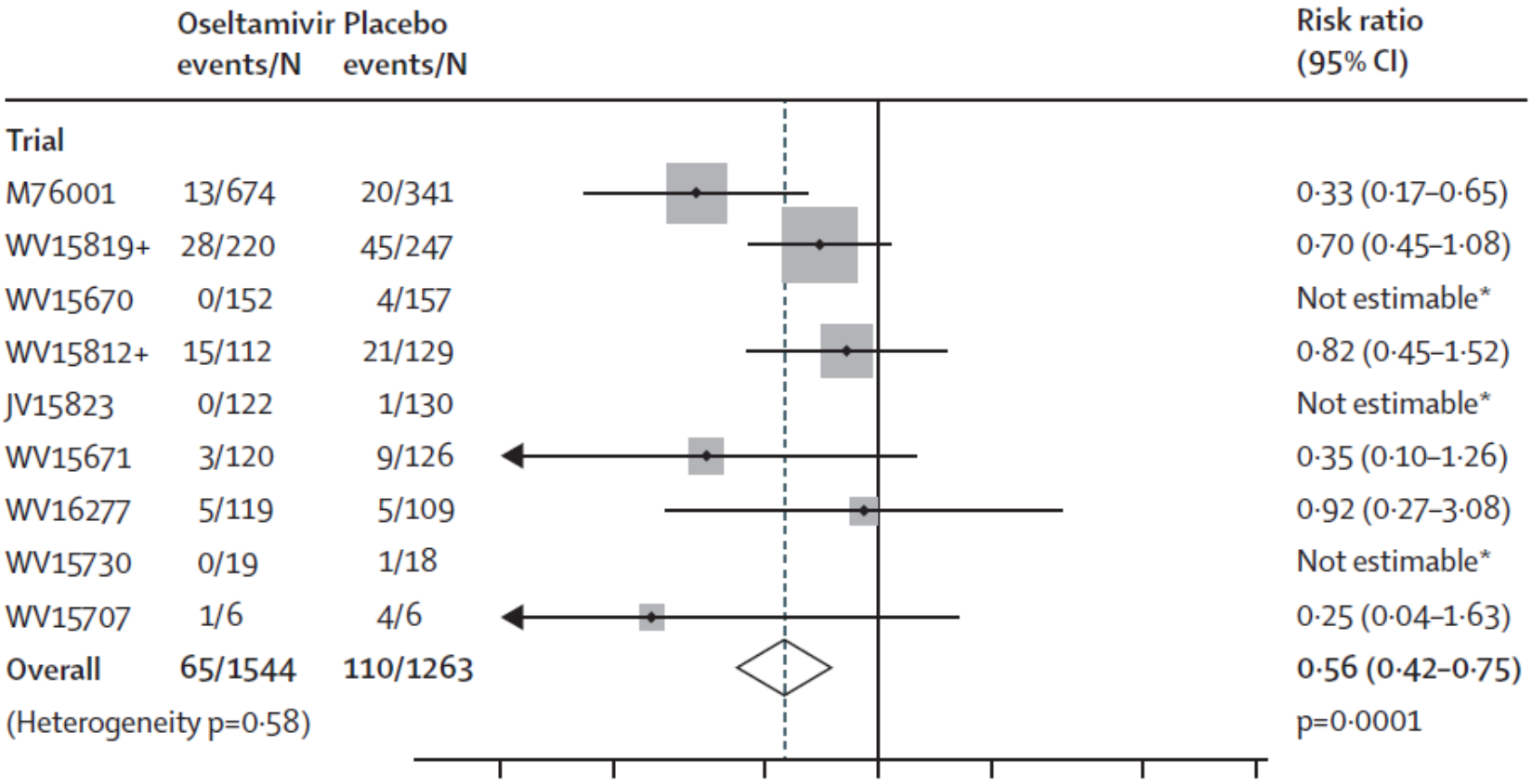
LRTC, intention-to-treat infected population



Articles

www.thelancet.com Published online January 30, 2015

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

- oseltamivir in adults with influenza ↓↓
  - time to clinical symptom alleviation,
  - risk of lower respiratory tract complications, and admittance to hospital,

but

- increases the occurrence of nausea and vomiting.

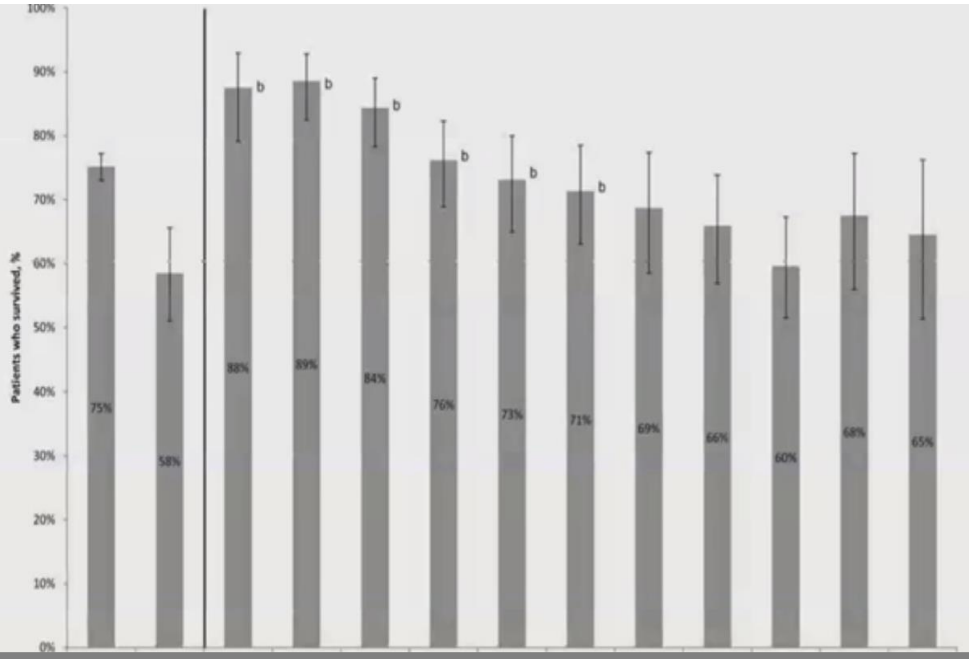
Νοσηλευόμενοι ασθενείς & early Rx

- **No available antiviral is licensed for treatment of hospitalized or severe influenza**
- Effectiveness data available for NAI (mostly oseltamivir)
- Retrospective study 653 pediatric ICU admissions 2009-2012: NAI-treated, 6% died compared with 8% untreated cases (OR = 0.67, 95% CI: 0.34–1.36). The estimated risk of death was reduced in NAI-treated cases (OR 0.36, 95% CI: 0.16–0.83, multivariate model-severity factors). Treatment within 48 hr of illness onset was significantly associated with survival (P = .04).
- Retrospective study over 5 seasons 2009-2014 (> 600 adults): Treatment within 6 hr of hospitalization was associated with shorter hospital LOS (P < 0.001) and no deaths compared to 18 deaths (4.5%) in patients receiving NAI after 6 hours and 4 deaths (3.4%) in patients not receiving NAI.

Louie JK Pediatrics, 2013, 132;e1539 (US Kaiser/CDC)
Katzen J, CID 2019, 69(1):42-58 (US UPenn, Duke, Northwestern)

Νοσηλευόμενοι ασθενείς & late Rx
? Διάρκεια Rx

- Benefit of treatment with initiation up to 5-7 days after onset of symptoms (but none if longer)*
- Prolonged duration (>5 days) may be considered in certain high-risk populations (immunocompromised, severely ill)
- No evidence of benefit with higher



ZANAMIBIPH

- Ενδοφλέβια μορφή σε κλινικές μελέτες

- Φάσης II μελέτη Harvard
  - 130 pts w influenza received zanamivir
    - mdn of 5 days, mdn 4.5 days after onset
  - 83% ICU, A/H1N1 pdm09 71%
  - 28 day all mortality rate 17%
  - 93 pts (+) at baseline by q PCR
    - ↓ 1.42log10 c/mL after 2 days of Rx

Marty F et al. JID 2014;209:542

ΔΟΣΟΛΟΓΙΑ

TREATMENT	0-1 month	1-3 months	3-12 months	1-13 years: Dose according to weight below				Adults (13 years and over)
				<15kg	15-23kg	23-40kg	>40kg	
Oseltamivir PO (treatment course: 5 days)	**2mg/kg/dose bd**	**2.5mg/kg/dose bd**	**3mg/kg/dose bd**	**30mg bd**	**45mg bd**	**60mg bd**	**75mg bd**	**75mg bd**
Zanamivir INH (treatment course: 5 days)	**Not licensed for children <5 years old. Adults and children >5 years: 10mg bd**							**10 mg bd**

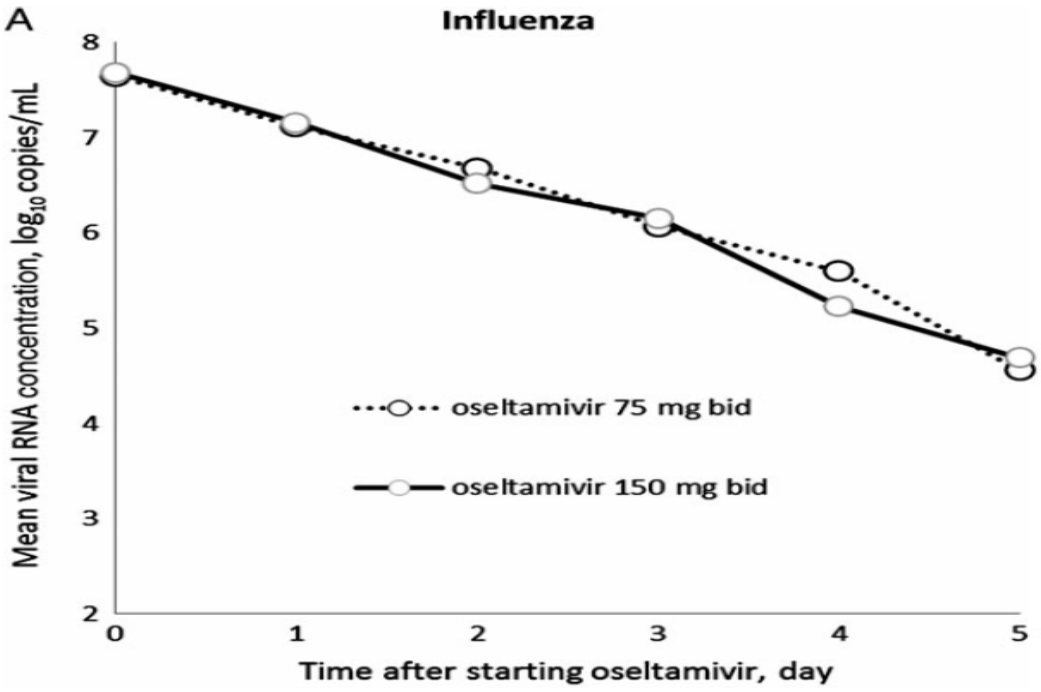
- Διάρκεια 5 ημέρες
  - ↑ σε σοβαρή νόσο/ανοσοκαταστολή
- ? Υψηλότερες δόσεις για σοβαρή νόσο

MAJOR ARTICLE

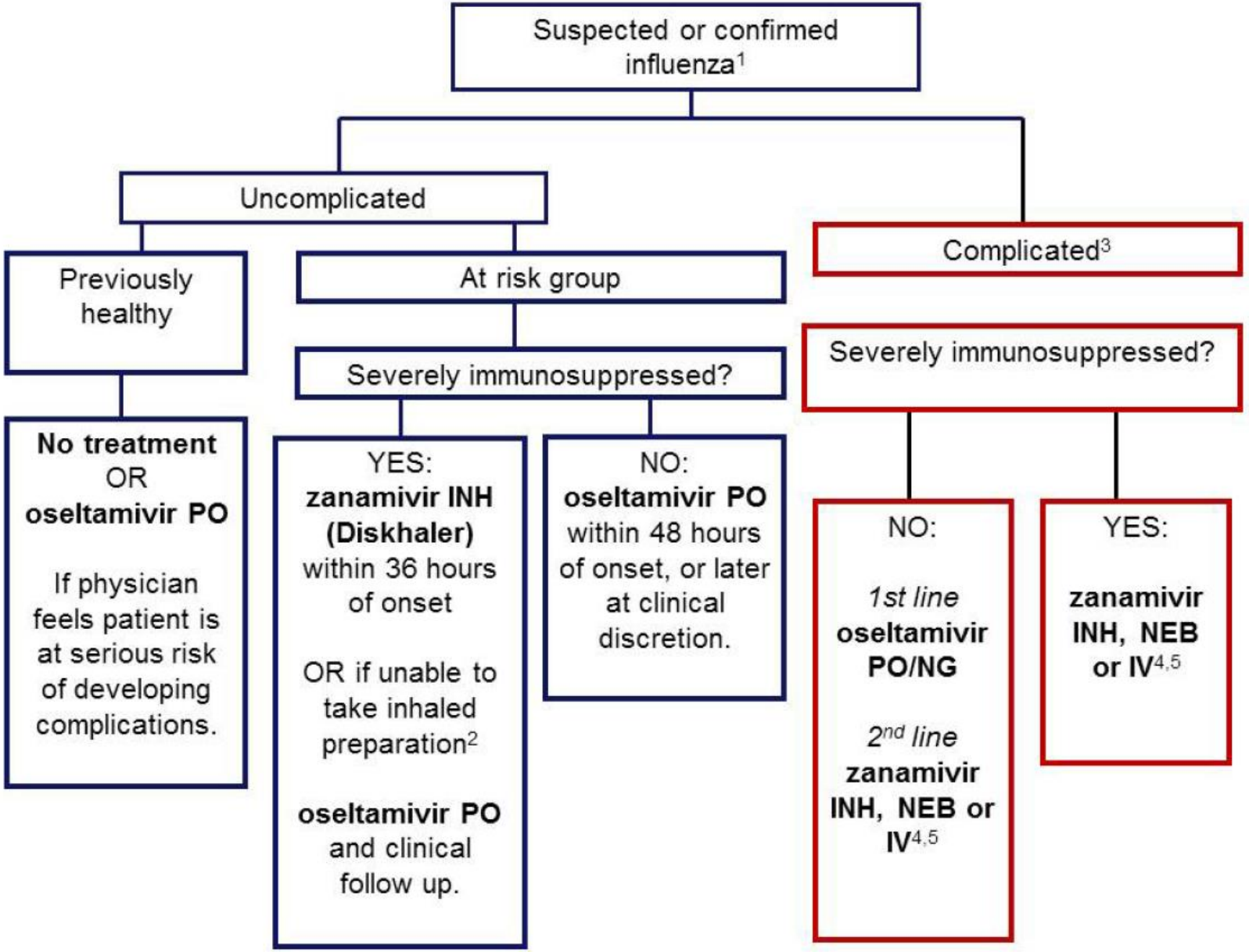
A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

N. Lee,[1,2] D. S. C. Hui,[1,2] Z. Zuo,[3] K. L. K. Ngai,[4] G. C. Y. Lui,[1] S. K. Wo,[3] W. W. S. Tam,[5] M. C. W. Chan,[4] B. C. K. Wong,[1] R. Y. K. Wong,[1] K. W. Choi,[1] W. W. Y. Sin,[1] E. L. Y. Lee,[1] B. Tomlinson,[1] F. G. Hayden,[6] and P. K. S. Chan[2,4]

[1]Department of Medicine and Therapeutics, [2]Stanley Ho Centre for Emerging Infectious Diseases, [3]School of Pharmacy, [4]Department of Microbiology, and [5]School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; and [6]School of Medicine, University of Virginia, Charlottesville



Clin Infect Dis. 2013 Dec;57(11):1511-9



Public Health England

Post exposure prophylaxis

	Exposed to circulating influenza H1N1 (2009), H3N2, or B	**Exposed to suspected or confirmed oseltamivir resistant influenza**
Previously healthy (excluding pregnant women)	No prophylaxis	No prophylaxis
At risk of complicated influenza (including pregnant women but excluding severely immunosuppressed patients and children under 5 years)	**Oseltamivir PO 10 days, once daily,** if therapy can be started within 48 hrs of last contact; or after 48 hrs on specialist advice only	**Zanamivir INH 10 days, once daily,** if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only.
Severely immunosuppressed patients (excluding children under 5 years)	**Zanamivir INH 10 days, once daily,** if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, **oseltamivir PO 10 days once daily,** (if therapy can be started within 48 hrs of last contact; or after 48 hours on specialist advice only).	**Zanamivir INH 10 days, once daily,** only if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, discuss with specialist and consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment.
Children under 5 years in at risk groups and severely immunocompromised children	**Oseltamivir PO 10 days, once daily** if therapy can be started within 48 hrs of last contact; or after 48 hrs on specialist advice only	**Discuss with specialist**. Consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment.

Public Health England

Oseltamivir
Ανεπιθύμητες ενέργειες

- Γαστρεντερικό
  - ναυτία
  - Έμετος
    - Λήψη μαζί με φαγητό

- ? Εγκεφαλίτιδα, self injury, delirium
  - Ιαπωνία, παιδιά 2006

- Αλλεργικό εξάνθημα

Zanamivir
Ανεπιθύμητες ενέργειες

- Εισπνεόμενο – ΠΡΟΣΟΧΗ !!! σε άσθμα & ΧΑΠ
  - Βρογχόσπασμος

- < 5% διάρροια, ναυτία, βήχας, κεφαλαλγία & ζάλη
- Ηπατικές διαταραχές σε iv μορφή

Kiatboonsri S et al. CID 2010;50:620

Zanamivir

Ανεπιθύμητες ενέργειες

Fatal Respiratory Events Caused by Zanamivir Nebulization

To the Editor—A 25-year-old pregnant woman (26 weeks gestation) was referred from a private hospital in Au… because of severe hy… fluenza A (… chain re-a… mptoms commenced wi… week of fever, followed by intense cough and dyspnea requiring mechanical ventilation. Chest radiograph showed bi-

time, rapid removal of the disposable filter led to immediate resumption of ventilator function. Examination of the removed … ter demonstrated inside-bl… by sticky mate… epi… …ient …ic (SpO_2, 71%– …eloped bilateral pneumo- …races. Despite all aggressive measures, her oxygenation failed to improve and the patient expired on the eighth hospital day.

Diagnosis and treatment of influenza A (H1N1) pneumonia in this patient was late, which resulted in severe acute res-

were taken by … he Unit… …his- …notification to …ssionals and hospital risk …agers [4].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

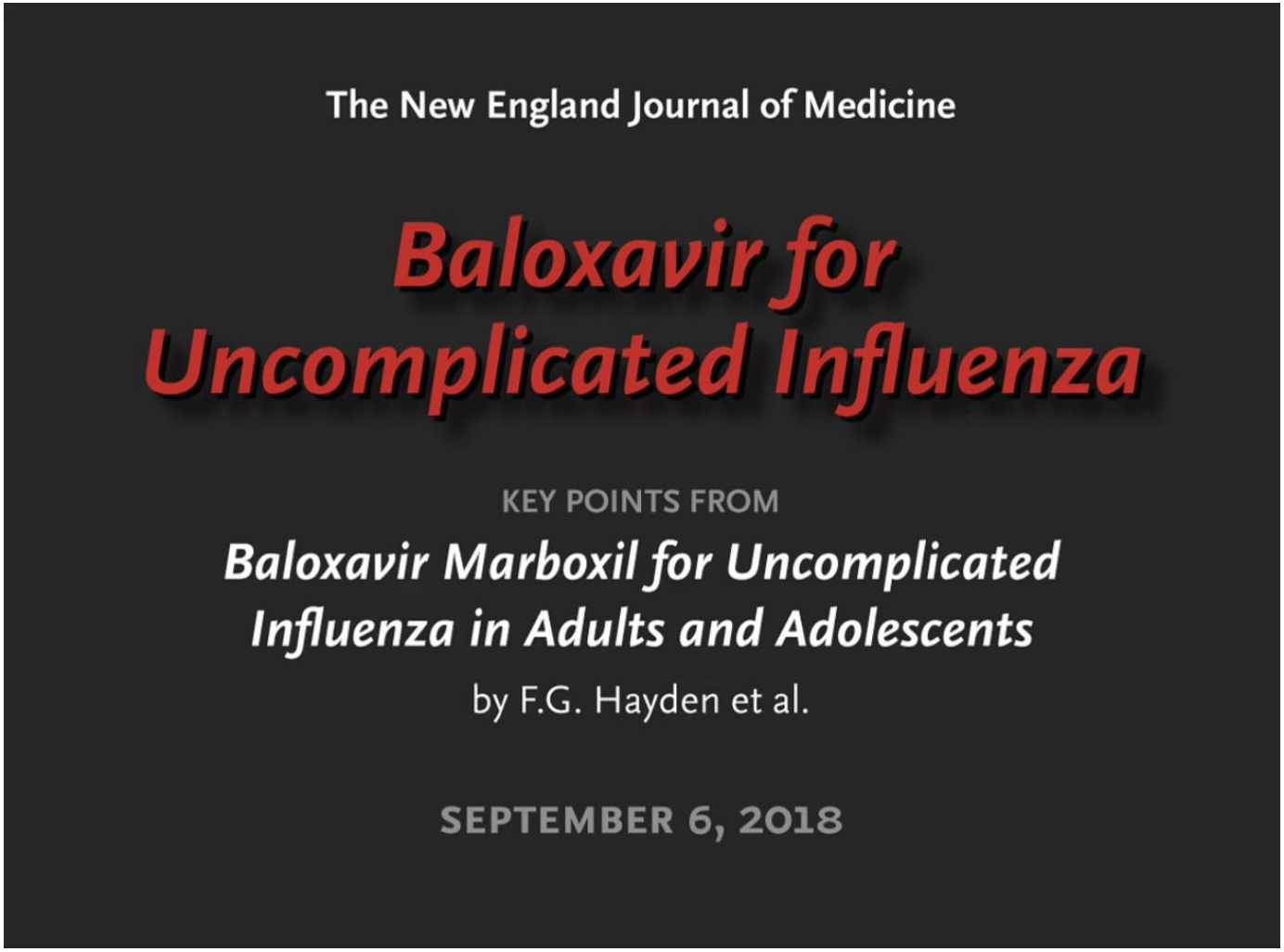
Sumalee Kiatboonsri, Charn Kiatboonsri, and Pongdhep Theerawit

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

'ΟΧΙ σε νεφελοποιητές ή μηχανική αναπνοή
'Εκδοχο λακτόζης & απόφραξη σωλήνα αναπνευστήρα

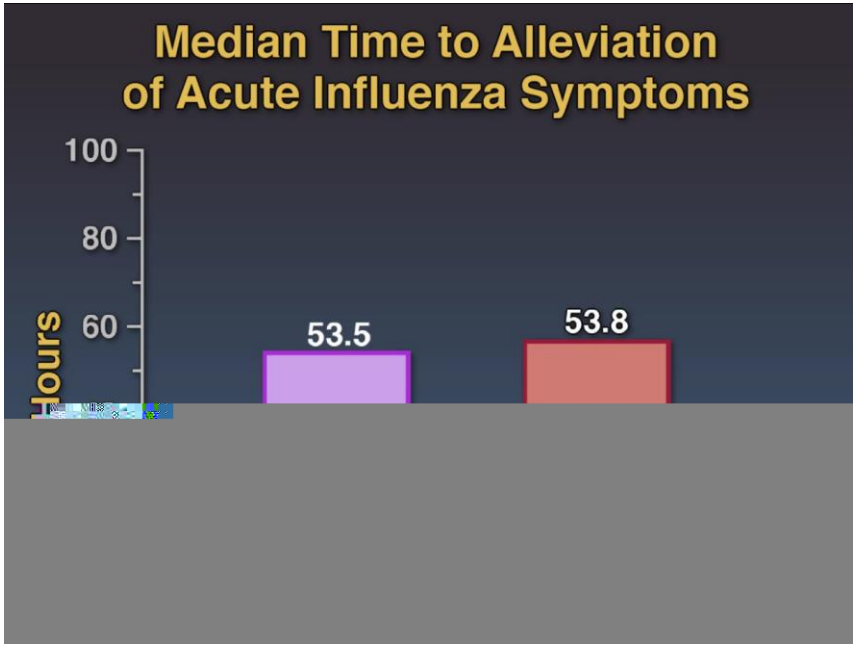
Kiatboonsri S et al. CID 2010;50:620

Influenza, new med!



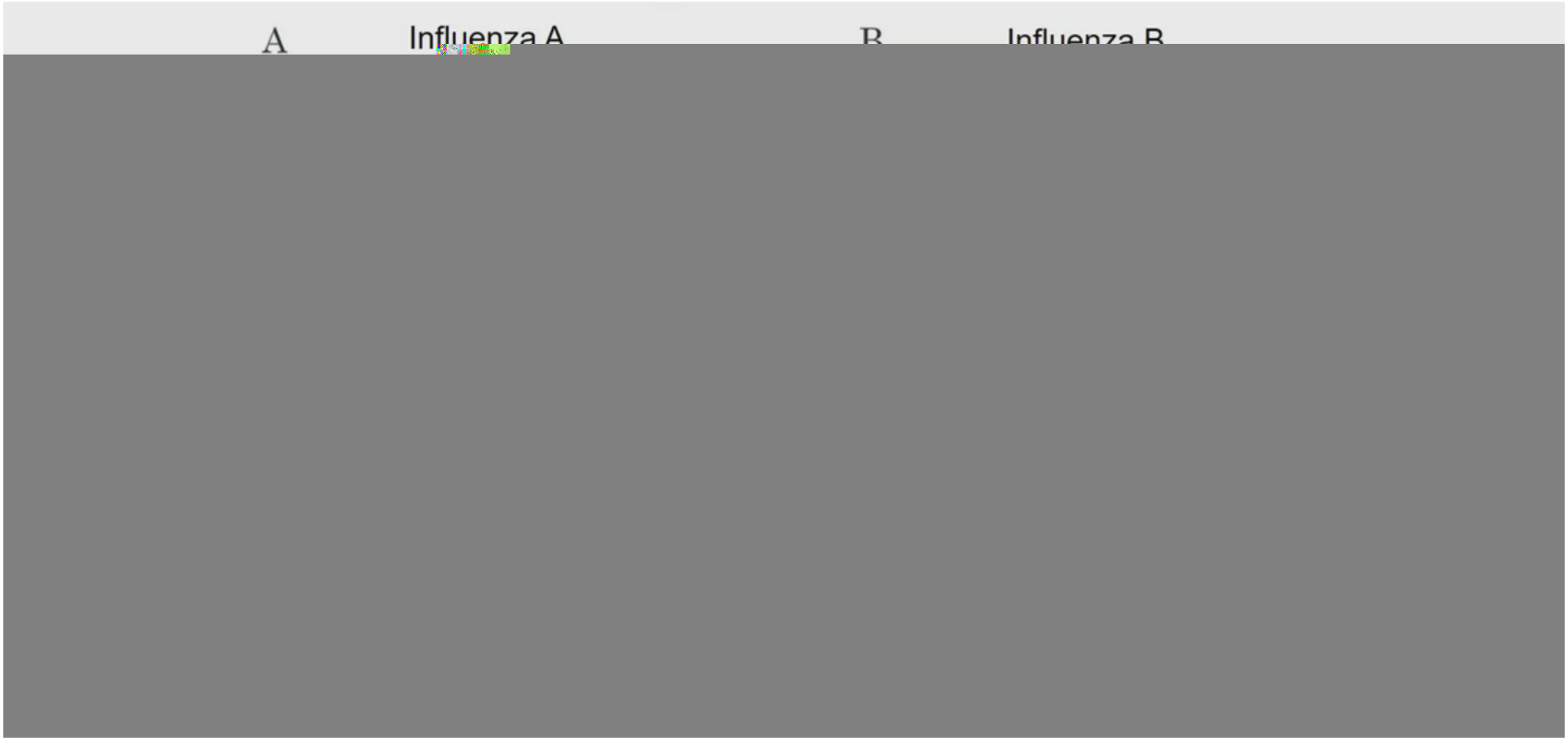
Influenza, new med!

Influenza, baloxavir!



Influenza, baloxavir!

Peramivir, Laninamivir



HAI …nitazoxanide

- Antiparasitic Thiazolide ⇨ Tizoxanide active metabolite
- Inhibits hemagglutinin maturation and intracellular trafficking in infected cells
- Ongoing Phase 3 clinical trial for patients with uncomplicated influenza
- Non-specific effect for viral URI – other viruses?
- Clinical trials for rhinovirus/enterovirus infection
- One study failed to demonstrate efficacy in hospitalized, severe influenza

Gamino-Arroyo A, et al. CID, 2019 (Mexico)

- Phase 2 study in 100 children 1–11 years with ILI symptoms of < 7 days 100-200 mg BID 5d: NTZ cohort showed symptom resolution in 4 days vs >7 days in the placebo group (P < .001)
- Phase 2 study in adults and adolescents (≥12 years) with ILI, 500 mg BID 5d: Time to resolution of symptoms was md 4 days vs 7 days in the placebo group (P = .04)
- Phase 2b/3 RCT in adolescents and adults with confirmed influenza in US, 600 mg BID 5d: Reduction in duration of clinical symptoms (95.5 vs 116.7 h ; P = .008) and infectious virus titers over time (P = .0006)

Haffizulla J, Lancet Infect Dis, 2014

Polymerase inhibitors

Ongoing clinical trials studying polymerase inhibitor effectiveness.

Antiviral	Current status	Future and ongoing clinical trials	Masking	Clinical trial reference number
Baloxavir	Licensed for use in uncomplicated outpatients in Japan and USA	Phase III:	Double blind	NCT03684044
		• Hospitalised patients		
		• Pediatric patients between 1 and 12 years of age	Double blind	NCT03629184
		• Pediatric patients less than 1 year old	Double blind	NCT03653364
		• Post-exposure prophylaxis	Open labelled	JapicCTI-184180
Favipiravir	Limited licensure in Japan for use only in pandemics	Phase II:	Open labelled	NCT03394209
		• Critically ill patients receiving current standard of care		
Pimodivir	Phase IIb	Phase III:	Double blind	NCT03381196
		• High risk patients		
		• Hospitalised patients	Double blind	NCT03376321
AL-794	**Phase 1**	**Discontinued**		

Antivirals targeting the polymerase complex of influenza viruses

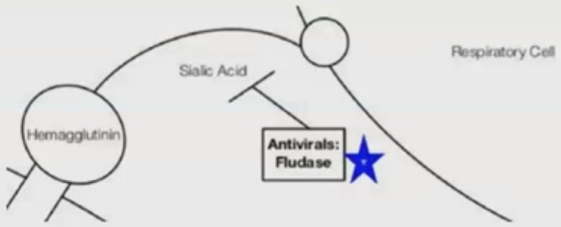
Edin J. Mifsud[a], Frederick G. Hayden[b], Aeron C. Hurt[a,c,*]

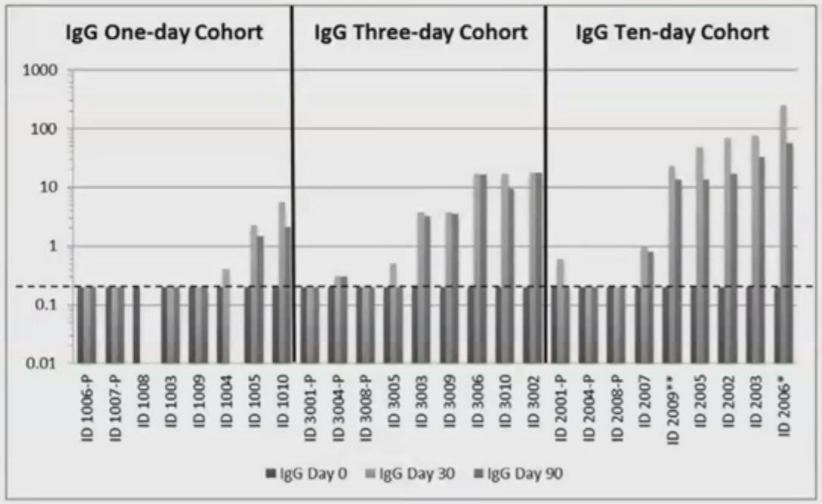
Antiviral Research 2019

DAS 181, Recombinant fusion protein

Fludase® – DAS181

- Recombinant fusion protein composed of a sialidase catalytic domain and a cationic amphiregulin (AR) glycosaminoglycan-binding sequence
- Targets the **host cell** receptors to prevent viral attachment and spread
- **Broad spectrum antiviral activity:** Influenza and Parainfluenza viruses; HMPV
- Dry particle inhalation
- Clinical trials in healthy hosts, asthma, and immunocompromised : cancer and HSCT patients
- Safe, well tolerated, no significant airway hyperreactivity in phase I-II studies when given in shorter courses (3-7 days), but present later-on
- Development of antibodies against drug after prolonged use (> 7 days)



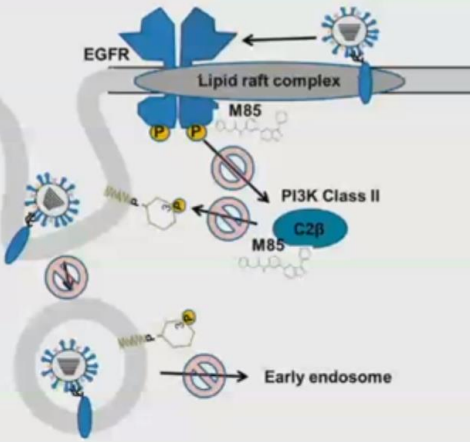


Zinilman, JM Antiviral Research 2015

Chemaly OFID 2018

Συνδυαστική Rx

Combination Therapy?



- Using drugs with different mechanisms of action might result in better efficacy, reduction in development of resistance. Eg: NAI + Baloxavir
- Amantadine + oseltamivir, ribavirin + oseltamivir, and favipiravir + oseltamivir combinations are synergistic, allowing for higher potency at lower doses
- The triple combination of amantadine + ribavirin + oseltamivir also shows synergy against influenza A viruses resistant to amantadine or oseltamivir.
- **New agents:** M85 targets epidermal growth factor receptor (EGFR) and phosphoinositide 3 class II β (or PIK3C2β) kinases, which control early stages of endocytosis, thereby inhibiting virus entry. Synergistic with Oseltamivir. Does not induce resistance. Has broad spectrum activity: Influenza A/B, human rhinovirus, Hep C.

OHanlon R, ACS, 2019 epub

Oseltamivir
Αντοχή

- Oseltamivir σε παιδιά
- Μεταλλαγμένα ανθεκτικά στελέχη
  - Έως και 500 Χ ↑ in vitro αντοχής
- 4η ημέρα θεραπείας και μετά
- ? Μετάδοση ιού μετά «θεραπεία»

Kiso M et al. Lancet 2004. 364:733-4

A H1N1pdm09

- Αντοχή - μετάλλαξη H274Y
- Ιαπωνία, ΗΠΑ, Κίνα, Σιγκαπούρη, Βιετνάμ, Δανία, Αυστραλία
- 37 στελέχη ΗΠΑ
  - 76% σε ανοσοκατεσταλμένους
  - 89% σε άτομα με λήψη οσελταμιβίρης
  - Επιδημίες σε νοσοκομείο, hem/onc pts
  - μετάδοση στην κοινότητα

Emerg Infect Dis. 2011;17(2):255.
N Engl J Med. 2010 Jan;362(1):86-7.

JAMA®

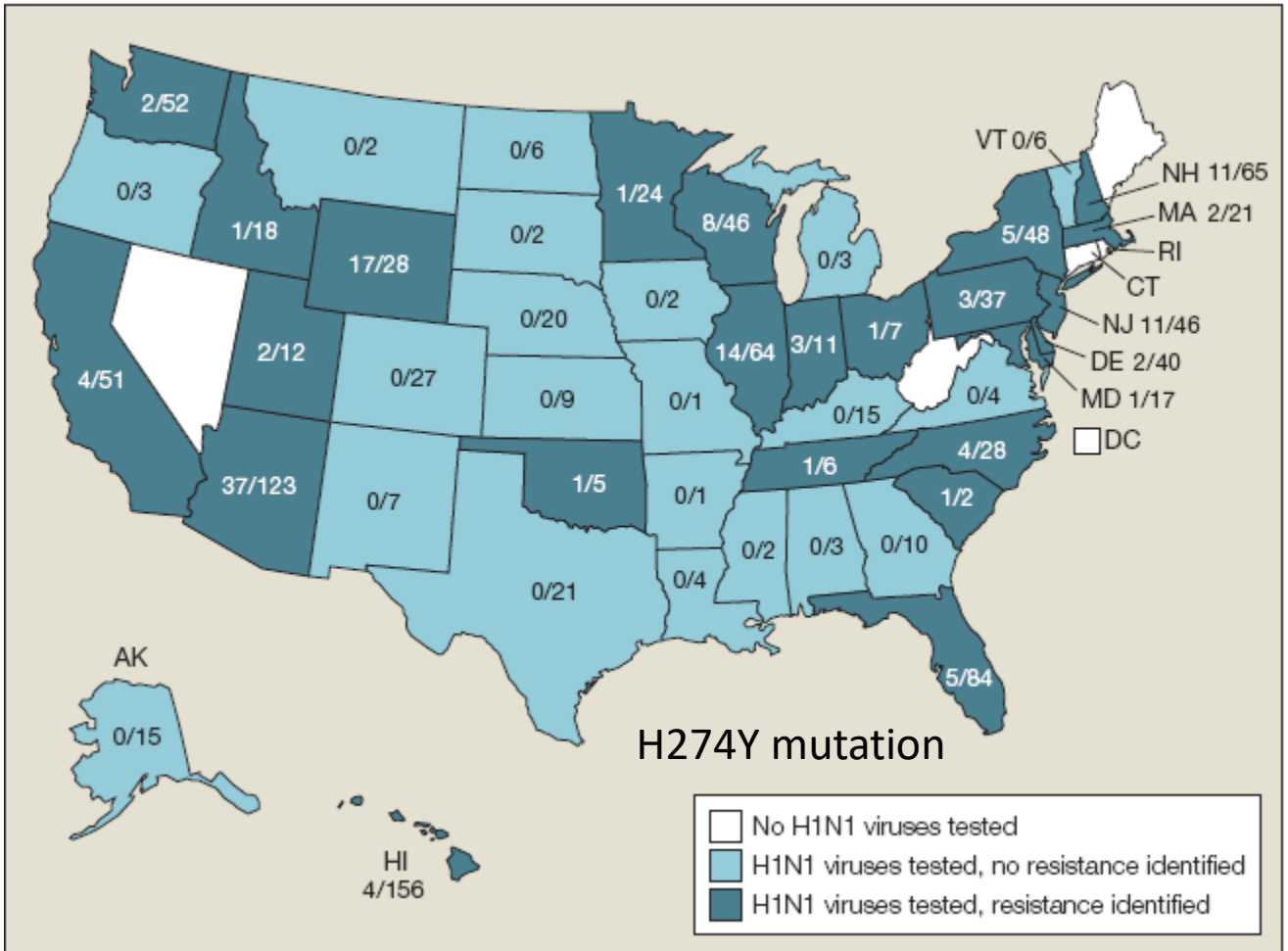
Online article and related content current as of June 17, 2009.

Infections With Oseltamivir-Resistant Influenza A(H1N1) Virus in the United States

Nila J. Dharan; Larisa V. Gubareva; John J. Meyer; et al.

JAMA. 2009;301(10):1034-1041 (doi:10.1001/jama.2009.294)

http://jama.ama-assn.org/cgi/content/full/301/10/1034



ΕΛΛΗΝΙΚΗ ΜΕΛΕΤΗ

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-016-2809-3

ORIGINAL ARTICLE

Antiviral susceptibility profile of influenza A viruses; keep an eye on immunocompromised patients under prolonged treatment

A. Kossyvakis[1] · A.-F. A. Mentis[1,2] · K. Tryfinopoulou[3,4,5] · V. Pogka[1] · A. Kalliaropoulos[1] · E. Antalis[6] · T. Lytras[7,8,9] · A. Meijer[10] · S. Tsiodras[6] · P. Karakitsos[11] · A. F. Mentis[1]

Kossyvakis A et al. EJCMID 2017

ΠΡΟΣΟΧΗ ΣΕ ΑΝΟΣΟΚΑΤΕΣΤΑΛΜΕΝΟΥΣ

Table 1 Summary of the viral characteristics and clinical aspects of the immunocompromised patients with oseltamivir-resistant A(H1N1)pdm09 virus and mixed virus populations [oseltamivir-susceptible (275H-S) and oseltamivir-resistant virus (275Y-HRI)]

Patient	Gender	Age (years)	Geographic location	Received influenza vaccine	Isolation year	Exposed to oseltamivir before specimen collection	Medical condition[a]	IC50 fold-change values[b]	Mixed virus populations detected during the course of oseltamivir and/or zanamivir treatment
A	Female	76	Rhodes Island	No	2009	Not known	Multiple myeloma	1092	No
B	Female	56	Athens	No	2010	No[c]	Multiple myeloma	732	Yes
C	Male	67	Patra	No	2010	Yes	Cancer	340	No
D	Male	61	Lamia	No	2011	Yes	Cancer	502	No
E	Female	76	Athens	No	2011	No[c]	Mantle cell lymphoma	604	Yes

[a] All lymphopenic patients

[b] Compared to the median IC50 value of normal inhibited viruses (excluding outliers)

[c] Resistant virus was confirmed in specimen under NAI treatment

Kossyvakis A et al. EJCMID 2017

ΚΕΕΛΠΝΟ

ΚΕΝΤΡΟ ΕΛΕΓΧΟΥ & ΠΡΟΛΗΨΗΣ ΝΟΣΗΜΑΤΩΝ (ΚΕΕΛΠΝΟ)

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ

ΔΕΛΤΙΟ ΤΥΠΟΥ

Εποχική Γρίπη 2014 - 2015

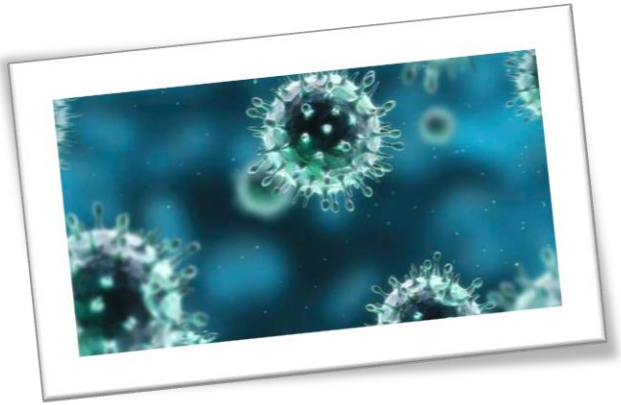
Αθήνα, 03 Οκτωβρίου 2014

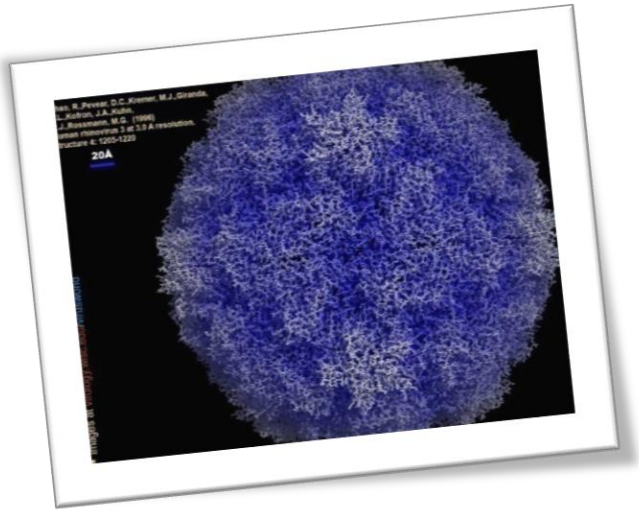
Ο ετήσιος εμβολιασμός κατά της γρίπης είναι ο καλύτερος τρόπος προφύλαξης από τη νόσο

ΚΕΝΤΡΟ ΕΛΕΓΧΟΥ & ΠΡΟΛΗΨΗΣ ΝΟΣΗΜΑΤΩΝ (ΚΕ.ΕΛ.Π.ΝΟ.)

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ

ΚΟΙΝΟ ΚΡΥΟΛΟΓΗΜΑ





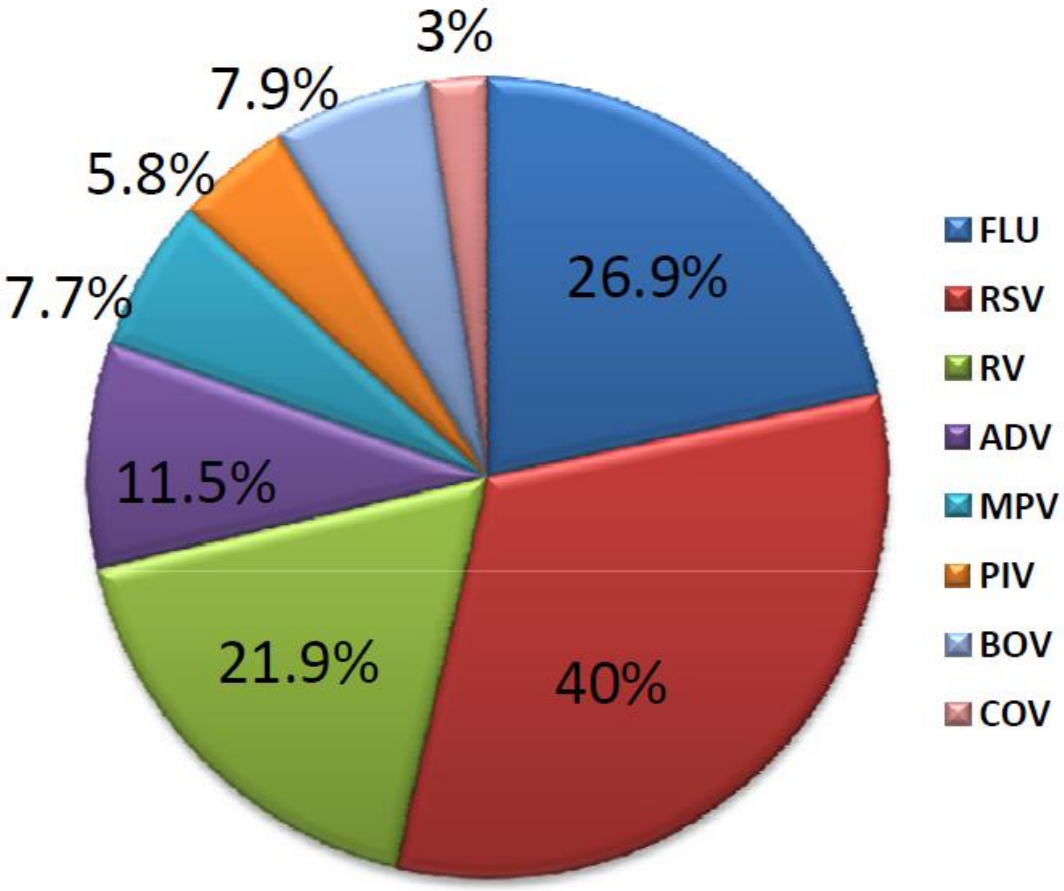
- συμπτώματα παρόμοια με της γρίπης
- ΔΔ δυσχερής στα παιδιά

Γρίπη 2016-2017

Ενημερώσου Εμβολιάσου Προφυλάξου

ΚΕΝΤΡΟ ΕΛΕΓΧΟΥ & ΠΡΟΛΗΨΗΣ ΝΟΣΗΜΑΤΩΝ (ΚΕ.ΕΛ.Π.ΝΟ.)
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ

Μελέτη Pasteur, Ελλάδα



Pogka et al, J Med Virol, 2011

Γρίπη 2016-2017
Ενημερώσου Εμβολιάσου Προφυλάξου

Αντι-ιικά, RSV

Ribavirin : RSV

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.

Αντι-ιικά, RSV

Therapeutic uses Ribavirin

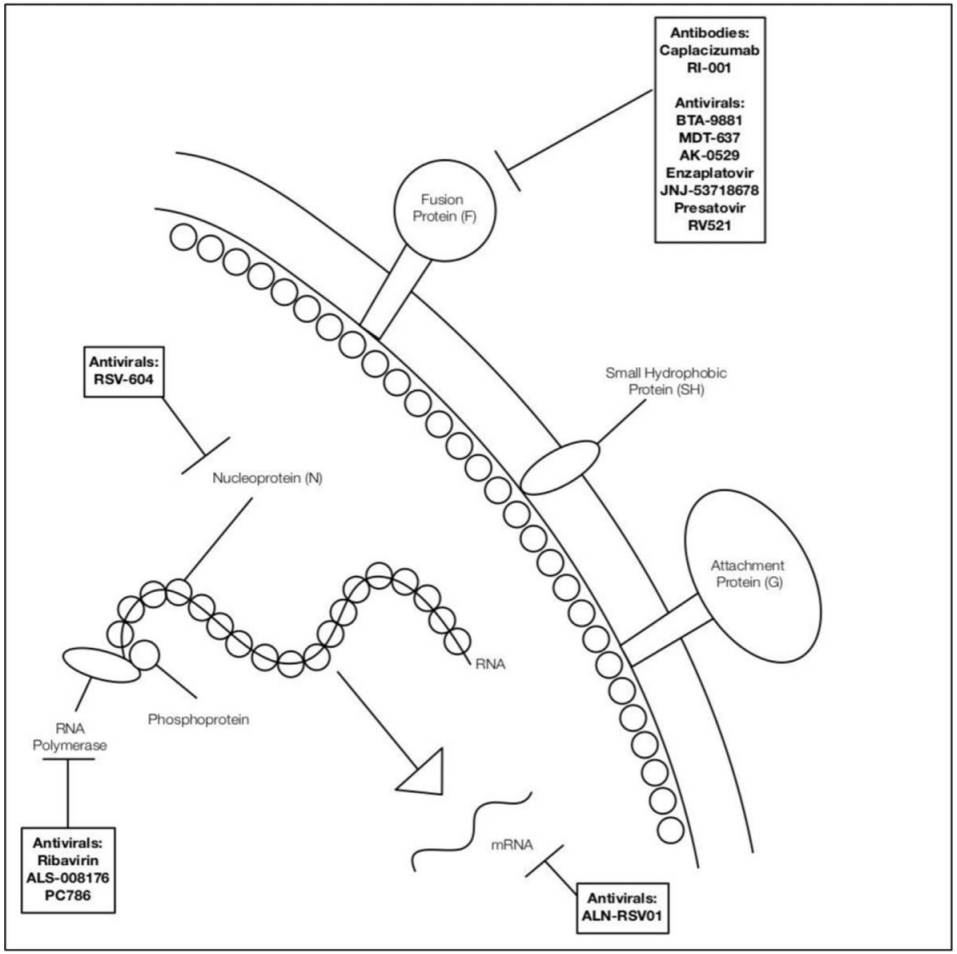
Ribavirin ->drug of choice for:

- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

alternative drug for:

- Influenza, parainfluenza, measles virus infection in immunocompromised patients

Αντι-ιικά, RSV



Nicholson 2018

HERPES SIMPLEX VIRUS (HSV)

HSV, Rx

- **3 preferred nucleoside analogues, oral meds**
  - acyclovir
  - valacyclovir
  - famciclovir

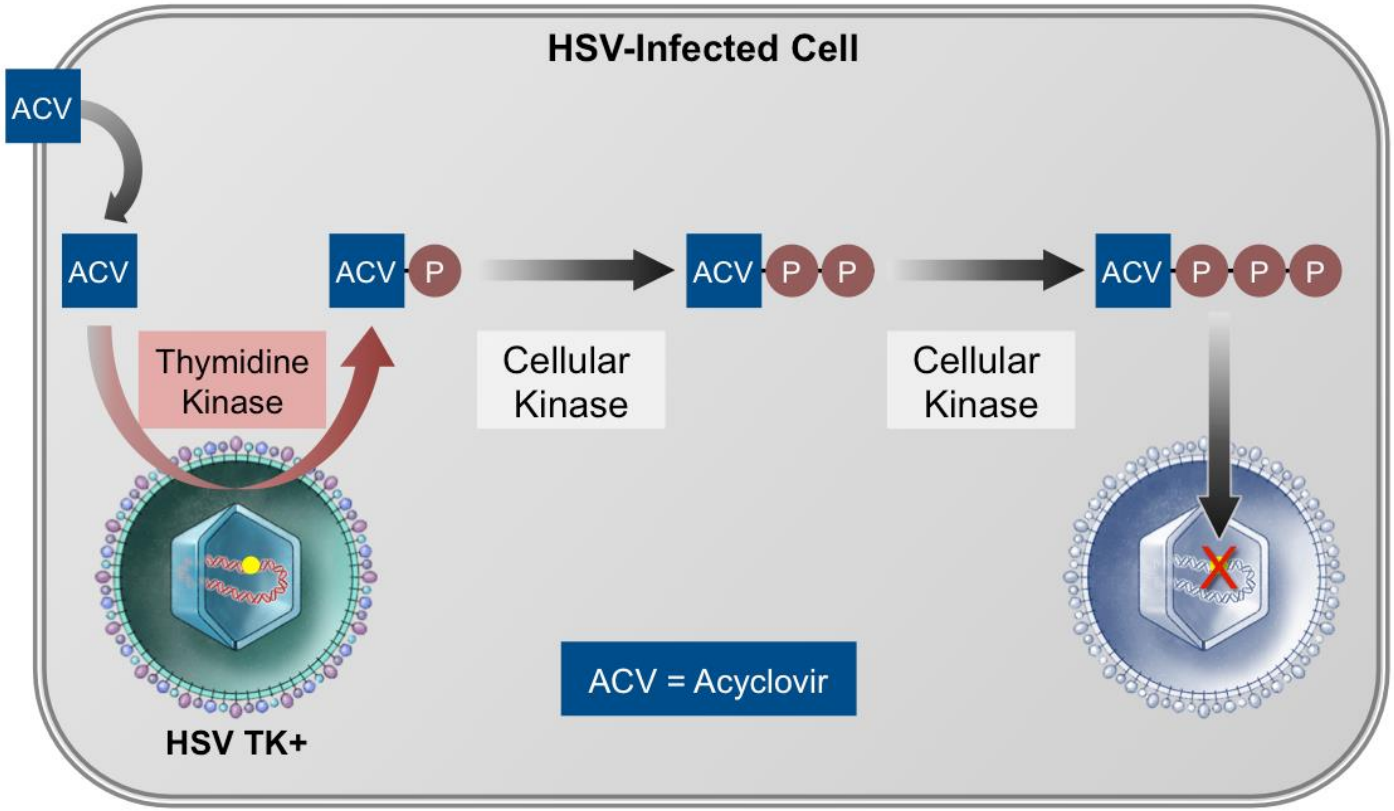
Anti-viral drugs

Acyclovir & Congeners :

- all are guanine nucleoside analogs.
- **Valacyclovir - prodrug of ACV -↑ bioavailability.**
- **Famciclovir** ->hydrolyzed to **Penciclovir**-> greatest bioavailability
  - Penciclovir is used only topically –Famciclovir-> pos

HSV, Rx

3-phosphorylation-TK enzyme -> nucleotide analogs -> inhibits DNA polymerase -> only replicating virus



HSV, Rx

- acyclovir
  - Greatest activity against HSV1, 2
- valacyclovir, famciclovir
  - greater oral bioavailability > ACV
  - dosed less frequently
  - more expensive

HSV, Rx

- **acyclovir**
  - **Only one that can be given intravenously**
  - Topical formulations available for herpes labialis
    - ACV X 5/d, PCV X 9/d
  - Penciclovir = related compound - oral

HSV 1, 2 - pos Rx

- Severe 1ry gingivostomatitis
- Genital HSV, proctitis
  - Long term prophylaxis for recurrences

HSV, Rx

- **acyclovir** beneficial if started early during 1ry HSV
  - most data from young children!
  - 72 children w HSV gingivostomatitis start within 3 days- 200mgx5
    - Earlier disappearance of fever 1d vs 3d
    - Shorted duration of lesions 1d vs 4d
    - ↓ duration of odynophagia 4d vs 7d
    - ↓ viral shedding 1d vs 5d

Amir J et al BMJ 1997

HSV 1, 2 – i.v. Rx
ACV only

- **IV Rx w Acyclovir** (slow infusion):
  - Encephalitis & meningitis, systemic dz, immunocoompromised
  - Acute retinal necrosis
  - Neonatal dz (20mg/kg q8h for 14-21 days)
  - Esophagitis (5-10mg/kg q8h for 5 days)
- **Watch --> crystalluria ---> ↑ Cr**
  - **Maintain adequate hydration**

Adverse effects of Acyclovir

- Malaise, HA, N/V, LFTs, CNS
- Nephrotoxicity - crystalluria, haematuria, renal insufficiency
  - Maintain adequate hydration

HSV encephalitis- Rx

- Acyclovir, 10 mg/kg iv q8 hrs 14-21 days

- **Mortality 28% at 18 months post Rx**
  - Predictors of adverse outcome
    - Age > 30 years,
    - ↓ level of consciousness, GCS < 6
    - Sx duration before starting ACV > 4 days
      - If < 4 days mortality -> 8%

HSV, i.v. Rx, severe Dz

- **disseminated, pneumonitis, or hepatitis, CNS dz**
  - IV acyclovir 5 to 10 mg/kg iv q8 hrs x 2 to 7 days or until clinical improvement is observed,
  - followed by pos Rx to complete at least 10 days of

- **HSV encephalitis -> 21 days of iv Rx**.

- ACV dose adjustment in impaired renal function

HSV Keratoconjuctivitis

- Trifluridine (Viroptic® 1% ophthalmic)
  - 1 drop q2h (max 9 drops/day)
  - Active against acyclovir resistant strains
  - Also active against vaccinia virus and smallpox

Recurrent HSV 1 - Rx

- **Episodic Rx**
  - **Must be initiated quickly – watch for prodromal Sxs**
- **Chronic Suppressive Rx**
- **No Rx**
- **? Prophylactic approach**

Recurrent HSV 1 – Rx
Herpes labialis

- **Topical Rx for HSV labialis**
  - **Modest benefit at best, Penciclovir study, n = 1573**
    - **Cream q 2 hrs x 4 d vs placebo**
    - **↓ time to healing 4.8d vs 5.5d**
    - **↓ duration of pain 3.5d vs. 4.1d**
  - **Other agents, docosanol, banzalconium - ?**

Spruance SL et al. JAMA 1997

Recurrent HSV 1 – Rx
Herpes labialis

- **Episodic Rx for HSV labialis, asap**
  - **ACV** **200-400mg x 5**
  - **FCV** **750mg bid x1 day or 1500 x1**
  - **VCV** **2g bid x 1 day**

Spruance SL et al. JAMA 1997

Recurrent HSV 1 – Rx
Herpes labialis

- **Chronic suppressive Rx for HSV**
  - **Frequent, bothersome recurrences**
  - **Serious systemic complications**
    - **Erythema multiforme, eczema herpeticum, recurrent aseptic meningitis**
  - **If no specific prodrome**
  - **Does not change natural hx of dz**

Spruance SL et al. JAMA 1997

HSV, Rx

Genital HSV-1st episode

2015 STD Treatment Guidelines: Genital Herpes

Table 1. Treatment of First Clinical Episode of Genital Herpes

Recommended
Acyclovir 400 mg orally three times a day for 7–10 days
Note: Treatment can be extended if healing is incomplete after 10 days of therapy.
or
Acyclovir 200 mg orally five times a day for 7–10 days
Note: Treatment can be extended if healing is incomplete after 10 days of therapy.
or
Valacyclovir 1 g orally twice a day for 7–10 days
Note: Treatment can be extended if healing is incomplete after 10 days of therapy.
or
Famciclovir 250 mg orally three times a day for 7–10 days
Note: Treatment can be extended if healing is incomplete after 10 days of therapy.

HSV, Rx

Genital HSV-episodic Rx for recurrences

2015 STD Treatment Guidelines: Genital Herpes

Table 2. Episodic Therapy for Recurrent Genital Herpes

Recommended
Acyclovir 400 mg orally three times a day for 5 days
or
Acyclovir 800 mg orally twice a day for 2 days
or
Acyclovir 800 mg orally three times a day for 2 days
or
Valacyclovir 500 mg orally twice a day for 3 days
or
Valacyclovir 1 g orally once a day for 5 days
or
Famciclovir 125 mg orally twice daily for 5 days
or
Famciclovir 1 g orally twice daily for 1 day
or
Famciclovir 500 mg once, followed by 250 mg twice daily for 2 days

HSV, Rx

Genital HSV-suppressive Rx for recurrences

2015 STD Treatment Guidelines: Genital Herpes

Table 3. Suppressive Therapy for Recurrent Genital Herpes

The frequency of genital herpes recurrences diminishes over time in many persons, potentially resulting in psychological adjustment to the disease. Therefore, periodically during suppressive treatment (e.g., once a year), providers should discuss the need to continue therapy.

Recommended

Acyclovir
400 mg orally twice a day

or

Valacyclovir
500 mg orally once a day

Note: Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in persons who have very frequent recurrences (i.e., ≥10 episodes per year).

or

Valacyclovir
1 g orally once a day

or

Famciclovir
250 mg orally twice a day

HSV, Rx

Genital HSV in HIV - episodic Rx

2015 STD Treatment Guidelines: Genital Herpes

Table 4. Episodic Therapy for Recurrent Genital Herpes in Persons with HIV

For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

Recommended

Acyclovir
400 mg orally three times a day for 5–10 days

or

Valacyclovir
1 g orally twice a day for 5–10 days

or

Famciclovir
500 mg orally twice a day for 5–10 days

HSV, Rx

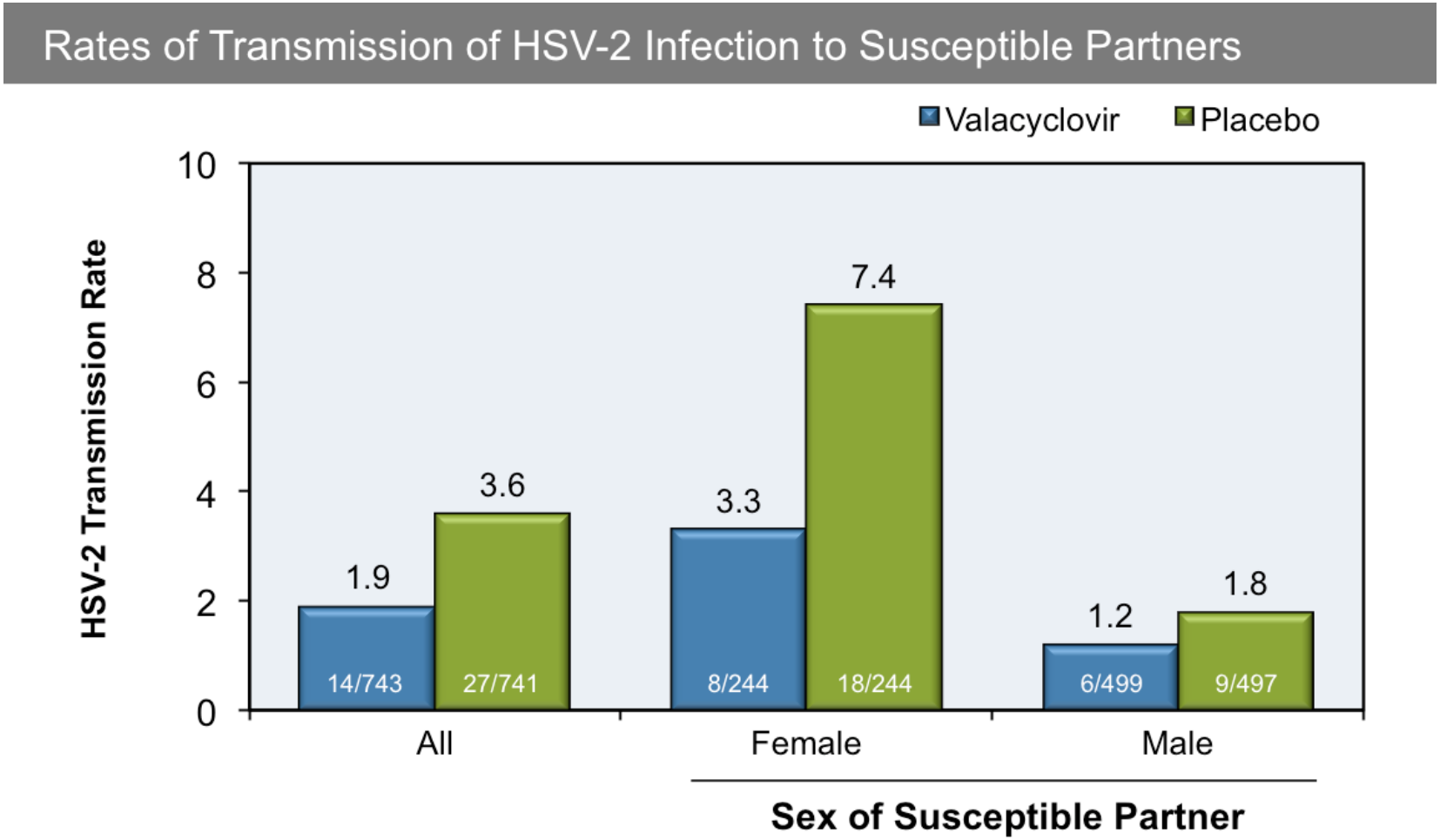
Genital HSV in HIV - suppressive Rx

2015 STD Treatment Guidelines: Genital Herpes

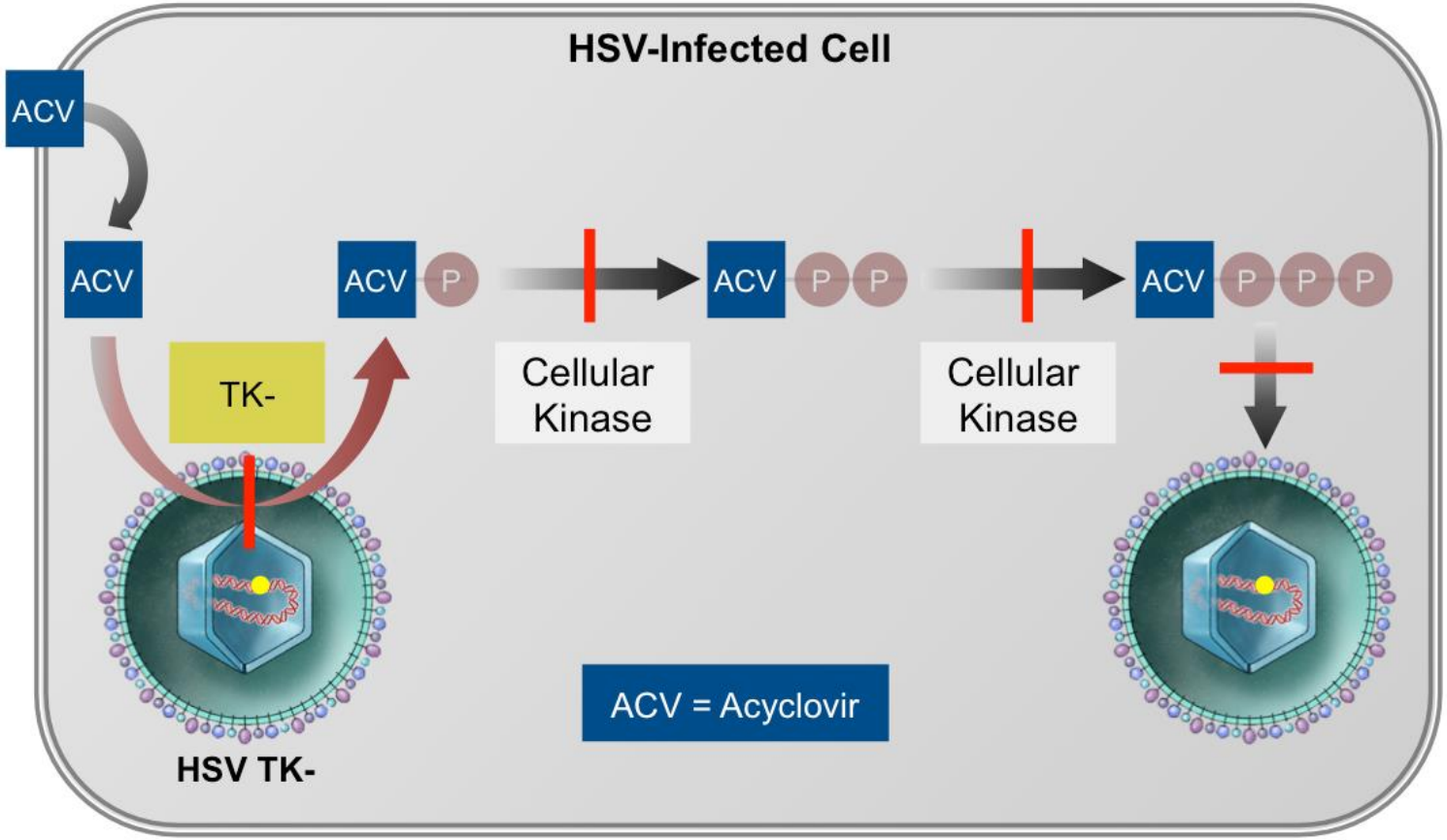
Table 5. Suppressive Therapy in Persons with HIV

Recommended
Acyclovir 400–800 mg orally twice to three times a day
or
Valacyclovir 500 mg orally twice a day
or
Famciclovir 500 mg orally twice a day

Genital HSV, Prevention daily suppressive Rx



Acyclovir R-HSV



Acyclovir R HSV

- **Foscarnet**: 40 mg/kg IV every 8 to 12 hours for 21 to 28 days or until clinical resolution is attained. Foscarnet can potentially cause severe adverse effects, including nephrotoxicity and electrolyte disturbances.
- **Cidofovir**: 5 mg/kg IV once weekly for 21 to 28 days or until clinical resolution is attained. Note the cidofovir can cause severe renal abnormalities.
- **Imiquimod 5% cream**: Apply to lesions three times per week for 21 to 28 days.
- **Cidofovir 1% gel**: Apply to lesions three times per week for 21 to 28 days, or longer based on the clinical response. This preparation is not commercially available and must be compounded by a pharmacist.

Famciclovir Resistance

- Mutations in viral TK or DNA polymerase
- Cross-R with ACV in TK negative strains
- May still have activity in TK altered strains

HSV in pregnancy

re[illegible]t Genital but no Sxs->start at 36 wks

the risk of HSV recurrence at delivery by 75%,

2015 STD Tre[illegible]es: Genital Herpes

Table 6. Suppre[illegible]y of Pregnant Women with Recurrent Genital Herpes

Recommended

Acyclovir
400 mg orally three times a day

Note: Treatment recommended starting at 36 weeks of ge[illegible]merican College of Obstetricians Gynecologists. Clinical management guidelines for obstetricia[illegible]anagement of herpes in preg ACOG Practice Bulletin No. 82. Obstet Gynecol 2007;109:1489–98.)

or

Valacyclovir
500 mg orally twice a day

Note: Treatment recommended starting at 36 weeks of gestation. (Source: American Colleg[illegible] Gynecologists. Clinical management guidelines for obstetrician-gynecologists. Management of [illegible] ACOG Practice Bulletin No. 82. Obstet Gynecol 2007;109:1489–98.)

Genital HSV, Prevention
investigational strategies

- HSV vaccines
  - Preventive & therapeutic
- **Tenofovir Disoproxil Fumarate gel or oral**
  - Pre-exposure Prophylaxis (PrEP) in studies for HIV prevention
  - ↓ HSV acquisition by 46%, no ↓ in shedding if HSV-2 sero(+)

Αντιμικροβιακή χημειοπροφύλαξη intermediate risk-NCCN 2019

• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (eg, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis[p] • Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis[q] • Consider for at least 6–12 months after autologous HCT

• Prophylaxis[c]: HSV (400–800 mg PO BID); VZV in allogeneic HCT recipients (800 mg PO BID)[1]

Αντιμικροβιακή χημειοπροφύλαξη
Υψηλός κίνδυνος-Cancer, NCCN 2019

High	• Acute leukemia	HSV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis during active therapy including periods of neutropenia[p]
	• Proteasome inhibitors	VZV		VZV prophylaxis during active therapy including periods of neutropenia[q]
	• Alemtuzumab therapy • Allogeneic HCT • GVHD requiring steroid treatment	HSV VZV		HSV prophylaxis[p] • Minimum of 2 mo after alemtuzumab and until CD4 ≥200 cells/mcL VZV prophylaxis[q] • Prophylaxis should be considered for at least 1 y after allogeneic HCT

- Prophylaxis[c]: HSV (400–800 mg PO BID); VZV in allogeneic HCT recipients (800 mg PO BID)[1]

Candidate HSV antivirals

- Inhibitors of helicase-primase enzyme
- BILS 179 BS, BAY 57-1293, ASP1251 (amenamivir) – effective in murine models

EPSTEIN-BARR VIRUS (EBV)

EBV & Rx

- **Supportive , iv ACV** may have modest benefit
  - **Effect on replication but not on latent stage, ? EBV-HLH**
- **Corticosteroids** indicated in certain scenarios
  - **Airway obstruction**
  - Consider steroids (no data) in
    - life threatening infection e.g. liver failure
    - Autoimmune hemolytic or aplastic anemia

EBV & Rx

- **EBV-PTLD**, malignancies, ACV, GCV may prevent
  - **Adoptive cell Rx w cytotoxic T-lymphocytes (CTL)**
  - ? IL-2, IFN-a, IVIG
- Immunization
  - GP350/220 vaccine against EBV cancers-safe immunogenic
    - Did not prevent infection

Odumade et al Clin Microbiol Rev 2011

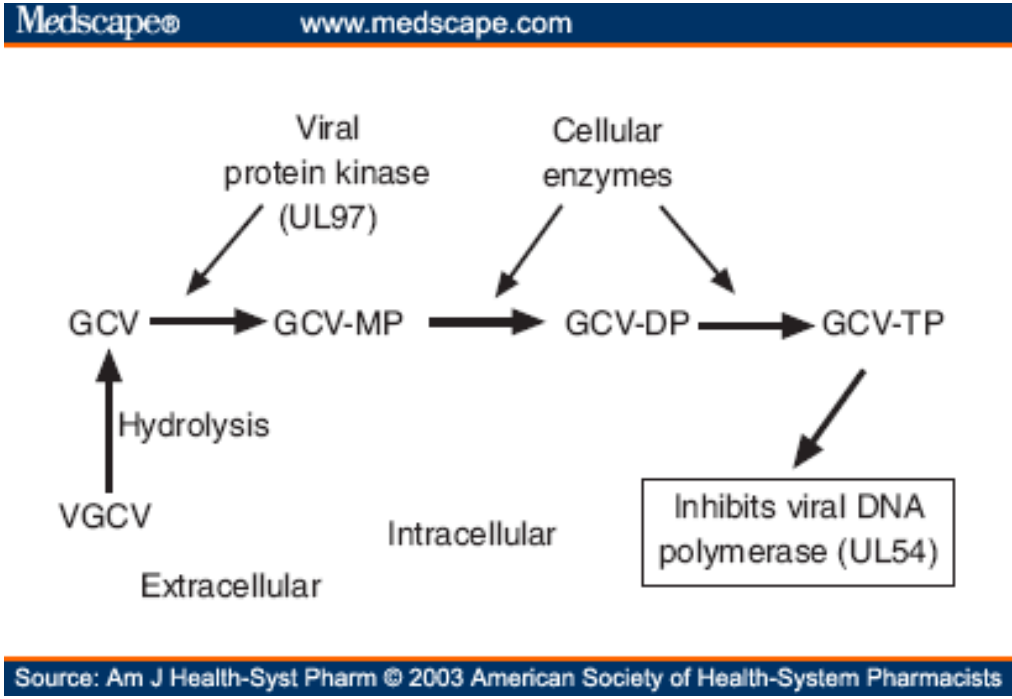
CYTOMEGALOVIRUS (CMV)

CMV – Rx

- **NO in immunocompetent -> self-limited illness**
  - **If severe can use GCV or val-GCV or Foscarnet**
- **Ganciclovir iv** – Valganciclovir pos
  - **toxicities!!! ---> bone marrow, kidneys**
- **if Resistance --> foscarnet, cidofovir**

Ganciclovir Mechanism of Action

- Competes w deoxy-guanosine triphosphate similar to acyclovir
- However in CMV, viral-encoded phosphotransferase converts to ganciclovir triphosphate
- Unlike acyclovir, ganciclovir contains a 3'-hydroxyl group, allowing for DNA to continue



Ganciclovir (Cytovene®)

- Oral, intravenous, and intraocular

- Spectrum:
  - CMV (10X potency of acyclovir)
  - EBV (10X potency of acyclovir)
  - HSV/VZV (equal to acyclovir)
  - Human Herpesvirus 6

Ganciclovir-AEs

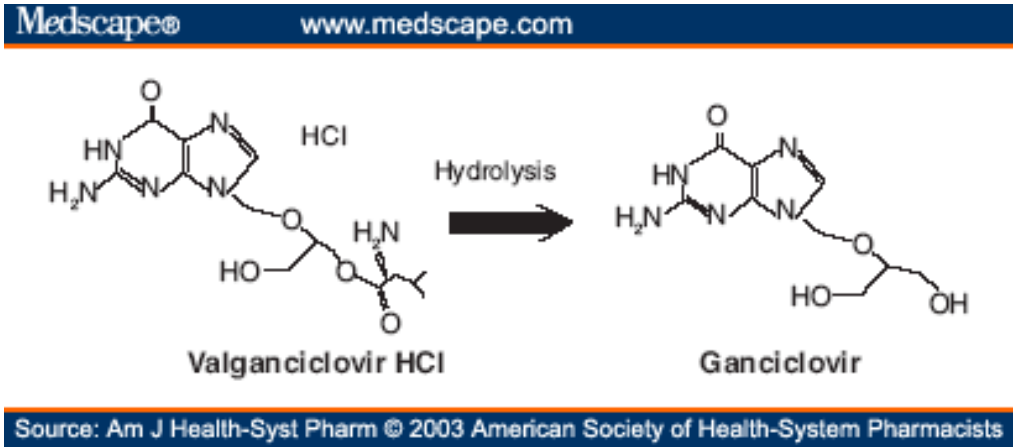
- **Reversible pancytopenia** (most common)
- Fever, Rash
- Phlebitis
- Renal dysfunction
- Confusion, Psychiatric disturbances
- Seizures

Adverse effects of Ganciclovir

- Myelosuppression – Neutropenia and thrombocytopenia

Vanganciclovir (Valcyte®)

- L-valyl **prodrug of ganciclovir**
- Available **orally only**
  - Quickly hydrolysed after absorption
- Spectrum: similar to ganciclovir
- Adverse effects: similar to ganciclovir



(Val)ganciclovir

- **Resistance**
  - Mutations in the viral protein kinase (**UL97**)
    - Responsible for monophosphorylation
    - Confers **resistance to ganciclovir alone**
  - Mutations in the viral polymerase gene (UL54)
    - May show cross resistance to similar antivirals

Foscarnet – Mechanism of Action

- Trisodium phosphonoformate hexahydrate
  - Inorganic pyrophosphate analog
- **Does not require thymidine kinase**
  - Works on HSV strains deficient of this enzyme, directly inhibits viral DNA and RNA -polymerase and viral inverse transcriptase

Foscarnet – Mechanism of Action

- Selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerase
  - Non-competetive inhibitor
  - **Does not affect cellular DNA polymerase**

- **Resistance** by alterations to viral DNA polymerase
  - Not caused by thymidine kinase alterations
  - **Does not cause cross resistance to ganciclovir or cidofovir**

Foscarnet (Foscavir®)

- **Intravenous only** – controlled infusions
- **Spectrum:**
  - **CMV including ganciclovir resistant strains**, **acyclovir resistant HSV** or VZV, EBV, Influenza A and B, HBV, and HIV

Adverse effects of Foscarnet

- **Hypocalcemia and hypomagnesemia**
  - chelation of the drug with divalent cations
- **Neurotoxicity**
  - headache, hallucinations, seizures
- **Nephrotoxicity**
  - acute tubular nephrosis, interstitial nephritis
    - Can require dialysis
- Other -> nausea, vomit, anemia, arrhythmias, neutropenia

Foscarnet (Foscavir®)

- **↓ dose in renal failure**
  - Saline loading (adequate hydration)
  - Appropriate renal dosing adjustments
  - Avoidance of concurrent nephrotoxic medications

Cidofovir – Mechanism of Action

- Acyclic nucleoside phosphonate derivative
- **Phosphorylation not dependent on viral kinases**
  - May actually enhance activity to TK deficient strains
- **Selective inhibition of CMV DNA**
  - Active drug as cidofovir diphosphate
  - DNA polymerase
- Incorporation into viral DNA chain results in reductions of the rate of viral DNA synthesis

Cidofovir (Vistide®)

- **intravenous only**
- **Spectrum**:
  - **CMV including acyclovir and foscarnet resistant strains, HSV 1 and 2,** VZV, EBV, HHV-6, HHV-8
  - Also has activity against DNA viruses: papilloma virus, polyomavirus, poxvirus, and adenovirus

Cidofovir (Vistide®)

- Must be avoided in preexisting **renal impairment**
- AEs: **nephrotoxicity** (dose-limiting), neutropenia, metabolic acidosis
- Must be given with adequate hydration and PO probenecid---see labeled dosing directions

Cidofovir Resistance

- Due to point mutations in viral DNA polymerase in CMV, pox, and adenovirus
- **Confers resistance to GCV in CMV**

- **Foscarnet activity not affected** by cidofovir resistance
  - Still **active against UL97** mutation
  - Not active against the UL54 mutation

Dosing for CMV

	Load	Maintenance
Ganciclovir	5mg/kg IV q12 X 14-21 days	5 mg/kg IV daily 1 g PO TID
Valganciclovir	900 mg PO BID X 21 days	900 mg PO daily
Foscarnet	90 mg/kg IV q12 X 14-21 days	90-120 mg/kg IV daily
Cidofovir	5 mg/kg IV qwk X 2 doses	5 mg/kg IV every 2 weeks

Dosing for Resistant HSV/VZV

Drug	Dosage	Duration
Acyclovir-Resistant Herpes Simplex (severe infection, immunocompromised)		
Foscarnet	40 mg/kg IV q8hrs	14-21 days
Acyclovir-Resistant Zoster (not FDA approved)		
Foscarnet	40 mg/kg IV q8hrs	10 days

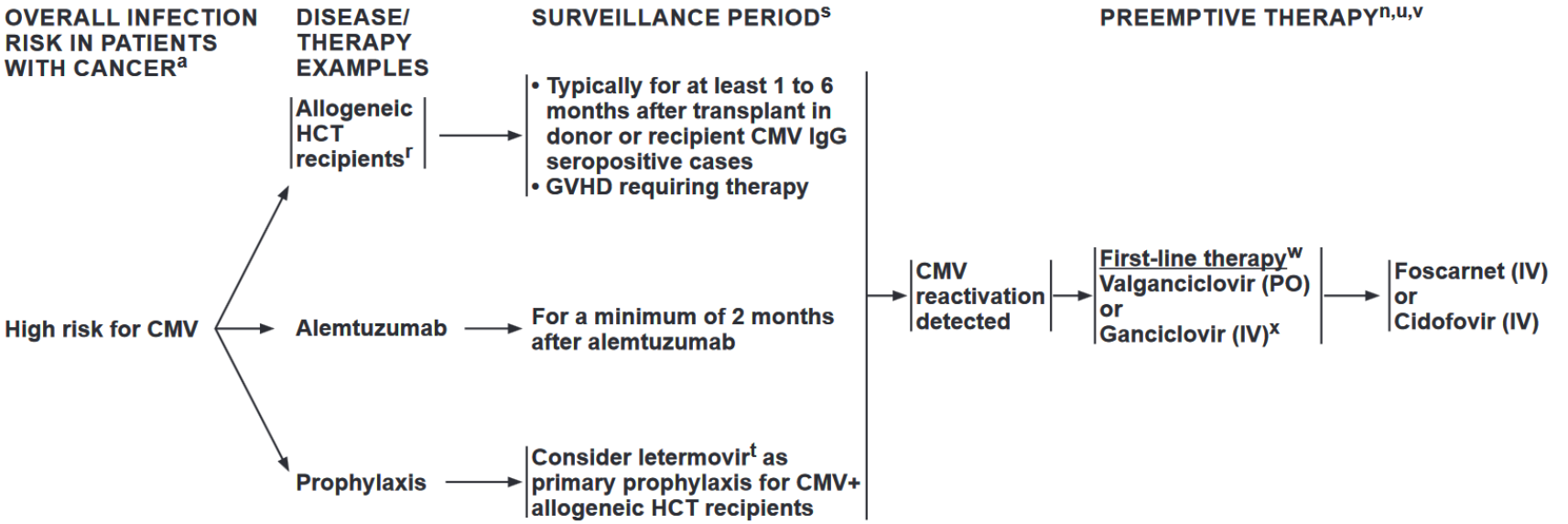
CMV reactivation or dz

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE



Surveillance = weekly monitoring by PCR-> if viremia w no Sxs -> Pre-emptive Rx – at least 2wks & until PCR (-)

Doses of antivirals in CMV

ANTIVIRAL AGENTS[a]

Agent	Common Indication[b]	Spectrum	Comments/Cautions
Cidofovir[f]	Treatment: Cidofovir 5 mg/kg IV every wk for 2 wks, followed by cidofovir 5 mg/kg every 2 wks with probenecid 2 gm PO 3 h before the dose, followed by 1 gm PO 2 h after the dose and 1 gm PO 8 h after the dose and IV hydration	CMV HZV VZV Adenovirus	• Ocular toxicity, bone marrow toxicity • Hydration and probenecid required to reduce nephrotoxicity • Third-line for CMV
Foscarnet	Prophylaxis for CMV: 60 mg/kg IV every 8–12 h for 7 d, followed by 90–120 mg/kg IV daily until day 100 after HCT[e,7,8] Preemptive therapy for CMV: Induction for 2 wks, either 60 mg/kg IV every 8 h or 90 mg/kg IV every 12 h Therapy: Acyclovir-resistant HSV (40 mg/kg every 8 h for 7–10 days); CMV disease (90 mg/kg every 12 h for 2 wks followed by 120 mg/kg daily for at least an additional 2–4 wks and resolution of all symptoms). Add IVIG for CMV pneumonia.	HSV VZV CMV	Drug of choice for acyclovir-resistant HSV and VZV and ganciclovir-resistant CMV • Nephrotoxic; monitor electrolytes Clinical data are limited for HHV-6 and HHV-8
Letermovir	Primary prophylaxis for CMV+ allogeneic HCT recipients: 480 mg PO daily or daily IV infusion over 1 hour through beginning between day 0 and 28 post-transplantation and continue for 100 days post-transplant. Reduce dose to 240 mg PO/IV daily if co-administered with cyclosporine.	CMV	• Has not been studied as an agent for treatment • Has multiple drug interactions; see package insert. • Lacks activity against other herpes group virus (including HSV and VZV)

anti-CMV immunoglobulin to prevent severe congenital infection?

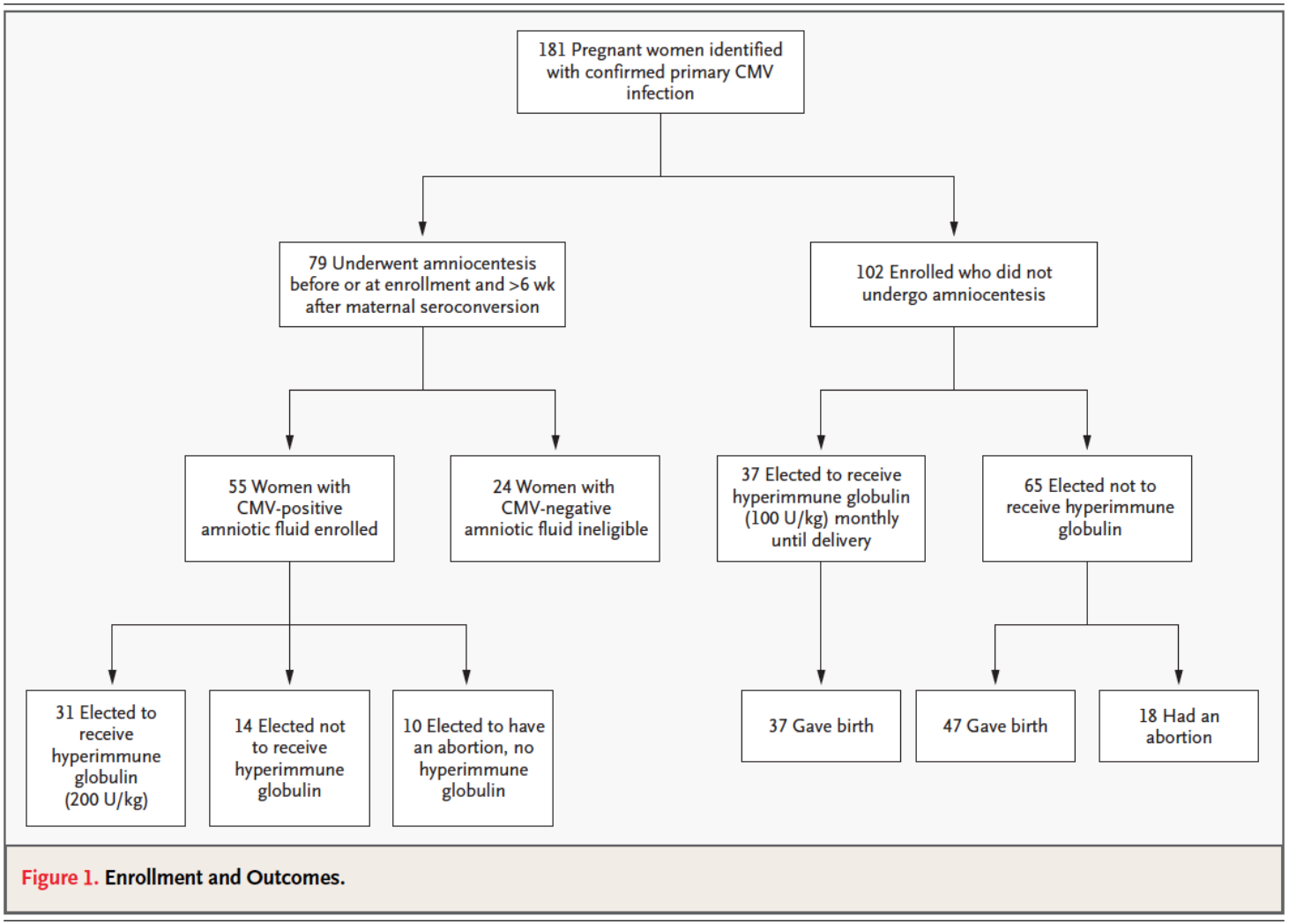


Figure 1. Enrollment and Outcomes.

Congenital CMV disease	1 (3%)	7 (50%)	6 (16%)	19 (40%)

N Engl J Med 2005; N Engl J Med 2014; 370:1316.

CMV – investigational/new agents

- Brincidofovir
- **Letermovir**
  - Viral terminase subunit Pul56
  - **Large RTC in HCT, good safety profile, no myelosuppression,** V236M mutation in low dose
- Maribavir

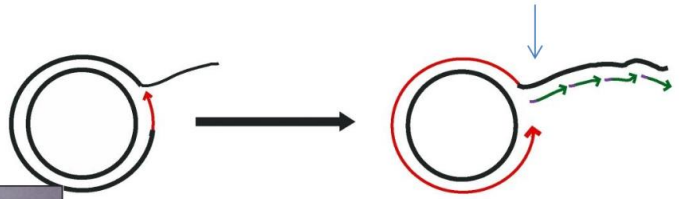
Chemaly et al NEJM 2014, Lischka P et al JID 2016, Marty fm et al

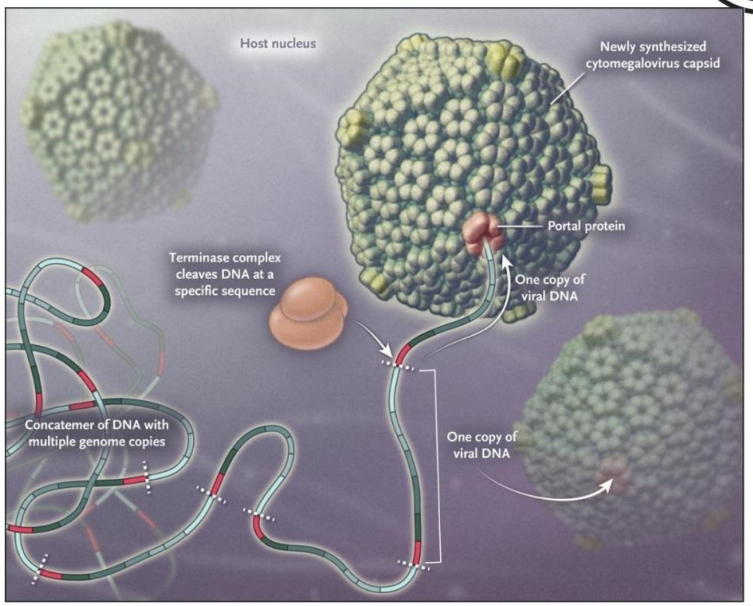
CMV – investigational/new agents

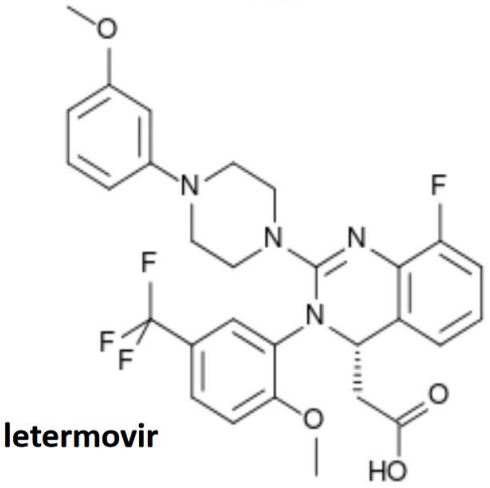
Letermovir

Targets the viral terminase:

Cleaves viral genomes







letermovir

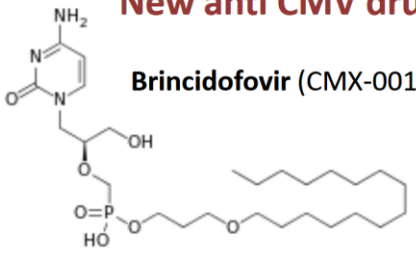
Griffiths PD, Emery VC. N Engl J Med 2014;370:1844-1846.

Resistance conferred by a single point mutation in UL56 (terminase)

Chemaly et al NEJM 2014, Lischka P et al JID 2016, Marty fm et al IDWEEK 2017

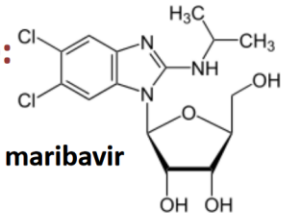
CMV – investigational/new agents

New anti CMV drugs in the pipeline:



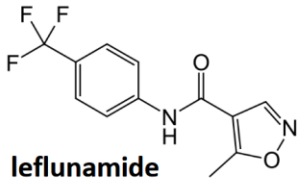
Brincidofovir (CMX-001)

Lipid conjugate of CDV
Acyclic nucleotide inhibitor of UL54
Lower toxicity, long t1/2
Broad spectrum activity against DNA viruses:
CMV, adenovirus, polyomaviruses, pox viruses
Phase 2 CMV prophylaxis trial(260 HSCT):
Significantly better than placebo
Dose limiting diarrhoea



maribavir

Targets pUL97
Low toxicity, effective in phase 2 trials
No benefit in phase 3 prophylaxis trial
- Dose too low
- Low rate of CMV events
Resistance pUL97 and pUL27



leflunamide

Immunosuppressive agent
Activity against CMV, HSV, BK
Blocks virion assembly

Chemaly et al NEJM 2014, Lischka P et al JID 2016, Marty fm et al IDWEEK 2017

CMV – letermovir

prophylaxis for CMV-seropositive adult recipients of allogeneic HCT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2014 VOL. 370 NO. 19

Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation

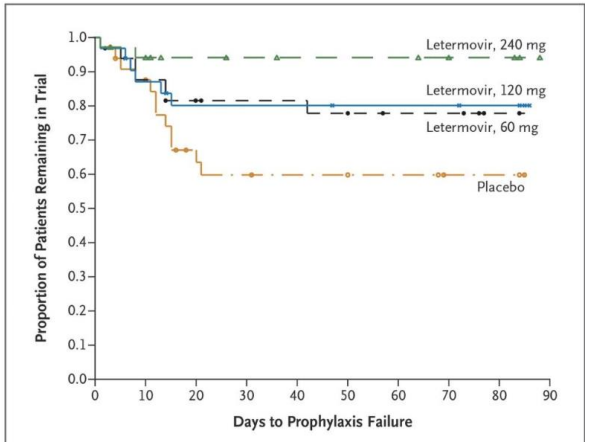
Roy F. Chemaly, M.D., Andrew J. Ullmann, M.D., Susanne Stoelben, M.D., Marie Paule Richard, M.D., Martin Bornhäuser, M.D., Christoph Groth, M.D., Hermann Einsele, M.D., Margarida Silverman, M.D., Kathleen M. Mullane, M.D., Janice Brown, M.D., Horst Nowak, Ph.D., Katrin Kölling, M.Sc., Hans P. Stobernack, D.V.M., Peter Lischka, Ph.D., Holger Zimmermann, Ph.D., Helga Rübsamen-Schaeff, Ph.D., Richard E. Champlin, M.D., and Gerhard Ehninger, M.D., for the AIC246 Study Team*

Phase 2 prophylaxis trial:
131 CMV sero-positive allo-HSCT recipients

Incidence and time to failure of prophylaxis
3 dosages, 12 weeks
60, 120, 240 mg or placebo

Dose dependent reduction in CMV viraemia episodes
Safety profile similar to placebo

KM plot of time to failure of prophylaxis:



Chemaly et al NEJM 2014, Blood Adv. 2018;2:2159-2175

CMV vaccine

- MF59-adjuvanted CMV glycoprotein B subunit vaccine had 40-50% efficacy in recent trials
- Likely no vaccine for several yrs

Vaccine 2016;34:313.

Varicella- Zoster Virus, VZV

Neonatal Varicella

- **Zoster immunoglobulin** ->
  - to susceptible pregnant women
  - w contact with suspected varicella cases

Neonatal Varicella

- **Zoster immunoglobulin** -> to infants
- whose mothers develop varicella
  - during the last 7 days of pregnancy or
  - the first 14 days after delivery

VZV - Rx

- **acyclovir** had been shown to accelerate the resolution of the disease and is prescribed to reduce complications
- 5-7 days w any of the agents, ACV, VCV, FCV

VZV - Rx

- **Acyclovir** should be given promptly
  - immunocompromised individuals with varicella infection
  - normal individuals with serious complications
    - pneumonia and encephalitis.

VZV - Zoster Rx

- **Acyclovir, valacyclovir, & famciclovir**.
  - **patients over 50 years of age -> offer corticosteroids**

    for decrease in incidence of post – herpetic neuralgia

Zoster - Prevention

- Preventive measures for individuals at risk of contracting severe varicella infection
  - e.g. leukaemic children, neonates, and pregnant women
  - Zoster immunoglobulin (ZIG)
- A live attenuated vaccine is available.
  - DO NOT USE in severe immunosuppression
- New recombinant vaccine IN USA

Other HHV (6,7,8)

Clinical Manifestations, HHV-6

- Primary HHV-6 infection -> **Roseola Infantum,** -a classical disease of childhood.
  - Most cases in infants between 4 m-2 yrs.
  - A **spiking fever** over 2 days followed by a **mild rash**.
  - The fever is high enough to cause **febrile convulsions.**
  - may be complicated by **encephalitis.**

Roseola Infantum

Diagnosis and Management

- Serology, PCR in immune-compromised
- There is **no specific antiviral treatment for HHV-6 infection.**
- **Same susceptibility as CMV**
  - **GCV, FOSCARNET, CDFV in transplant pts w pneumonitis, encephalitis in allo-HCT**
- Inheritent chromosommaly integrated virus -> 1-2% of population

HHV-7

- No firm role in human disease
  - Fever, rash, encephalitis, lichen planus, DRESS
- **>95% of adults seropositive**
- **Fever, rash, febrile seizures** in children
- **Cofactor for CMV** dz in renal Tx pts

HHV-7

- Dx only in research settings
- **No clear indications for Rx**
  - **In vitro foscarnet, cidofovir, Tenofovir**

Human Herpes Virus 8

- Belong to the γ-herpesviruses subfamily of herpesviruses
- Originally isolated from cells of **Kaposi's sarcoma (KS)**
- Associated w **Castleman's disease** and **primary effusion lymphomas**

Human Herpes Virus 8

- **HHV-8 DNA is found in almost 100% of cases of Kaposi's sarcoma**
  - **Most patients with KS have antibodies against HHV-8**
- **The seroprevalence** of HHV-8 is low among the general population but is **high in groups of individuals susceptible to KS, such as homosexuals.**
  - **Unlike other herpesviruses, HHV-8 does not have a ubiquitous distribution.**

Kaposi's Sarcoma

Human Herpes Virus 8

- **in vitro active**
  - **GCV, Cidofovir, foscarnet, adefovir, lobucavir**
- **In vivo**
  - **Val-GCV -> ↓ oropharyngeal shedding**
  - **HIV infected -> GCV/Foscarnet no effect**
  - **VCV, FCV modest to significant effect in HHV-8 detection in saliva**
  - **ART in HIV -> 90% reduction of detection in oropharynx**

Treatment of PML

- No effective antiviral strategy known
- Improving JCV-specific immune responses
  - HAART in HIV-AIDS patients
  - Reducing immunosuppression in transplant patients
  - Discontinuing natalizumab in MS or IBD
- Role of adjuvant therapies unclear
  - Plasmapheresis
  - Intravenous immunoglobulin
  - Cidofovir
- Cave: Immune reconstitution inflammatory syndome

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

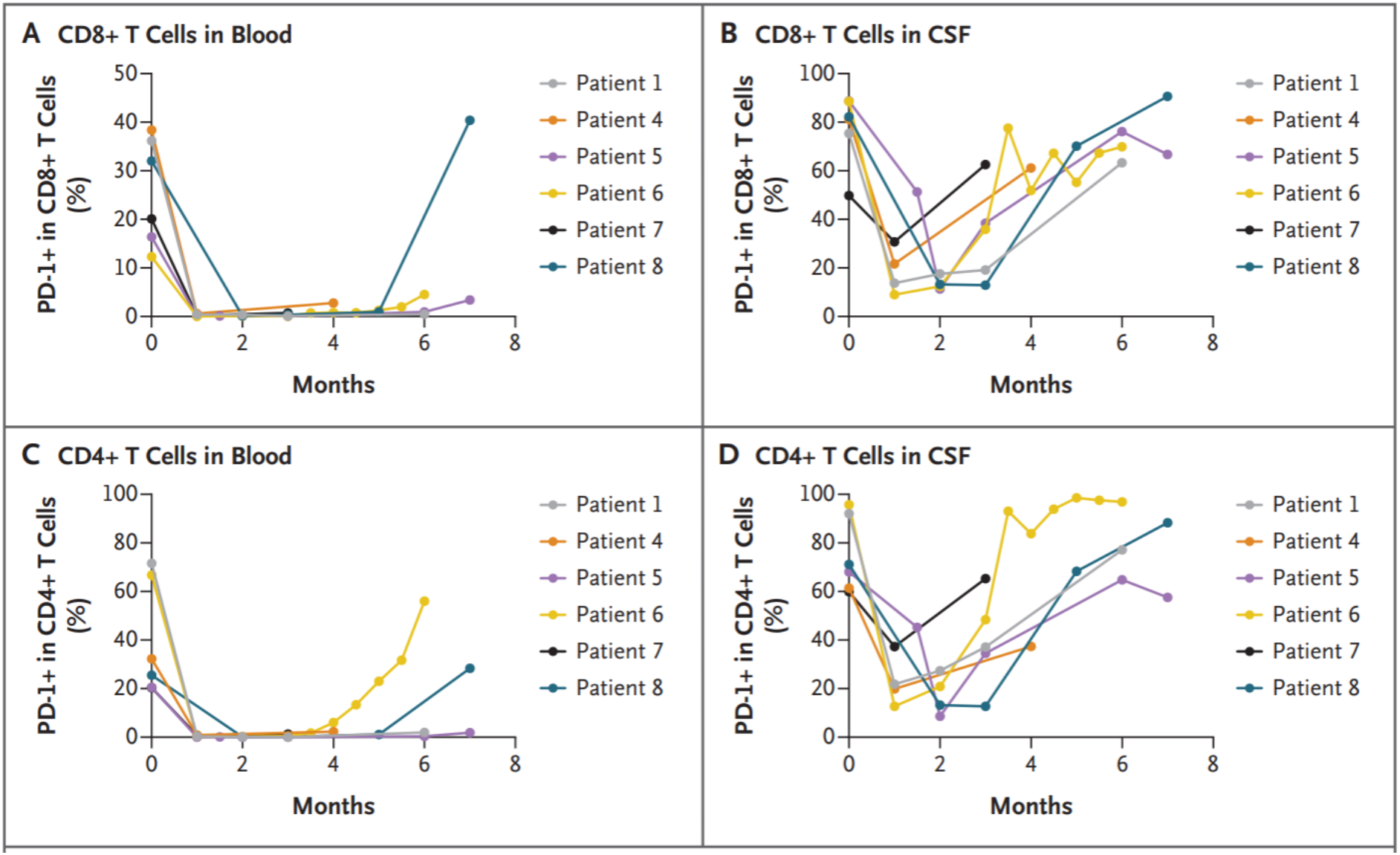
Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy

Irene Cortese, M.D., Pawel Muranski, M.D., Yoshimi Enose-Akahata, Ph.D., Seung-Kwon Ha, D.V.M., Ph.D., Bryan Smith, M.D., MariaChiara Monaco, Ph.D., Caroline Ryschkewitsch, B.S., Eugene O. Major, Ph.D., Joan Ohayon, M.S.N., Matthew K. Schindler, M.D., Ph.D., Erin Beck, M.D., Ph.D., Lauren B. Reoma, M.D., Steve Jacobson, Ph.D., Daniel S. Reich, M.D., Ph.D., and Avindra Nath, M.D.

ABSTRACT

BACKGROUND

Progressive multifocal leukoencephalopathy (PML) is an opportunistic brain infection that is caused by the JC virus and is typically fatal unless immune function can be restored. Programmed cell death protein 1 (PD-1) is a negative regulator of the immune response that may contribute to impaired viral clearance. Whether PD-1 blockade with pembrolizumab could reinvigorate anti–JC virus immune activity in patients with PML was unknown.


A CD8+ T Cells in Blood
PD-1+ in CD8+ T Cells (%)
50
40
30
20
10
0
0
2
4
6
8
Months
Patient 1
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
B CD8+ T Cells in CSF
PD-1+ in CD8+ T Cells (%)
100
80
60
40
20
0
0
2
4
6
8
Months
Patient 1
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
C CD4+ T Cells in Blood
PD-1+ in CD4+ T Cells (%)
100
80
60
40
20
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2
4
6
8
Months
Patient 1
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
D CD4+ T Cells in CSF
PD-1+ in CD4+ T Cells (%)
100
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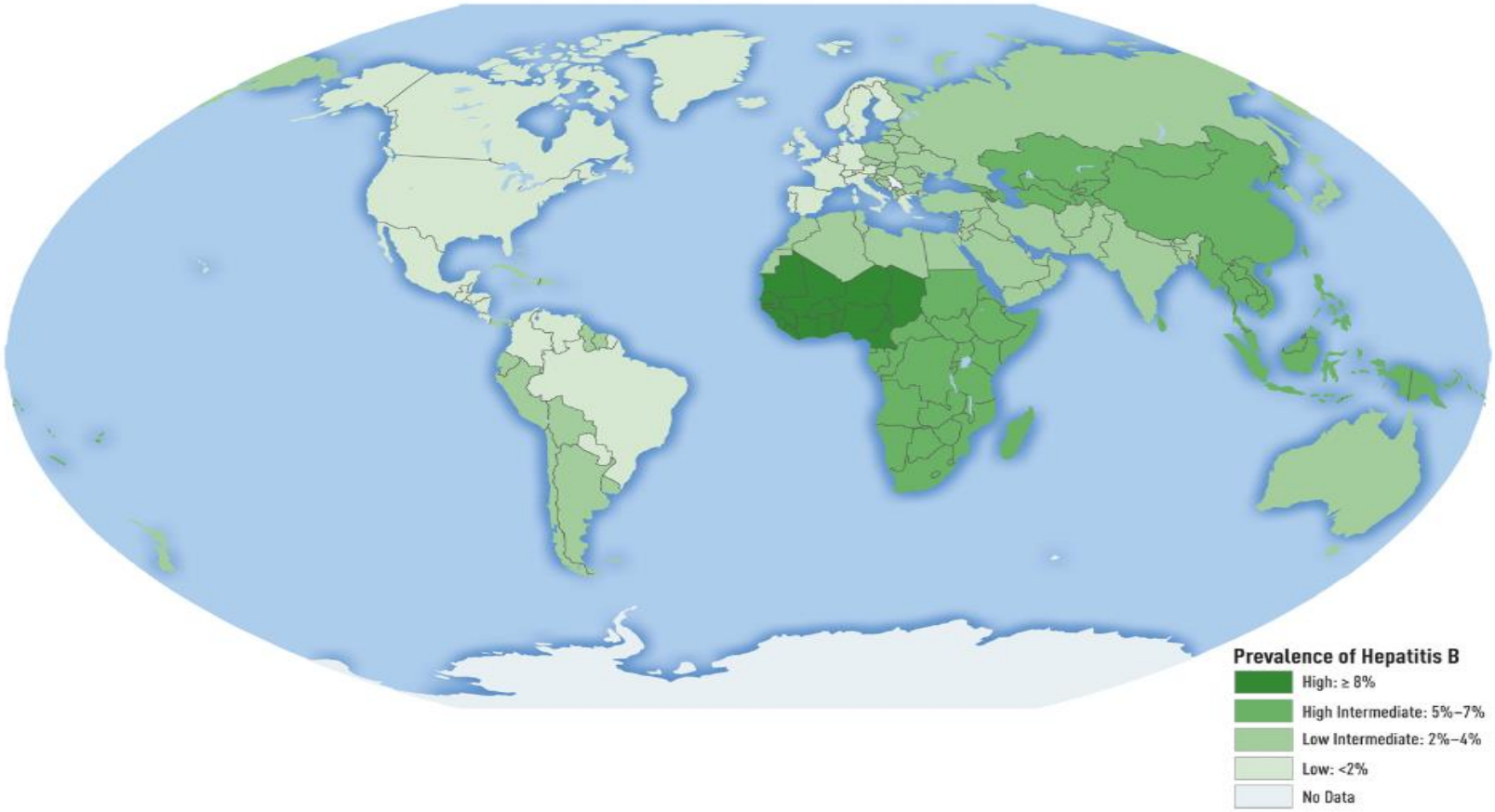
Months
Patient 1
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8

NEJM 2019

Hepatitis B, epidemiology

Worldwide prevalence hepatitis B

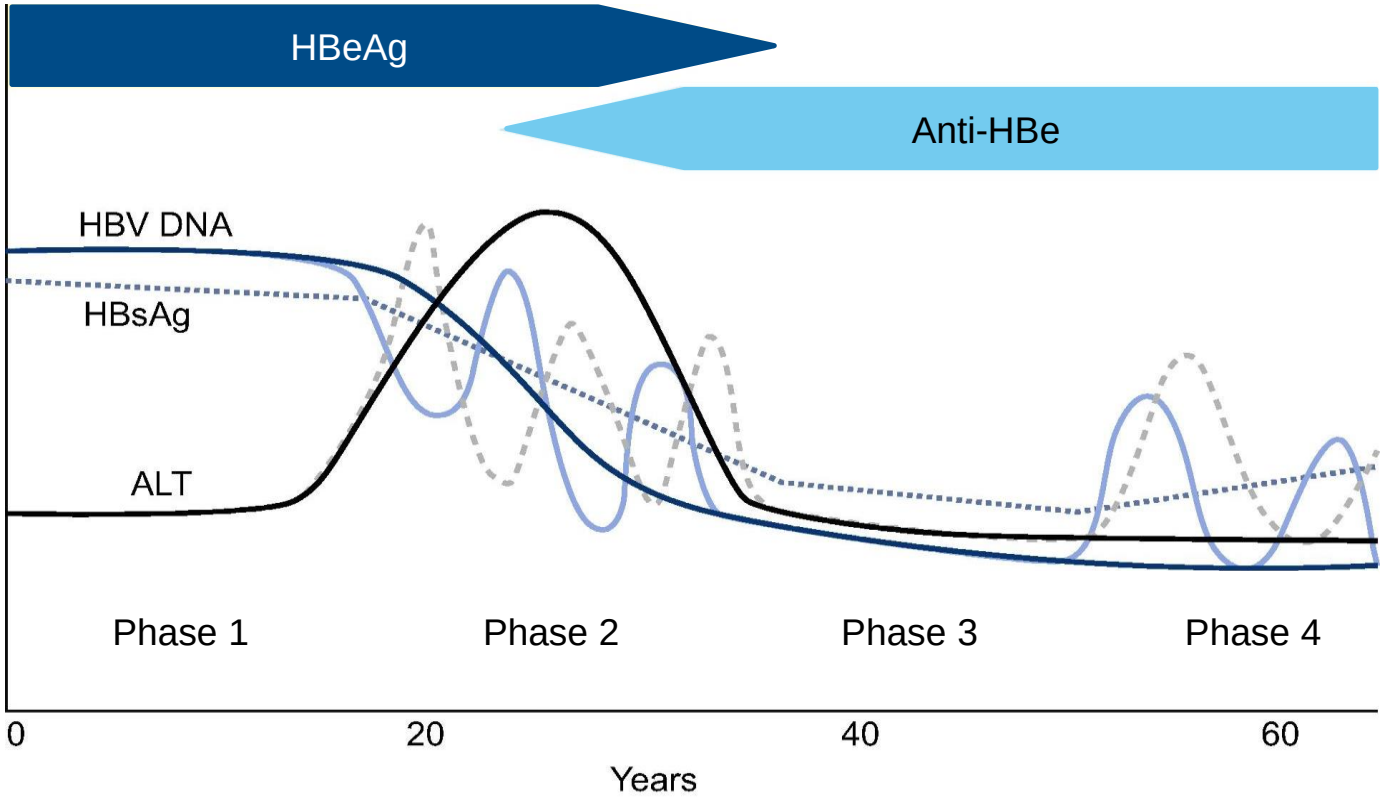
(Source: CDC http://www.cdc.gov/travel-static/yellowbook/2016/map_3-04.pdf)



MAP 3-4. PREVALENCE OF CHRONIC HEPATITIS B VIRUS INFECTION AMONG ADULTS[1]

[1] Disease data source: Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012; 30(12): 2212-2219.

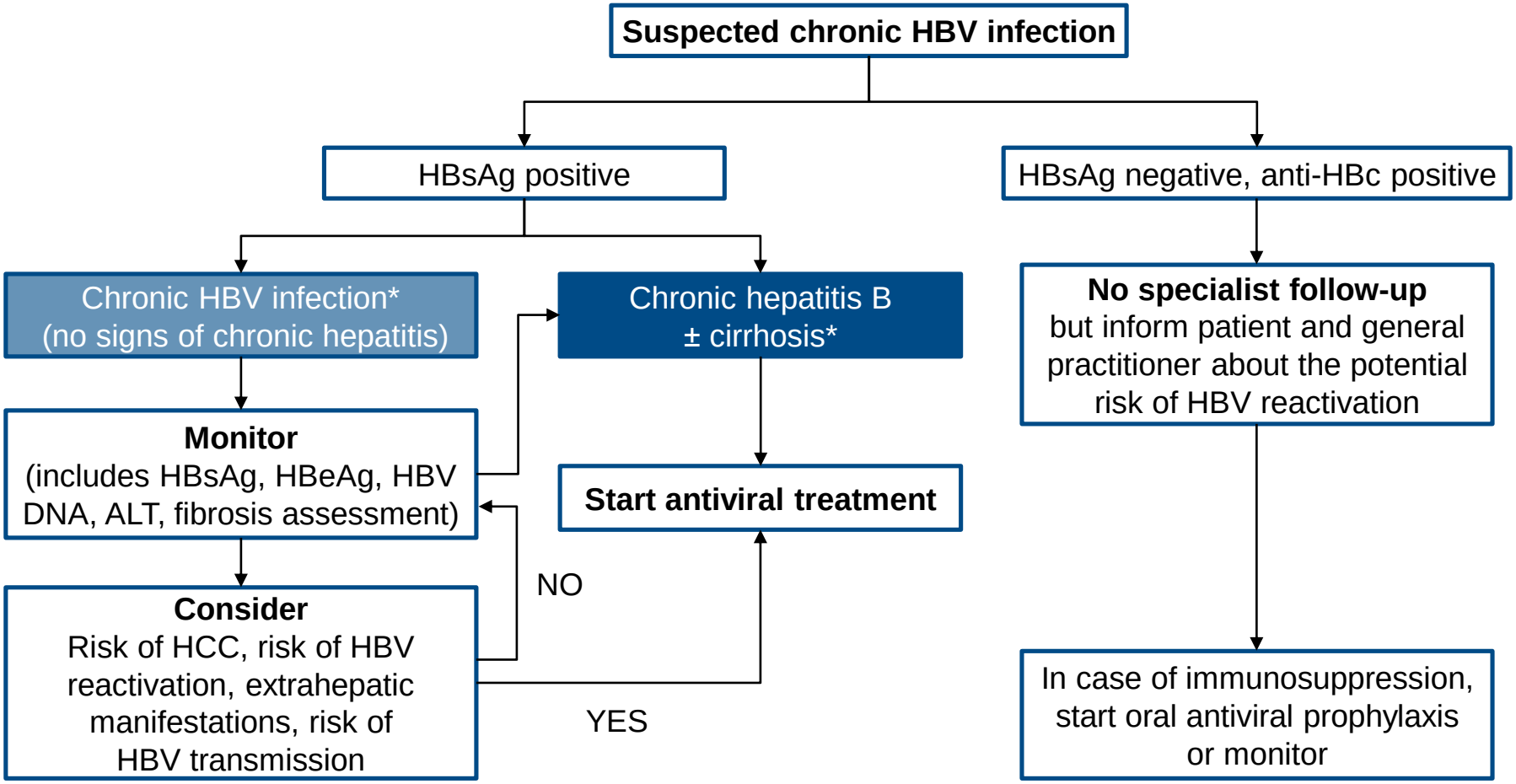
Phases of chronic HBV infection[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Algorithm for the management of chronic HBV infection



*See new nomenclature slide.

EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

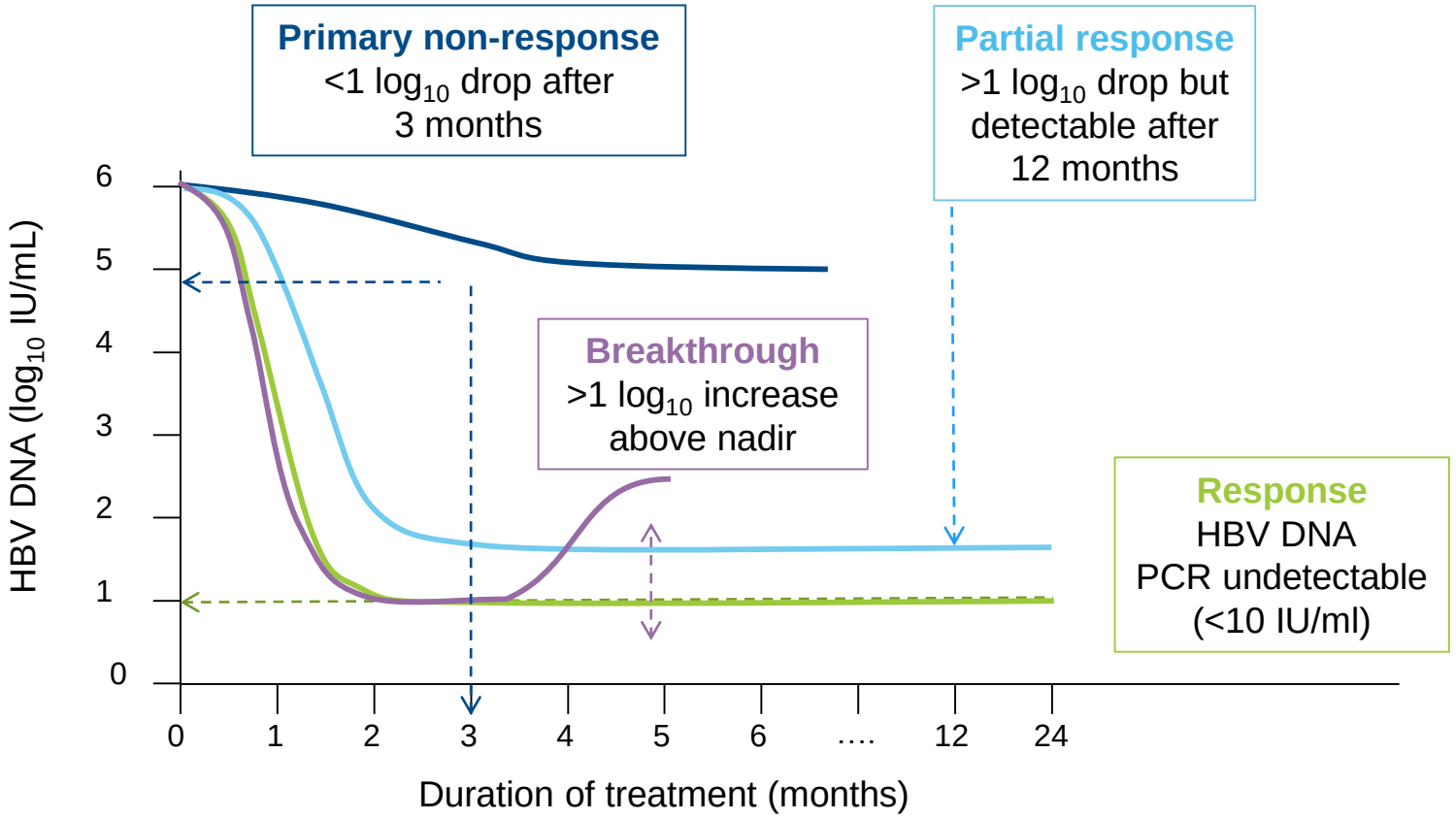
NA monotherapy for treatment-naïve patients

- Long-term administration of a potent NA with a **high barrier to resistance** is the treatment of choice
  - Regardless of severity of liver disease

Recommendations	Grade of evidence	Grade of recommendation
Treatment of choice • Long-term administration of a potent NA with high barrier to resistance (regardless of severity of liver disease)	I	1
Preferred regimens • ETV, TDF and TAF as monotherapies	I	1
NOT recommended • LAM, ADV and TBV	I	1

EASL CPG HBV. J Hepatol 2017;67:370–98

Virological responses on NA therapy



EASL CPG HBV. J Hepatol 2017;67:370–98

Indications for selecting ETV or TAF over TDF*

- In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF

Age	• >60 years
Bone disease	• Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration†	• eGFR <60 ml/min/1.73 m^2 • Albuminuria >30 mg/24 h or moderate dipstick proteinuria • Low phosphate (<2.5 mg/dl) • Haemodialysis

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis

EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

Management of patients with NA failure

- Treatment should be adapted as soon as virological failure under NAs is confirmed*

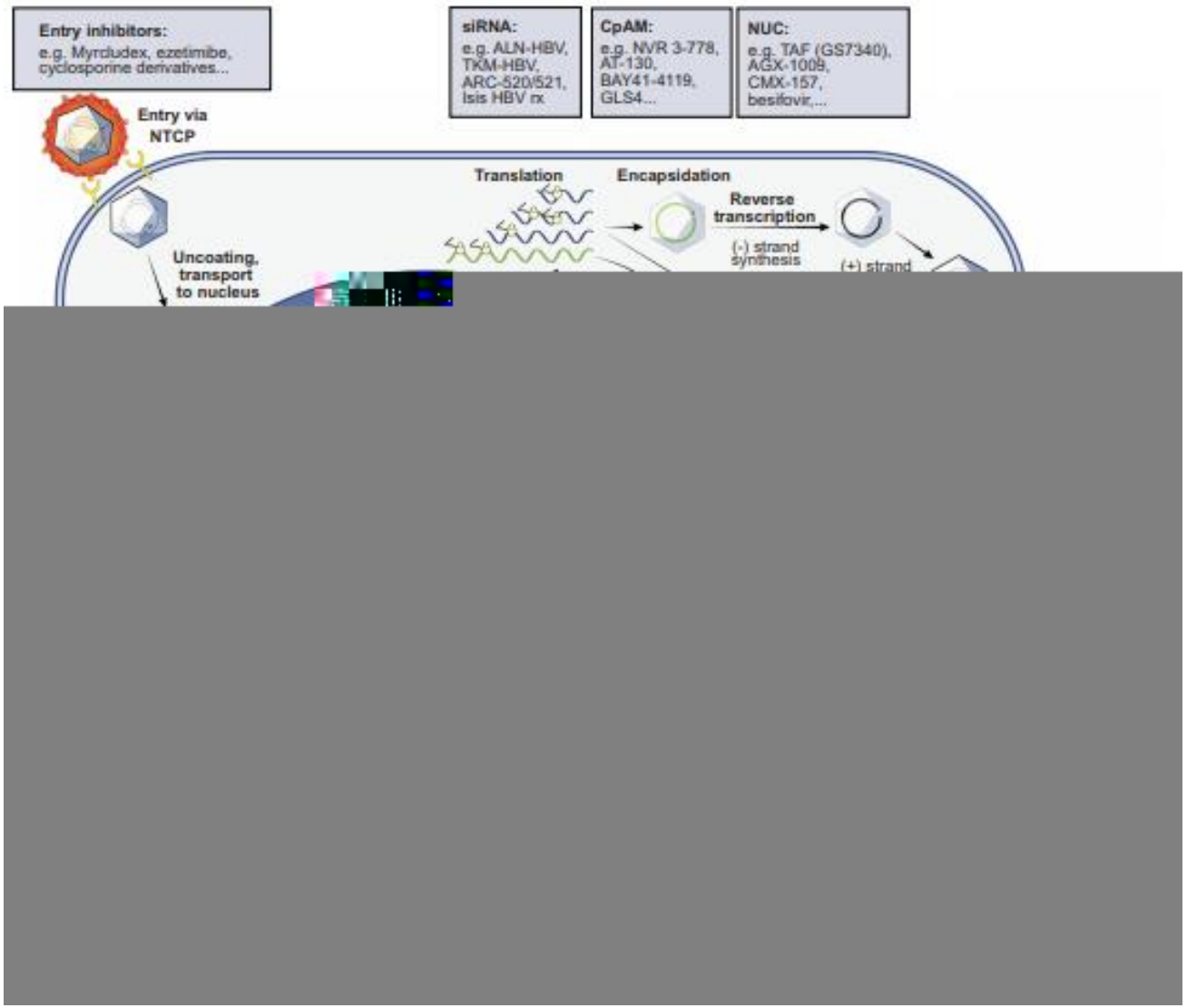
Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistant: switch to TDF or TAF If HBV DNA plateaus: add ETV† or switch to ETV
TDF or TAF resistance‡	If LAM-naïve: switch to ETV If LAM-resistant: add ETV§
Multidrug resistance	Switch to ETV + TDF or TAF combination

*Evidence level II-1, grade of recommendation 1; †Especially in patients with ADV-resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted; ‡Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile; §The long-term safety of these combinations is unknown

EASL CPG HBV. J Hepatol 2017;67:370–98

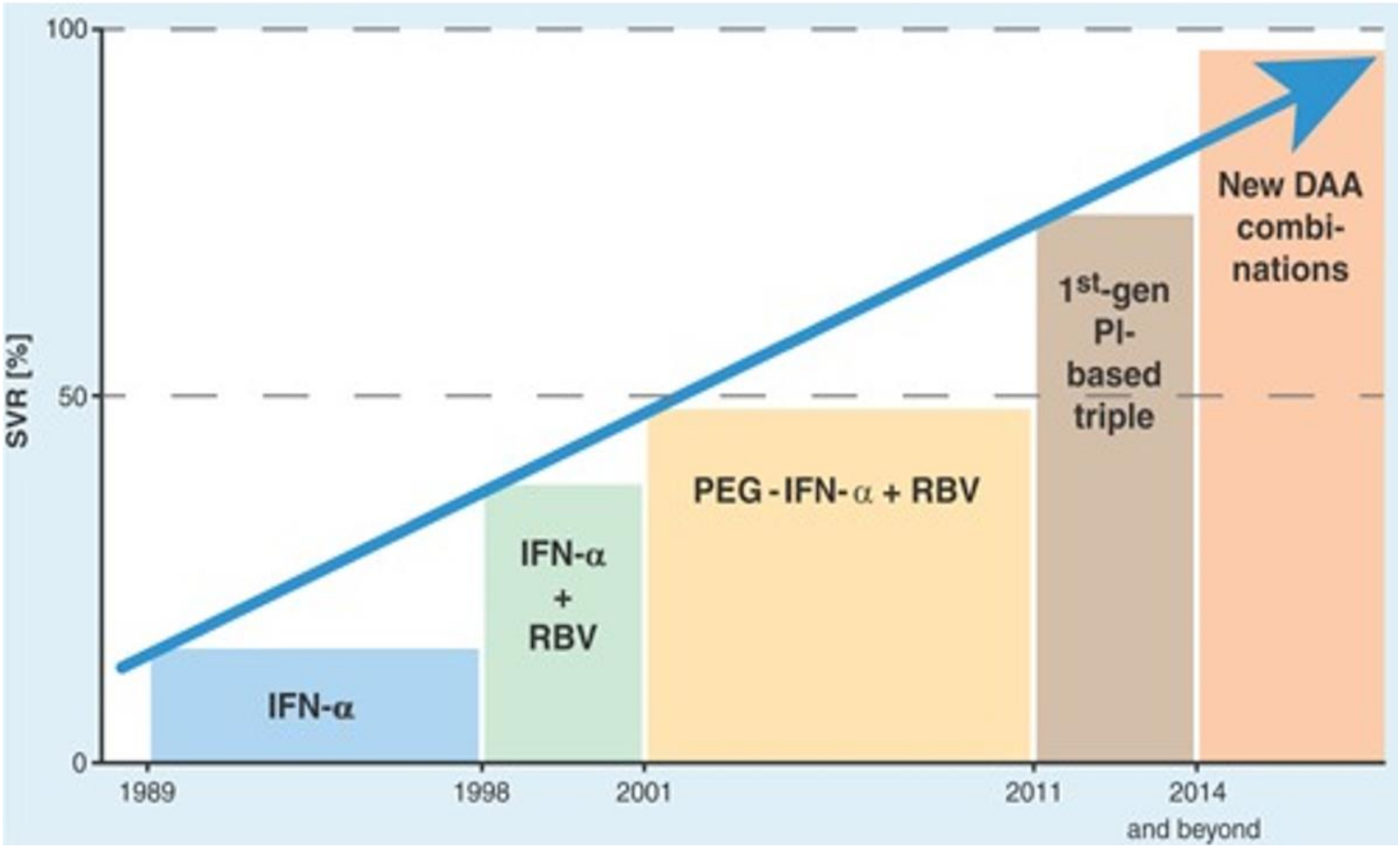
EASL™ The Home of Hepatology

New concepts for antiviral drugs targeting HBV



Durantel D, Zoulim F. J Hepatol 2016;64:S117–31

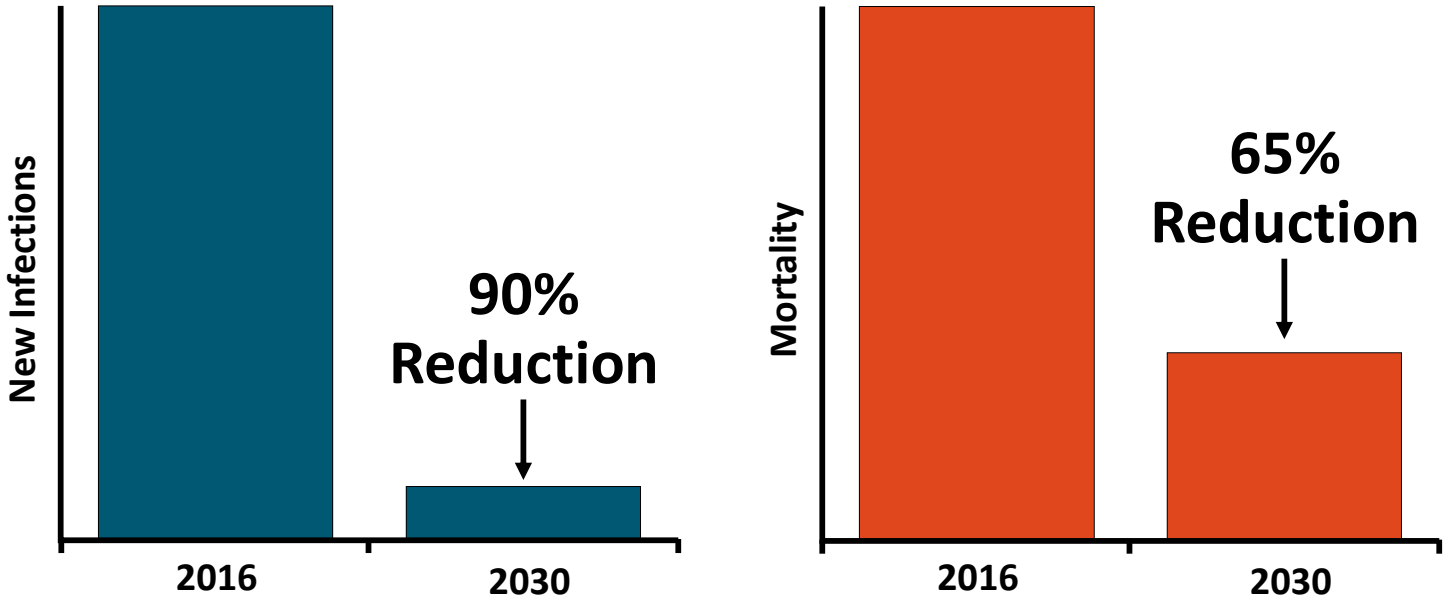
New Rx regimens - hepatitis C



New Rx regimens - hepatitis C

- > 90 % cure (SVR rate)
- Minimal side effects
  - Fatigue
  - Headache
  - Nausea
  - Insomnia
- Treatment selection influenced by
  - Genotype (viral load)
  - Presence/absence of cirrhosis
  - Prior therapy (interferon)
  - Renal function

WHO HCV Elimination Targets

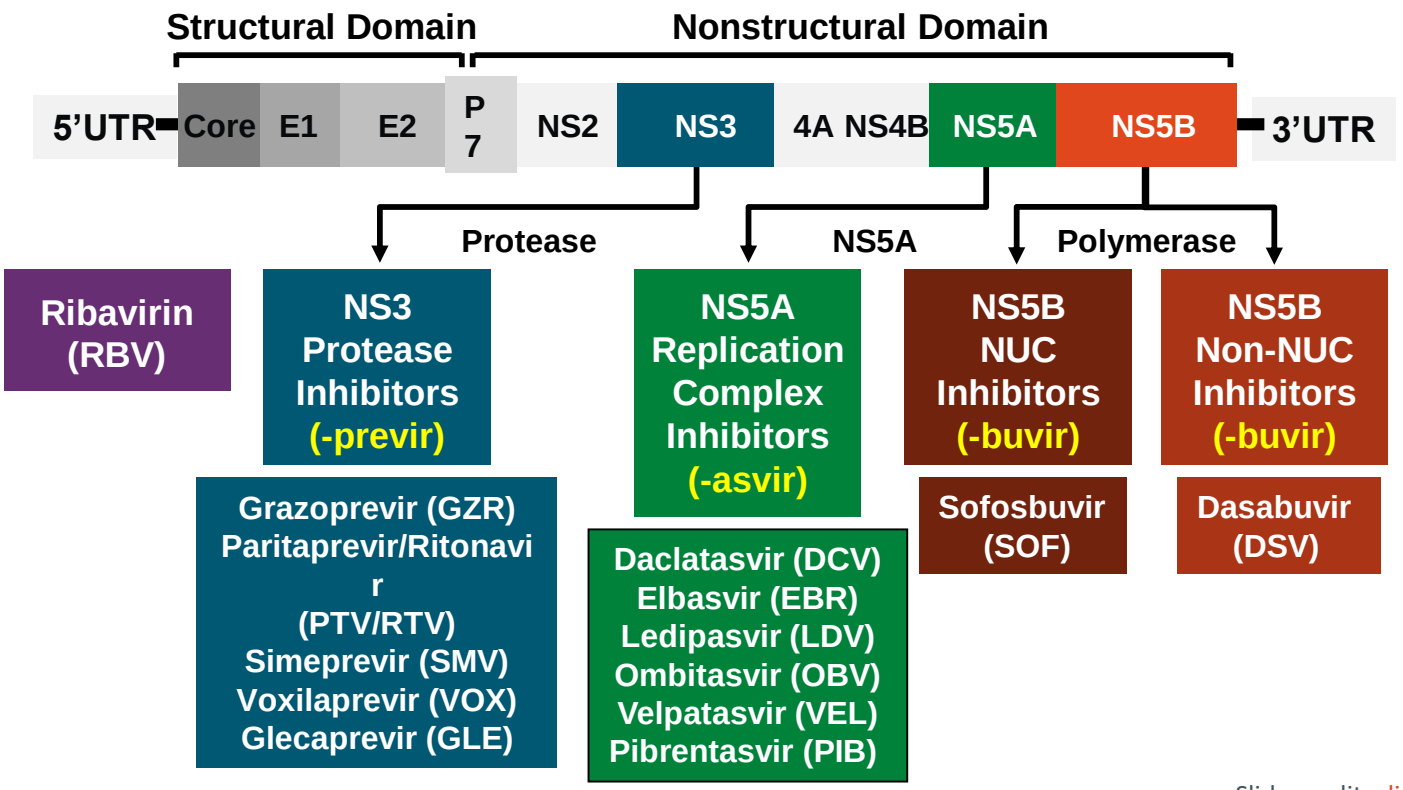


- Ambitious goals
- Requires National Action Plan → good data to design policy

WHO. Draft WHO Global Hepatitis Strategy, 2016-2021.

Slide credit: clinicaloptions.com

Great Tools Available



Slide credit: clinicaloptions.com

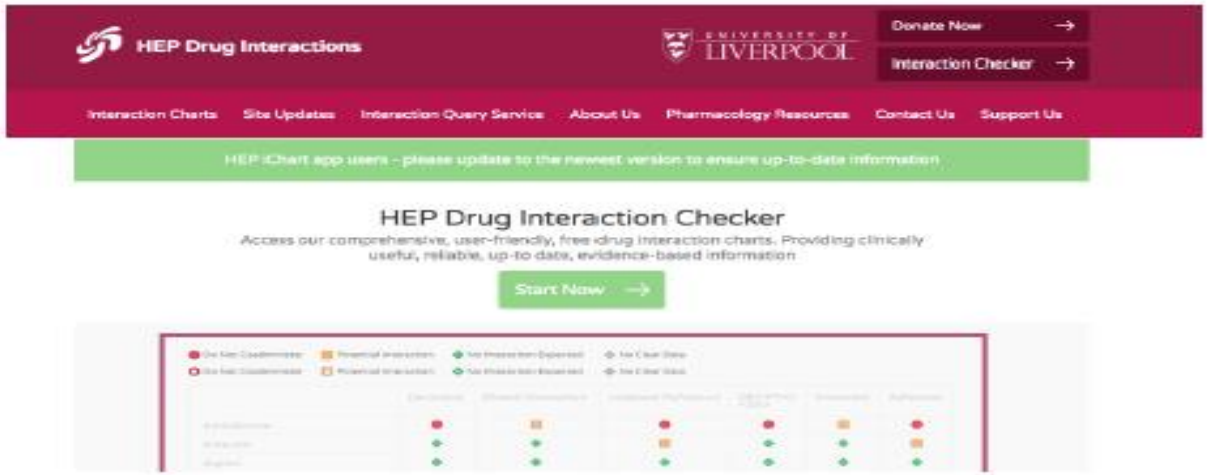
Recommended Treatment Regimens

- **Genotype-specific**
  - Elbasvir/Grazoprevir: GT 1, 4
  - Ledipasvir/Sofosbuvir: GT 1, 4, 5, 6
- **Pangenotypic**
  - Sofosbuvir/Velpatasvir – GT 1-6
  - Glecaprevir/Pibrentasvir – GT 1-6
  - Sofosbuvir/Velpatasvir/Voxilaprevir – GT 1-6 (reserved for salvage therapy)

AASLD/IDSA. HCV Guidance. 2018.

Slide credit: clinicaloptions.com

Drug-Drug Interactions

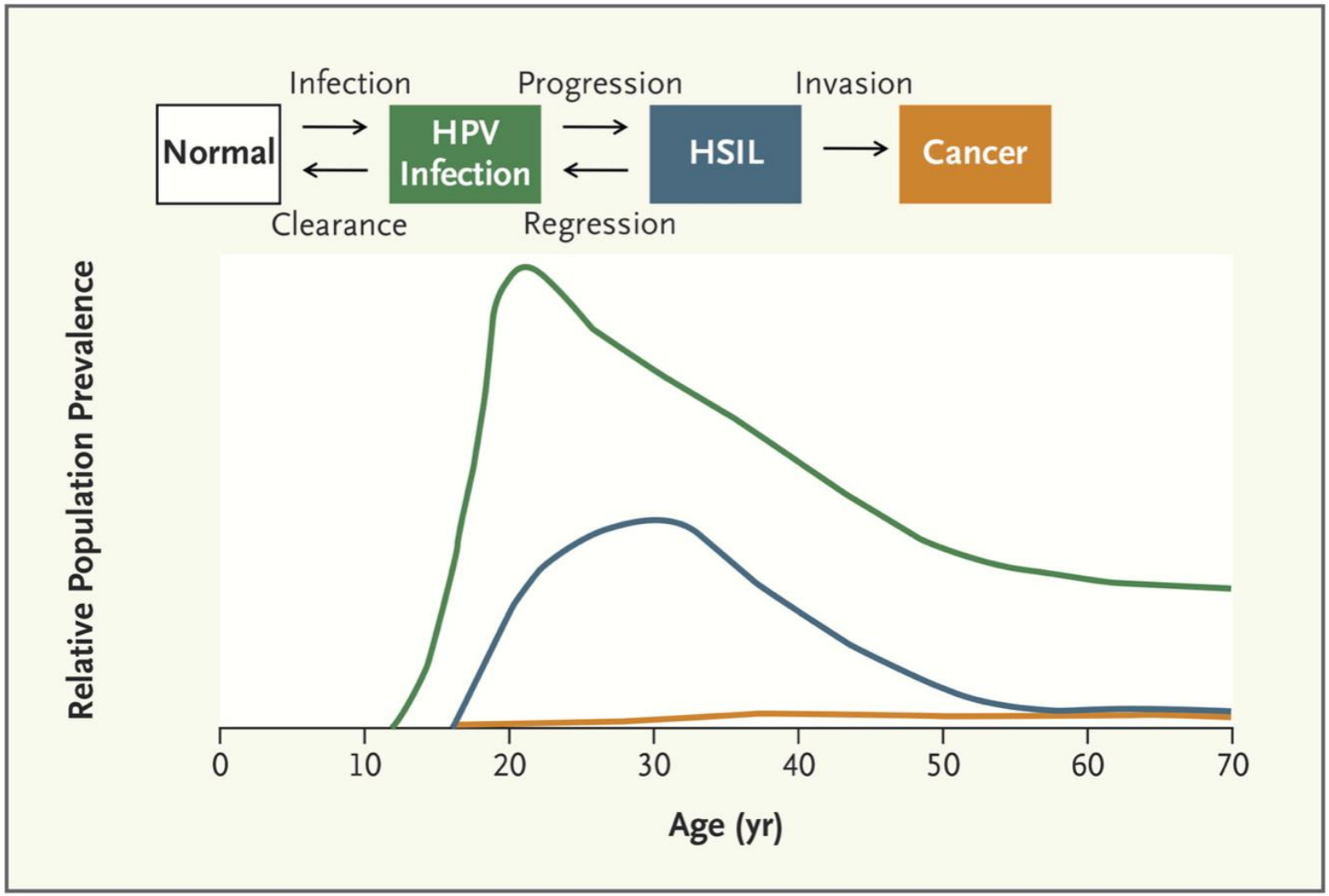


http://www.hep-druginteractions.org/

Don’t trust your memory – look up all drugs including OTC!

Slide credit: clinicaloptions.com

HPV - Natural history



HPV, Rx, internal warts

2015 STD Treatment Guidelines: Anogenital Warts

Table 4. Treatment of Internal Anogenital Warts

Internal anogenital warts include urethral meatus, vaginal, cervical, or intra-anal. Management of cervical warts or intra-anal warts should include consultation with a specialist.

Recommended for Urethral Meatus Warts

Cryotherapy with liquid nitrogen

Health care providers must be trained on the proper use of cryotherapy because over- and under-treatment can result in complications or low efficacy.

or

Surgical removal

Recommended for Vaginal Warts

Cryotherapy with liquid nitrogen

The use of a cryoprobe in the vagina is NOT recommended because of the risk for vaginal perforation and fistula formation.

or

Surgical removal

or

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80-90% solution
A small amount should be applied only to the warts.

Rx - MERS-CoV 2016

INTERIM GUIDANCE DOCUMENT

Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do

11 February 2013

World Health Organization

Rx - MERS-CoV 2016
ISARIC & WHO

- Benefit likely to exceed risk
  - Convalescent serum
  - Interferons esp b
  - Lopinavir
  - Monoclonal & polyclonal Abs

World Health Organization

Rx - MERS-CoV

Strength of evidence

	Study Focus: *	Quality of Best Available Evidence®	Order of Recommendation¥
Convalescent plasma ≠	SIV; SA; SC; MIV	SC (Moderate)	1
Interferon	SIV; SA; SC; MIV	MIV (Low)	2
Protease Inhibitors	SIV; SA; SC	SIV (Very Low)	2
Intravenous Immunoglobulin	SIV; SA; SC; MIV	Nil	3
Nitazoxanide	Nil	Nil	3
Others e.g. Cyclosporin A	SIV; MIV	MIV (Very Low)	3
Ribavirin	SIV; SA; SC	SIV (Very Low)	4
Corticosteroids	SIV; SA; SC	SA (Low)	4
Interferon plus ribavirin	SIV; SC; MIV; MA	MA (Very Low)	4

≠ Hyperimmune globulin or human neutralising monoclonals when available. The latter were shown active in SARS animal models.

* SARS *in vitro* (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV *in vitro* (MIV); MERS animal (MA)

WHO Interim guidance, 2015

Άλλοι ιοί

- Zika, Chikungunya, Dengue, YF, WNV ->

  υποστηρικτική

- Ebola -> RTC on field, DRC 2019, 4 drugs, ZMAPP
  - 2 continue to be used!!! 2019-20 field trial
  - mAb114 or REGN-EB3