



WEBINAIRE DES Maladies Infectieuses et Tropicales – Lundi 5 Octobre 2026

Séminaire n°3

Principaux antiviraux

Coordination : Valérie POURCHER – Sarah STABLER

Virus respiratoires : « indications » des nouveaux antiviraux (contexte des adultes immunodéprimés)

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Coordination OPEN-ReMIE Réseau opérationnel national de recherche clinique pour les maladies infectieuses émergentes, ANRS-MIE

Université Claude Bernard Lyon 1, Inserm 1111 CIRI, Equipe LYACTS – Activation et transduction du signal dans les lymphocytes, Lyon, France



Université Claude Bernard Lyon 1

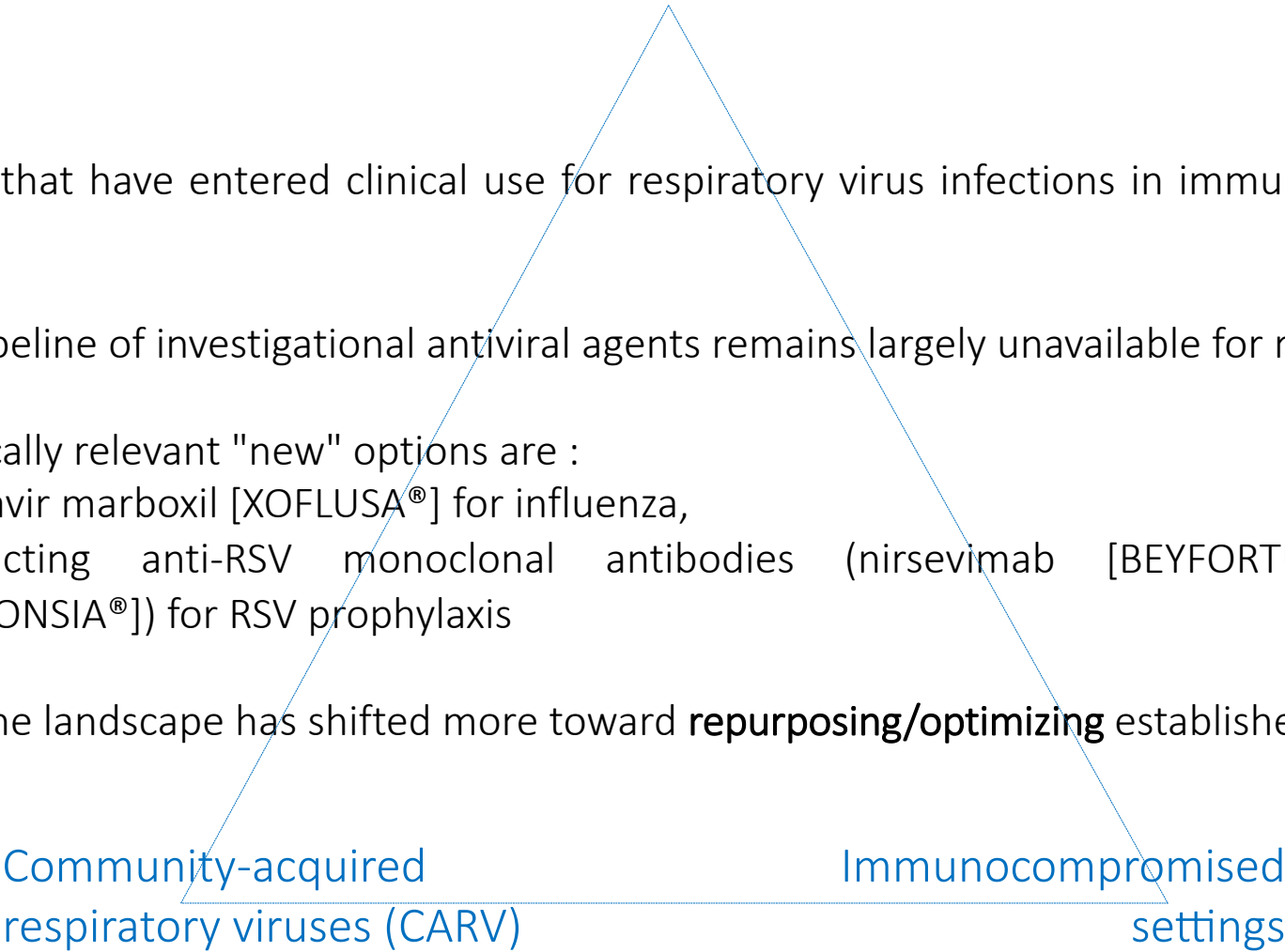


Déclaration de liens d'intérêt avec les industriels de santé
en rapport avec le thème de la présentation (loi du 04/03/2002) :

- Intervenant : ADER Florence
 - Titre : Recherche clinique en période de crise sanitaire

- | | |
|--|------------|
| • Consultant ou membre d'un conseil scientifique | NON |
| • Conférencier ou auteur/rédacteur rémunéré d'articles ou documents | NON |
| • Prise en charge de frais de voyage, d'hébergement
ou d'inscription à des congrès ou autres manifestations | NON |
| • Investigateur principal d'une recherche ou d'une étude clinique avec un
industriel de la santé | OUI |

Antivirals (ATV)



Newer agents that have entered clinical use for respiratory virus infections in immunocompromised hosts are limited

The current pipeline of investigational antiviral agents remains largely unavailable for routine use

The most clinically relevant "new" options are :

- baloxavir marboxil [XOFLUSA®] for influenza,
- long-acting anti-RSV monoclonal antibodies (nirsevimab [BEYFORTUS®], and clesrovimab [ENFLONSIA®]) for RSV prophylaxis

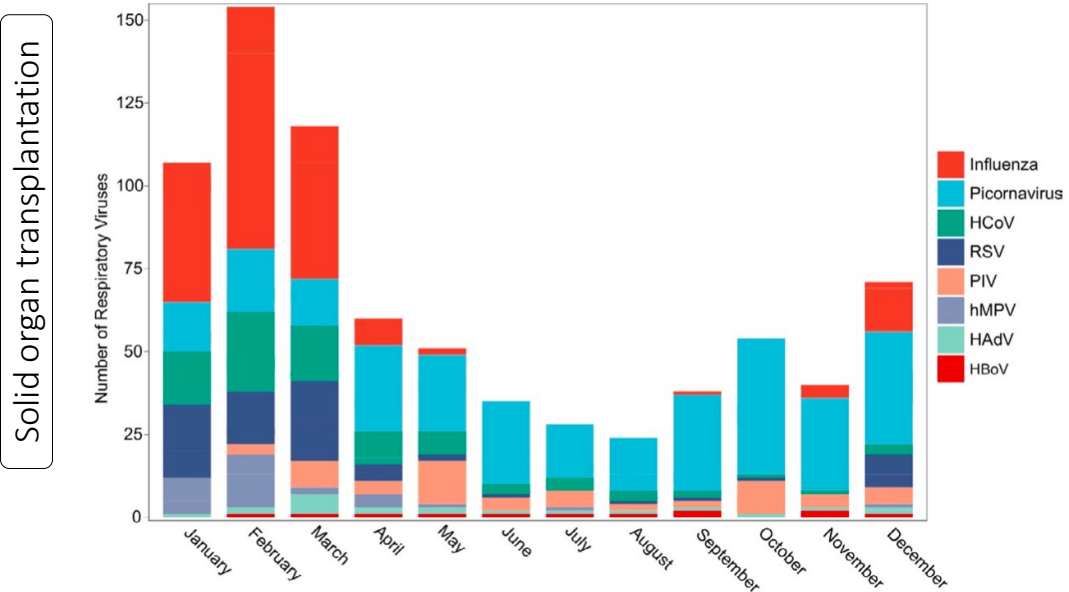
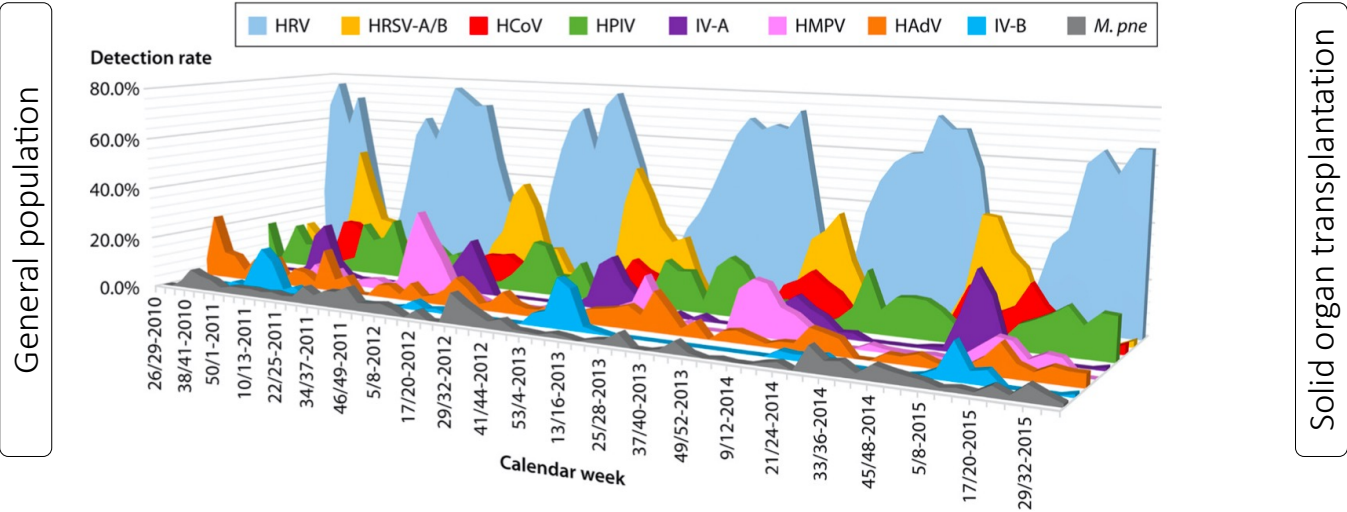
Recent guideline landscape has shifted more toward **repurposing/optimizing** established drugs

Community-acquired
respiratory viruses (CARV)

Immunocompromised
settings

Community-acquired respiratory viruses (CARV)

Diapo DES
2025



Seasonality

Fall ---- > winter

Influenza virus (IV) A/B, HRSV, Metapneumovirus (HMPV)

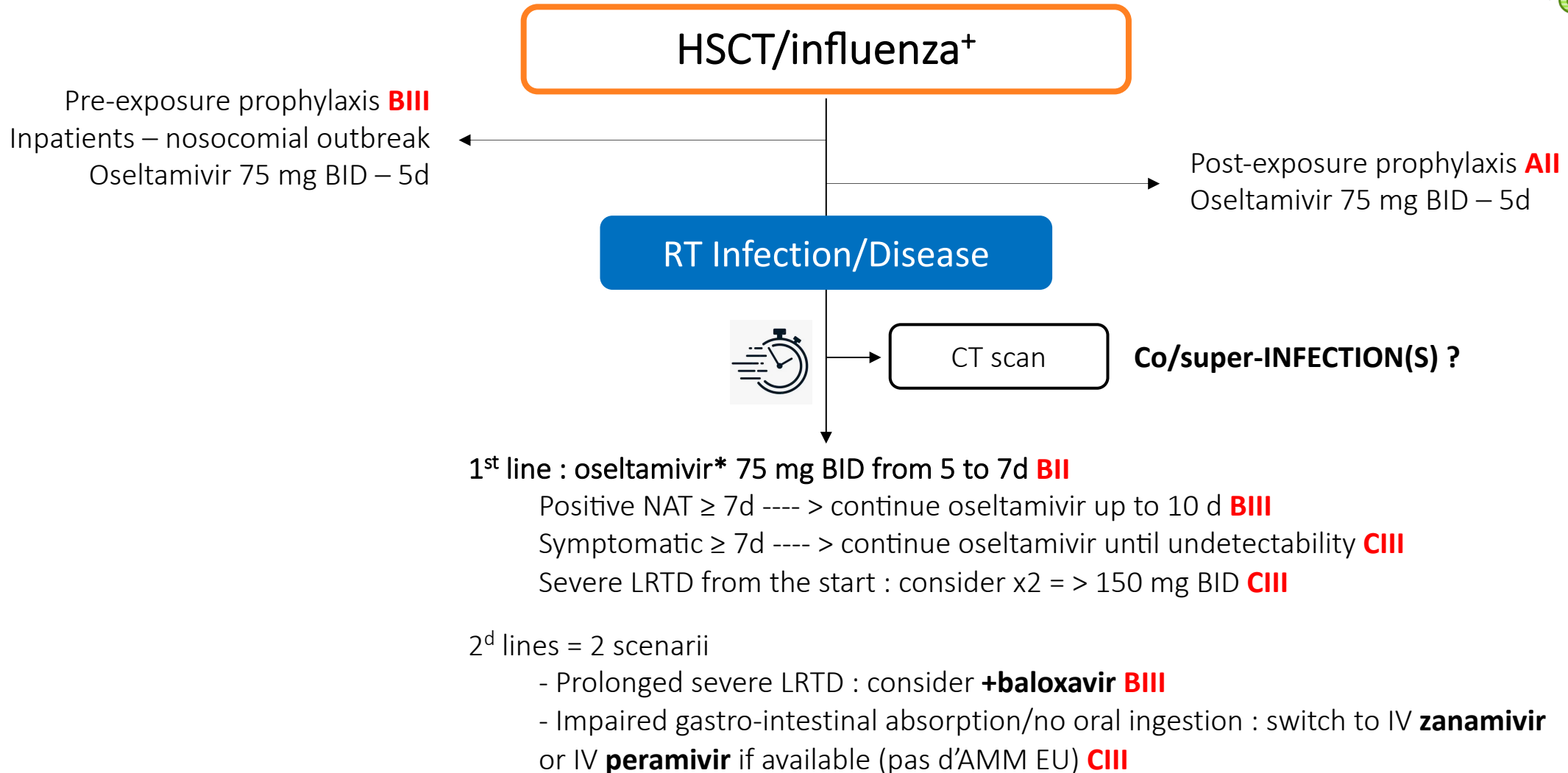
Spring, summer --- > fall

Picornavirus/Rhinovirus (HRV), CoV, Parainfluenza virus (HPIV)

Frequency : RhinoV
Severity : influenza/RSV
Co/super-infections

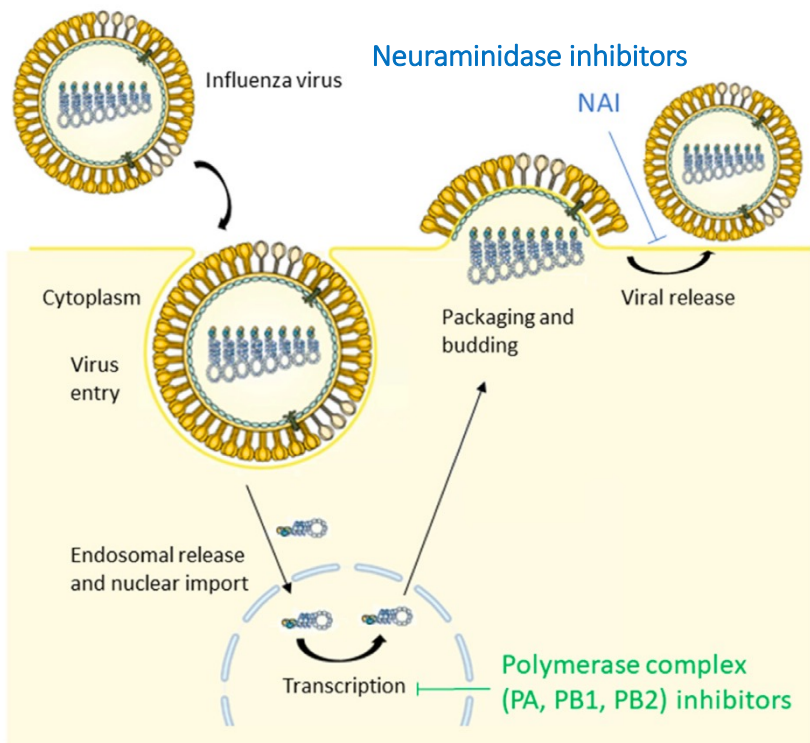
Influenza : therapeutic algorithm

Diapo DES
2025



NAT monitoring
Genotypic resistance testing

* Full dose oseltamivir 75 BID > 40 kgs



	Mechanism of action	EMA approval	Access in France (ANSM)
Oseltamivir	NAI: blocks viral release from cells	Yes (2022)	Yes
Zanamivir	NAI: blocks viral release from cells	Yes (2014)	Yes ATU nominative
Peramivir	NAI: blocks viral release from cells	No	No
Baloxavir marboxil	Endonuclease inhibitor that blocks mRNA cap-snatching --- > disrupt RNA transcription	Yes (2021)	No
Favipiravir	RNA polymerase inhibitor : inhibits RNA replication	No	No

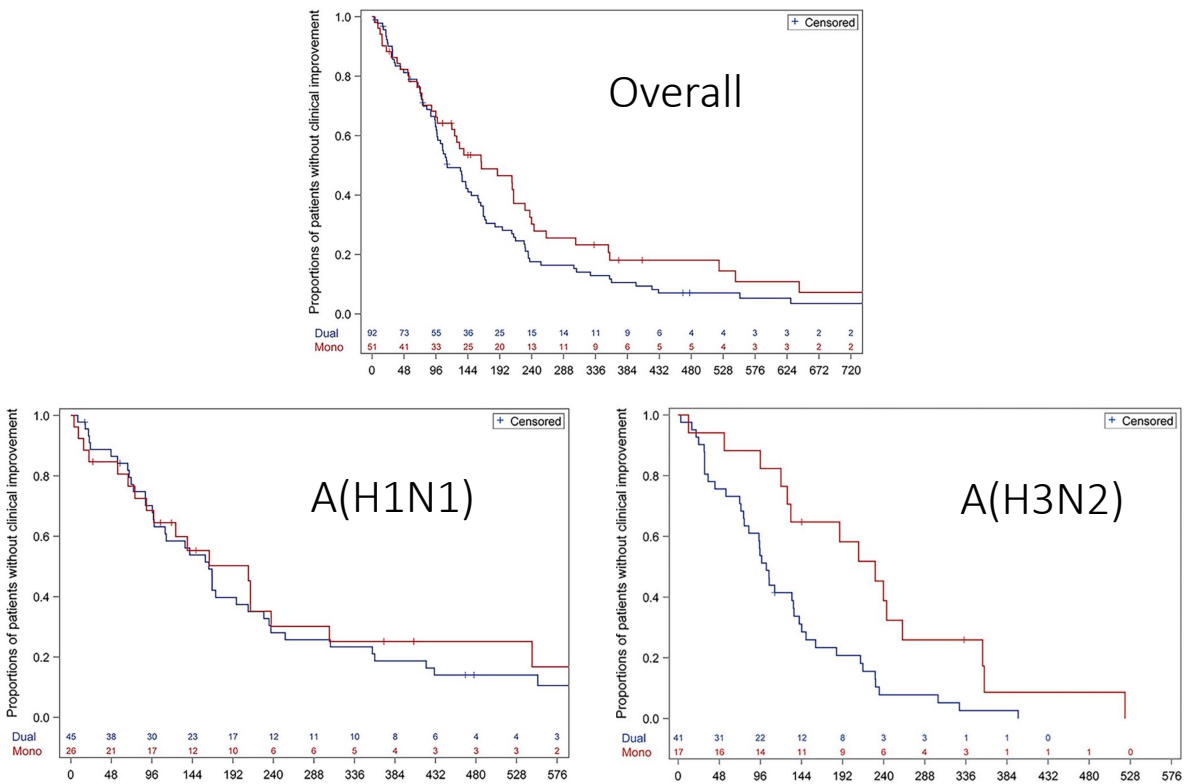
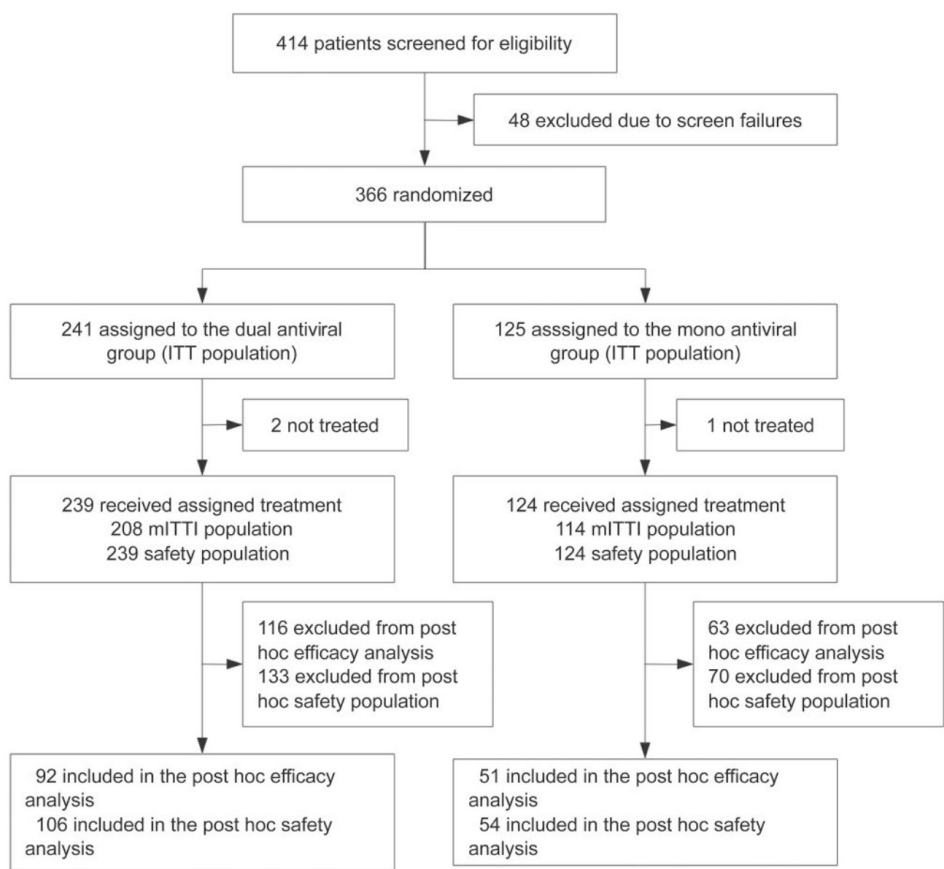
Figure from P. Bay et al. Clinical Microbiology and Infection 31 (2025) 1157e1165
 Table adapted from P. Bay et al. Clinical Microbiology and Infection 31 (2025) 1157e1165

Baloxavir marboxil – Pivotal trials

Trial name	Trial title	ClinicalTrials.gov number or trial identification	DOI
CAPSTONE-1	Baloxavir marboxil for uncomplicated influenza in adults and adolescents	NCT02954354	10.1056/NEJMoa1716197
CAPSTONE-2	Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza: a randomised, placebo-controlled, phase 3 trial	NCT02949011	10.1016/S1473-3099(20)30004-9
CENTERSTONE	Efficacy of baloxavir treatment in preventing transmission of influenza	NCT03969212	10.1056/NEJMoa2413156
FLAGSTONE	Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza: a randomised, parallel-group, double-blind, placebo-controlled, superiority trial	NCT03684044	10.1016/S1473-3099(21)00469-2
Registry funded by Shionogi	Baloxavir Marboxil for prophylaxis against Influenza in household contacts	Japan Primary Registries Network number JapicCTI-184180	10.1056/NEJMoa1915341

Baloxavir Marboxil – **FLAGSTONE**
Effects of Baloxavir Marboxil Plus Neuraminidase Inhibitor vs Neuraminidase Inhibitor in High-risk Patients Hospitalized With Severe Influenza: A Post Hoc Analysis of the Flagstone Trial.

Post-hoc analysis : immunocompromised patients, patients with diabetes, or patients with chronic lung disease (COPD, interstitial lung disease, bronchiectasis, and cystic fibrosis)



Lower 28-d mortality: 2 [2.17%] of 92 vs. 6 [11.76%] of 51; $P = .02$
Shorter time to cessation of viral shedding ($P < .001$).

Key resistance mutations and susceptibility reduction

Polymerase acidic substitution	Fold-change in IC50	Subtype/context
I38T	30-600	Multiple subtypes. Most frequent resistance marker
I38N	Around 90	A(H1N1)pdm09, Japan 2024
I38M	9-17	A(H5N1) human case, USA 2024
E23K/G	3-5	A(H3N2), A(H7N9)
D27G	Around 12	Novel; A(H1N1)pdm09, China

Most frequent in **children** and in **A(H3N2)** infections
EU sequence-based surveillance: **0.2%** of 87,266 PA sequences ≥ 1 resistance-associated substitution
Pre-treatment resistance variants remain rare; **limited community transmission** of resistant strains

Case, J., & Khaperskyy, D. A. (2025). Impaired host shutoff is a fitness cost associated with baloxavir marboxil resistance mutations in influenza A virus PA/PA-X nuclease domain. *PloS Pathogens*, 22. <https://doi.org/10.1371/journal.ppat.1013550>

Pascua, P et al. (2025). Antiviral susceptibility of clade 2.3.4.4b highly pathogenic avian influenza A(H5N1) viruses from humans in the United States, October 2024 to February 2025. *Emerging Microbes & Infections*, 15. <https://doi.org/10.1080/22221751.2025.2601372>

Takashita, E., et al. (2026). Baloxavir susceptibility of seasonal influenza viruses during the first seven seasons of clinical use in Japan, 2017/18 to 2023/24. *Eurosurveillance*, 31. <https://doi.org/10.2807/1560-7917.es.2026.31.1.2500336>

Oseltamivir

Zanamivir IV (ATU) : alternative pour souches résistantes à l'oseltamivir

Avenir et faisabilité de la bithérapie ?

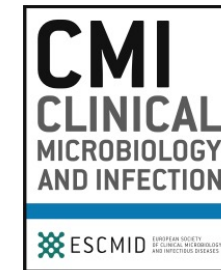
Au mieux 2 ATV dont la cible est $\neq$

Limiter émergence résistance

Narrative review

How to manage antivirals in critically ill patients with influenza?

Pierre Bay^{1, 2, 3, 4}, Ignacio Martin-Loeches⁵, Anne-Fleur Haudebourg^{1, 2, 3}, Minh P. Lê^{6, 7},
Gilles Peytavin^{6, 7}, Marie-Anne Rameix-Welti^{8, 9}, Slim Fourati^{2, 3, 4, 10},
Nicolas de Prost^{1, 2, 3, 4, *}



Domain	Research aim
Development of new antivirals	• Clinical endpoints • Virological endpoint (viral load kinetics and resistance) • Pharmacological endpoint
Development of monoclonal antibodies	• Clinical endpoints • Virological endpoint (viral load kinetics and resistance) • Pharmacological endpoint
Clinical studies on currently available antivirals	• Oseltamivir • Peramivir • Baloxavir marboxil • Combination therapies
Pharmaco-epidemiologic studies in critically ill patients	• Clinical endpoints • Virological endpoint (viral load kinetics and resistance) • Pharmacological endpoint
Resistance	• Rates of baloxavir marboxil-induced resistances in critically ill or immunosuppressed patients • Effect of combination therapies to decrease baloxavir marboxil-induced resistances in critically ill patients • Pharmacological endpoint (reservoir disposition concomitantly with resistance)

RSV : therapeutic algorithm

Diapo DES
2025

Palivizumab could be considered as **post-exposure prophylaxis** in severely immunodeficient adults when **nosocomial outbreak** is occurring. **CIII**

Allo-HSCT/VRS⁺

CT scan (no contrast)

Upper RT Infection

Allo-HSCT
(risk factors)
Lung Tx

Auto-HSCT
Other than
lung Tx

Oral or IV RIBAVIRIN

Ig G < 4.5 g/L --- > IV Igs 0.5
mg/kg x 3 **BIII**

Lower or no corticosteroids **CIII**

No first-hand DAAVT
But surveillance

DAAVT: direct-acting antiviral
treatment

Lower RT Disease

HSCT
Lung Tx
Other than lung Tx

IV RIBAVIRIN

7 to 10 days

Ig G < 4.5 g/L --- > IV Igs 0.5 mg/kg x 3 **BIII**

Lower or no corticosteroids **CIII**

NAT monitoring



Volume 64, Issue 8

April 22, 2021

Article | April 09, 2021

Prodrugs of a 1'-CN-4-Aza-7,9-dideazaadenosine C-Nucleoside Leading to the Discovery of Remdesivir (GS-5734) as a Potent Inhibitor of Respiratory Syncytial Virus with Efficacy in the African Green Monkey Model of RSV

Richard L. Mackman; Hon C. Hui; Michel Perron †; Eisuke Murakami; Christopher Palmiotti; Gary Lee; Kirsten Stray ‡; Lijun Zhang §; Bindu Goyal; Kwon Chun; Daniel Byun; Dustin Siegel; Scott Simonovich †; Venice Du Pont; Jared Pitts; Darius Babusis; Arya Vijapurapu; Xianghan Lu; Cynthia Kim; Xiaofeng Zhao; Julie Chan; Bin Ma; Diane Lye; Adelle Vandersteen; Sarah Wortman; Kimberly T. Barrett; Maria Toteva; Robert Jordan ⊥; Raju Subramanian; John P. Bilello; Tomas Cihlar

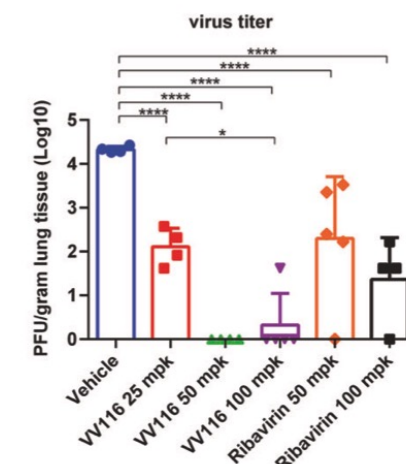
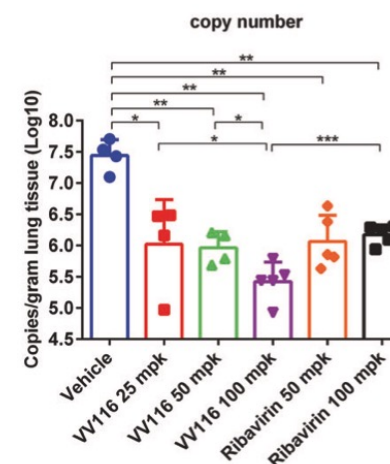
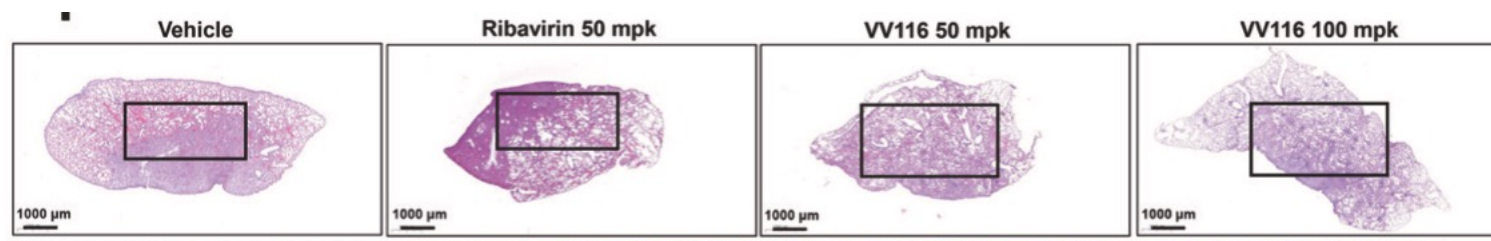
+ Author & Article Information

J. Med. Chem. (2021) 64 (8): 5001–5017.

<https://doi.org/10.1021/acs.jmedchem.1c00071> Article history

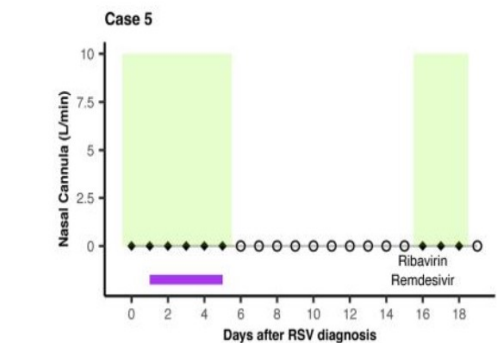
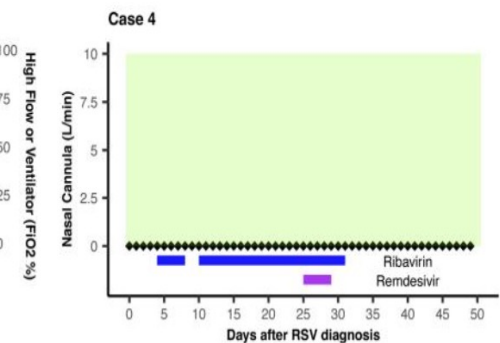
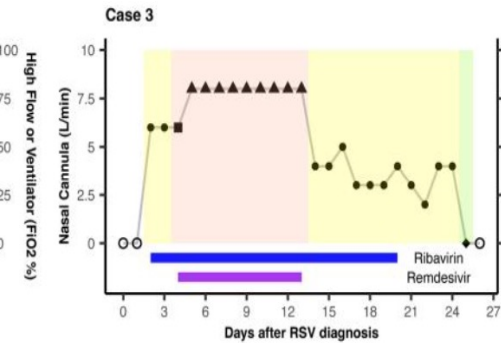
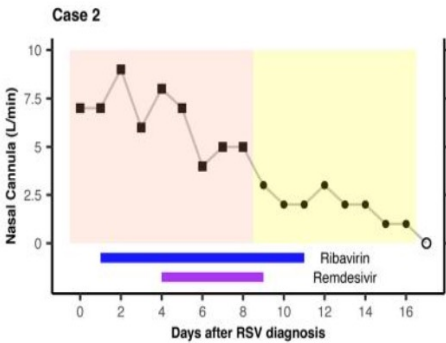
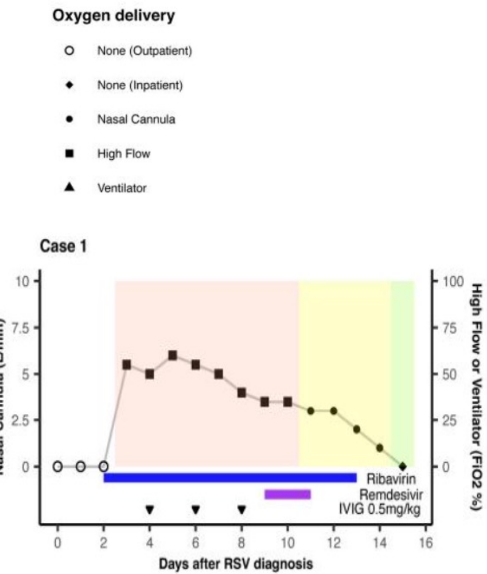
LETTER OPEN

Oral remdesivir derivative VV116 is a potent inhibitor of respiratory syncytial virus with efficacy in mouse model



First Report on Remdesivir Use for the Treatment of Respiratory Syncytial Virus in Five Allogeneic Hematopoietic Cell Transplant Recipients

Denise J. McCulloch,^{1,2,Ⓞ} Fareed Khawaja,^{3,Ⓞ} Frank P. Tverdek,⁴ Emily S. Ford,^{1,2,Ⓞ} Surabhi B. Vora,^{5,Ⓞ} Alpana Waghmare,^{1,5,Ⓞ} Nancy Vuong,⁶ Roy F. Chemaly,³ and Joshua A. Hill^{1,2,Ⓞ}



Age	Underlying setting	RSV infection	Remdesivir dose	Other treatment(s)	Outcome (follow up)
70s	Mismatched unrelated donor HSCT – Day 28	Lower RTI	Loading dose: 200 mg IV 100 mg IV daily on days 2 to <u>3</u>	IV Ig Ribavirin <u>13</u> -day course	Alive (12 months)
70s	Matched unrelated HSCT - Day 17	Lower RTI	Loading dose: 200 mg IV 100 mg IV daily on days 2 to <u>6</u>	Ribavirin <u>11</u> -day course	Alive (60 days)
50s	Matched unrelated HSCT – Month 10	Lower RTI	Loading dose: 200 mg IV 100 mg IV daily on days 2 to <u>10</u>	Ribavirin <u>19</u> -day course /!\ Non-invasive ventilation	Alive (36 months)
40s	Umbilical cord transplant relapsed – Month 18	Upper RTI	Loading dose: 200 mg IV 100 mg IV daily on days 2 to <u>5</u>	Ribavirin <u>21</u> -day course	Alive (24 months)
2 y	Matched related donor HSCT – Day 489	Lower RTI	5 mg/kg IV on day 1 2.5 mg/kg IV on days 2 to <u>5</u>	None	Alive (10 months)

Mostly R+R = remdesivir added to/in combination with ribavirin
Remdesivir use = median 5 days (range, 3–10)
Virologic outcome (PCR) reported in a single patient (case 3)

CORRESPONDENCE

Viral Culture Conversion With Use of Remdesivir for Respiratory Syncytial Virus Lower Respiratory Tract Infection

Mohammed Raja,^{1,✉} Anthony D. Anderson,² Michele I. Morris,¹ Noa Holtzman,³ and Jose F. Camargo¹

¹Transplant and Immunocompromised Host Infectious Diseases, Department of Medicine; ²Department of Pharmacy; and ³Transplantation and Cellular Therapy, Sylvester Comprehensive Cancer Center, University of Miami, Florida

Age	Underlying setting	RSV infection	Remdesivir dose	Other treatment(s)	Outcome
69 y	Matched unrelated donor HSCT – Day 3	Lower RTI Acute resp. failure	Loading dose: 200 mg IV 100 mg IV daily on days 2 to <u>10</u>	IV Ig Ribavirin <u>20</u> -day course /!\ Mechanical ventilation	Negative culture conversion day+6 remdesivir Deceased (ARDS)

Remdesivir for the Treatment of Upper Respiratory Tract Infection Due to RSV in Immunocompromised Individuals

ClinicalTrials.gov ID ⓘ **NCT06817889**

Sponsor ⓘ Fred Hutchinson Cancer Center

Information provided by ⓘ Fred Hutchinson Cancer Center (Responsible Party)

Last Update Posted ⓘ 2026-08-06

Recruiting ⓘ

[Find contact information](#)

[Check who can join](#)

☐ NCT06873633

Safety, Pharmacokinetics, and Antiviral Activity of Remdesivir (VEKLURY®) in Hospitalized Children With RSV

Conditions

Respiratory Syncytial Virus (RSV)

Recruiting

[Find contact information](#)

[Check who can join](#)

Case reports on other respiratory viruses of concern in immunocompromised settings

Imported case of MERS-CoV

77 y

Heart transplantation (2011, ischemic cardiomyopathy)

Immunosuppressants :

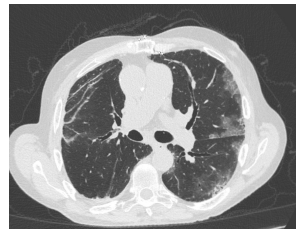
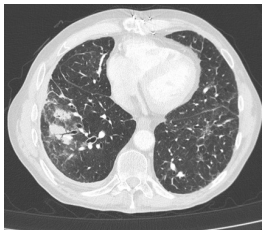
Everolimus 1.75 mg/d

MMF 360x3/d

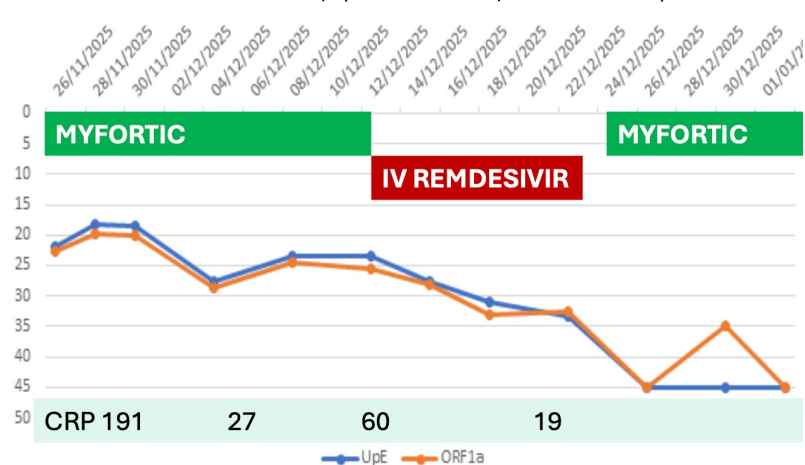
Corticosteroids 5 mg/d

Moderate chronic kidney dysfunction (40 mL/min)

Mild lung interstitial disease



MERS-CoV PCR Ct (UpE and ORF1a) over time in sputum



ARTICLE

<https://doi.org/10.1038/s41467-019-13940-6>

OPEN

Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV

The antiviral compound remdesivir potently inhibits RNA dependent RNA polymerase from Middle East respiratory syndrome coronavirus

Sheahan TP, et al. Nat Commun. 2020 Jan 10;11(1):222. doi: 10.1038/s41467-019-13940-6.

Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. J Biol Chem. 2020 Apr 10;295(15):4773-4779. doi: 10.1074/jbc.

Bal A. et al. Imported MERS-CoV Cases in France in late 2025: clinical management, virological investigations, and public health implications

NEJM 2026
Evidence

Summary

	EU EMA	Accès France	Virus respi
Oseltamivir	X	X	Influenza
Remdesivir VEKLURY®	X	X	SARS-CoV-2 MERS-CoV ? RSV ? PIV ?
Zanamivir RELENZA® (poudre aérosol) DECTOVA® (IV)	X	ATU nominative (ANSM)	Influenza
Peramivir	/	/	Influenza
Baloxavir marboxil XOFLUZA®	X	- Demande d'accès dérogatoire ou d'importation (ANSM) - Essais cliniques - Contingentement (stock stratégique d'état)	Influenza
Favipiravir AVIGAN®	/	Autorisation d'accès compassionnel (Ebola ANSM)	Influenza Autre(s) ?



Haut Conseil de la santé publique

AVIS

relatif au stock de l'État en médicaments antiviraux actifs contre les virus de la grippe

23 avril 2026

Almanach thérapeutique (prévention, traitement)

Antiviral	Approved Indications: Dose	ICIs in Phase 2/3 RCTs	Data Specific to ICIs	Considerations for ICIs
Oseltamivir (Oral)	Treatment: 75 mg BID × 5 d ^a	No	Observational cohorts [3, 4, 10] RCT for high dose vs standard dose in ICIs [28]	150 mg BID and/or extending duration to 10 d in high-risk groups
	Prophylaxis for household contacts and in community outbreaks: 75 mg daily for at least 10 d ^a	No	Observational cohorts [29–31] RCT for PrEP in transplant recipients [32]	Assume transmission has occurred after exposure and dose accordingly (eg, 75 mg BID)
Peramivir (IV)	Treatment: 600 mg as a single dose for mild to moderate influenza ^b	No	Case reports [33] RCT comparing oseltamivir to peramivir included ICIs but not specific to ICIs [34]	Daily dosing for severe illness
Zanamivir (INH; IV internationally)	Treatment: 10 mg INH BID × 5 d ^c . Inhaled formulation not appropriate for severe LRTI or mechanical ventilation.	No	Case reports, mostly with IV formulation [35, 36]	600 mg IV BID has been used in severe influenza [35]
	Prophylaxis for household contacts and in community outbreaks (10 mg INH daily)	No	...	Assume transmission has occurred after exposure and dose accordingly
Laninamivir octanoate (INH)	None in the United States Treatment and prophylaxis of household contacts in Japan	No	None	...
Favipiravir (Oral)	None in the United States Treatment in Japan	No	Case report [37]	...
Baloxavir marboxil (Oral)	Treatment of uncomplicated influenza (40 mg or 80 mg as a single dose) ^d	No	Case series (see Figure 1) RCT comparing NAI alone to NAI + baloxavir included ICIs but not specific to ICIs [38]	In hospitalized ICIs on concurrent NAI, repeated dosing on days 4 and 7 if ongoing severe influenza
	PEP (40 mg or 80 mg as a single dose) ^d	No	...	...

Abbreviations: BID, twice daily; ICIs, immunocompromised individuals; INH, inhaled; IV, intravenous; LRTI, lower respiratory tract infection; NAI, neuraminidase inhibitor; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; RCT, randomized clinical trial.

^aFor patients >12 years old with normal renal function, oseltamivir treatment dose is 75 mg twice daily and prophylaxis dose is 75 mg daily. For patients with a creatine clearance of 10–30 mL/minute, oseltamivir treatment dose is reduced to 75 mg daily and oseltamivir prophylaxis dose is 75 mg every other day or 30 mg daily. Oseltamivir is given as weight-based dosing for children ≤12 years old.

^bFor patients >12 years old with normal renal function, each peramivir dose is 600 mg IV. The recommended dose for patients with creatinine clearance 30–49 mL/minute is 200 mg and the recommended dose for patients with creatinine clearance 10–29 mL/minute is 100 mg. For children 2–12 years old, weight-based dosing (12 mg/kg) up to 600 mg is recommended.

^cZanamivir is approved for treatment of influenza in persons ≥7 years old and for chemoprophylaxis in persons ≥5 years old by the United States Food and Drug Administration (FDA). Aerosolized zanamivir is not appropriate for patients with severe hypoxemia from lower respiratory tract disease because it may induce bronchospasm and can clog ventilatory circuits.

^dBaloxavir is dosed at 40 mg for persons weighing 20–80 kg, 80 mg for persons weighing >80 kg, and 2 mg/kg for persons weighing <20 kg. Baloxavir is approved by the FDA for treatment of influenza within 48 hours of symptom onset and PEP in persons ≥5 years old. It is also approved for treatment of uncomplicated influenza in persons ≥12 years old who are at high risk of developing influenza complications.

PRÉVENTION DES INFECTIONS À VRS

Le bon produit pour le bon patient



Ne confondez pas anticorps monoclonal et vaccin

Anticorps monoclonal pour :
nourrisson / nouveau-né / enfant ≤ 24 mois

Vaccin pour :
femme enceinte / adulte

Ne cumulez pas les deux sauf exception

Avant toute injection, vérifiez : 1. Le patient | 2. Le médicament | 3. La dose | 4. La voie d'administration

Ces traitements doivent être utilisés conformément aux recommandations officielles du ministère chargé de la santé figurant dans le calendrier vaccinal en vigueur



Nouveau-né et nourrisson

Première saison d'exposition au VRS

Anticorps monoclonal

Beyfortus (nirsévimab)

Moins de 5 kg : 1 seule injection de 50 mg

5 kg ou plus : 1 seule injection de 100 mg

- En intramusculaire
- Dans la face antérolatérale de la cuisse
- Dès la naissance pour les enfants nés pendant la campagne VRS ou dès le début de la campagne pour les autres

⚠ Ne pas administrer dans le muscle fessier

Enflonia (clesrovimab)

1 seule injection de 105 mg

- En intramusculaire
- Dans la face antérolatérale de la cuisse
- Dès la naissance pour les enfants nés pendant la campagne VRS ou dès le début de la campagne pour les autres

⚠ Ne pas administrer dans le muscle fessier



Enfant ≤ 24 mois

Vulnérable à une infection sévère

Deuxième saison d'exposition au VRS

Anticorps monoclonal

Beyfortus (nirsévimab)

2 injections de 100 mg le même jour, chacune sur un site différent

- En intramusculaire
- Dans la face antérolatérale de la cuisse
- Au cours de la campagne VRS lors de la 2e saison VRS

⚠ Ne pas administrer dans le muscle fessier



Femme enceinte

Pour la protection passive du nourrisson

Vaccin

Abrysvo

1 seule injection de 0,5 mL

- En intramusculaire
- Dans le deltoïde
- Entre 32 et 36 semaines d'aménorrhée, pendant la campagne d'immunisation VRS
- Si la naissance survient moins de 14 jours après vaccination ou si prématurité = rattrapage par anticorps monoclonal recommandé chez le nouveau-né



Chez les femmes enceintes immunodéprimées ou déjà vaccinées contre le VRS lors d'une grossesse précédente => privilégier l'immunisation du bébé avec un anticorps monoclonal



Adulte

≥ 75 ans

ou

≥ 65 ans avec pathologie respiratoire chronique ou cardiaque susceptible de décompenser

Vaccin

Abrysvo ou Arexvy ou mResvia

1 seule injection de 0,5 mL

- En intramusculaire
- Dans le deltoïde
- Vaccination saisonnière. La nécessité d'une revaccination avec une dose supplémentaire n'a pas été établie

Ribavirin (RBV): 1972 !! Guanosine analogue

Bio-availability **45-65%**

Ingestion with **fat meal** : bio-availability optimization **x 1.5**

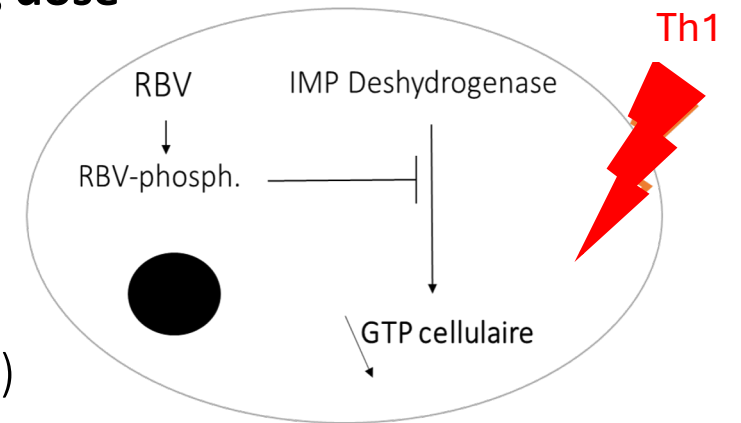
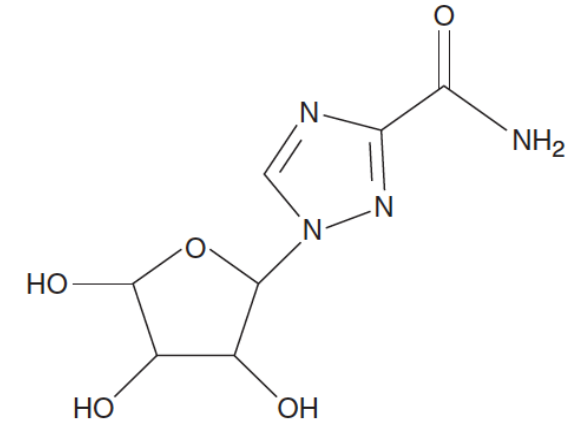
Important but slow **tissular diffusion index**, CNS included

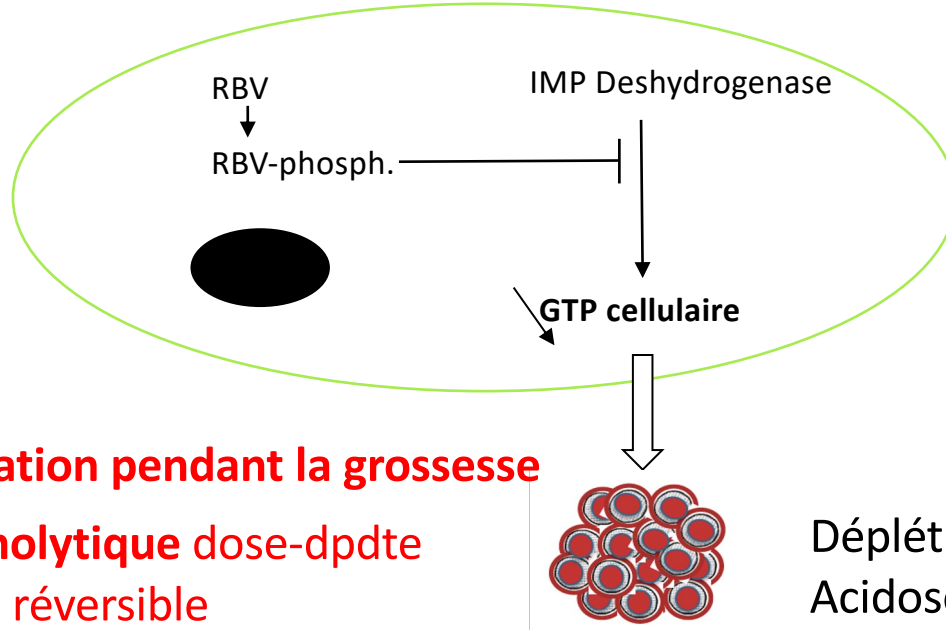
Long half-life = **150h** (1 dose) up to **300h** (cumulative doses)---- > **loading dose**

Drug clearance dpdt on :

- **weight** (adaptation dose/weight)
- **renal function**

No hepatic metabolization = no dose adaptation (end-stage liver diseases)



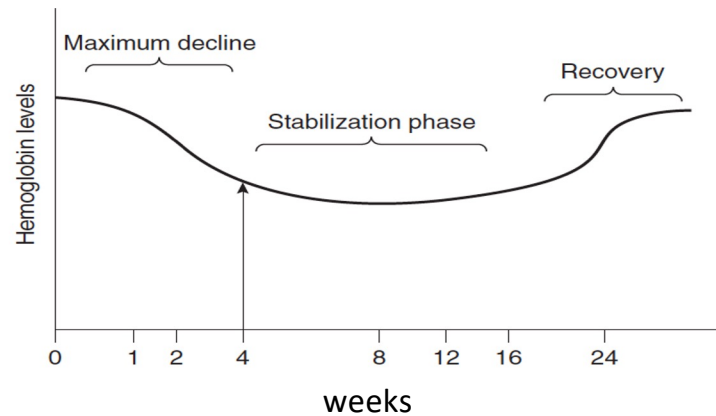


Anemia (11-35%)
Hemolytic anemia (10-13%)
 Neutropenia (8-40%)
 Lymphopenia (14%)
MOSTLY IF >14 days



Contre-indication pendant la grossesse
Anémie hémolytique dose-dépendante et réversible

Déplétion GTP et ATP
 Acidose lactique



Use of systemic ribavirin for RTI/D with RSV, PIV, and MPV

Treatment course	Description
Oral or intravenous ribavirin maximal dosing at 10 mg/kg body weight every 8 h for adults	Day 1: start with 600 mg loading dose, then 200 mg every 8 h Day 2: 400 mg every 8 h Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h In case of adverse events, decrease dose or discontinue ribavirin
Oral or intravenous administration according renal function	Dose for a creatinine clearance of 30 to 50 ml/min: a maximum of 200 mg every 8 h For a creatinine clearance of 10 to 30 ml/min, no dose recommendation can be given ^b

^bSome experts use 200 mg once daily under close clinical and laboratory monitoring