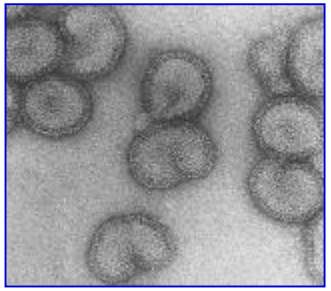
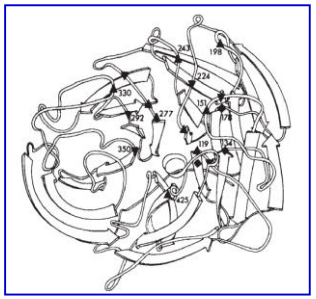
Introduction aux Antiviraux

« Qu'est ce qu'un antiviral ? »





Pr Patrice Morand

Laboratoire de Virologie

Diplôme Universitaire de Thérapeutiques Anti-Infectieuses
Université Grenoble Alpes
1ère session – Janvier 2023

Pas de lien d’intérêt pour cet exposé

Antiviraux : un peu d'histoire

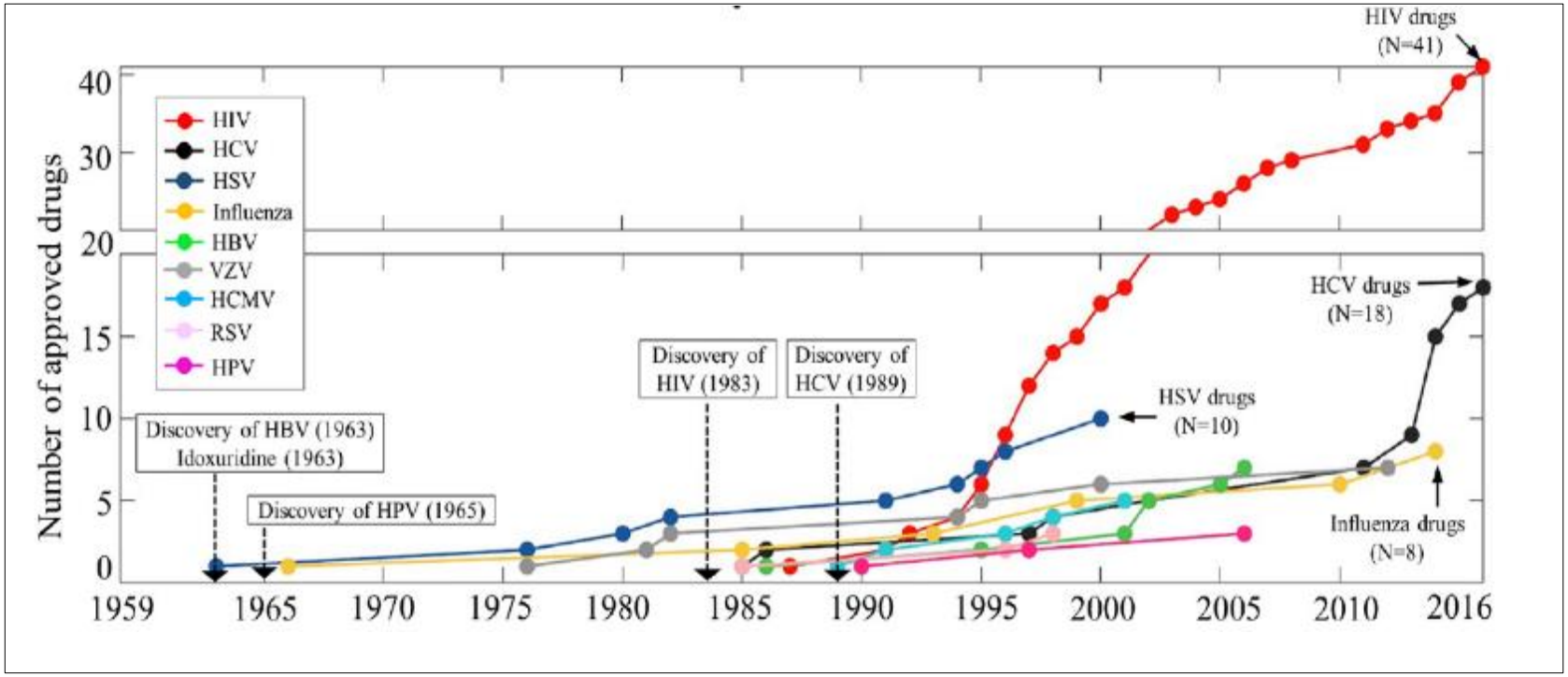
AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Approved Antiviral Drugs over the Past 50 Years

Erik De Clercq,[a] Guangdi Li[a,b] *2016*

1963 : Premier antiviral mis sur le marché chez l'homme: Idoxuridine

. tt local de la kératite herpétique
. analogue deoxyuridine décrit en 1959 (antitumoral)
. tjs sur le marché



Antiviraux : un peu d'histoire

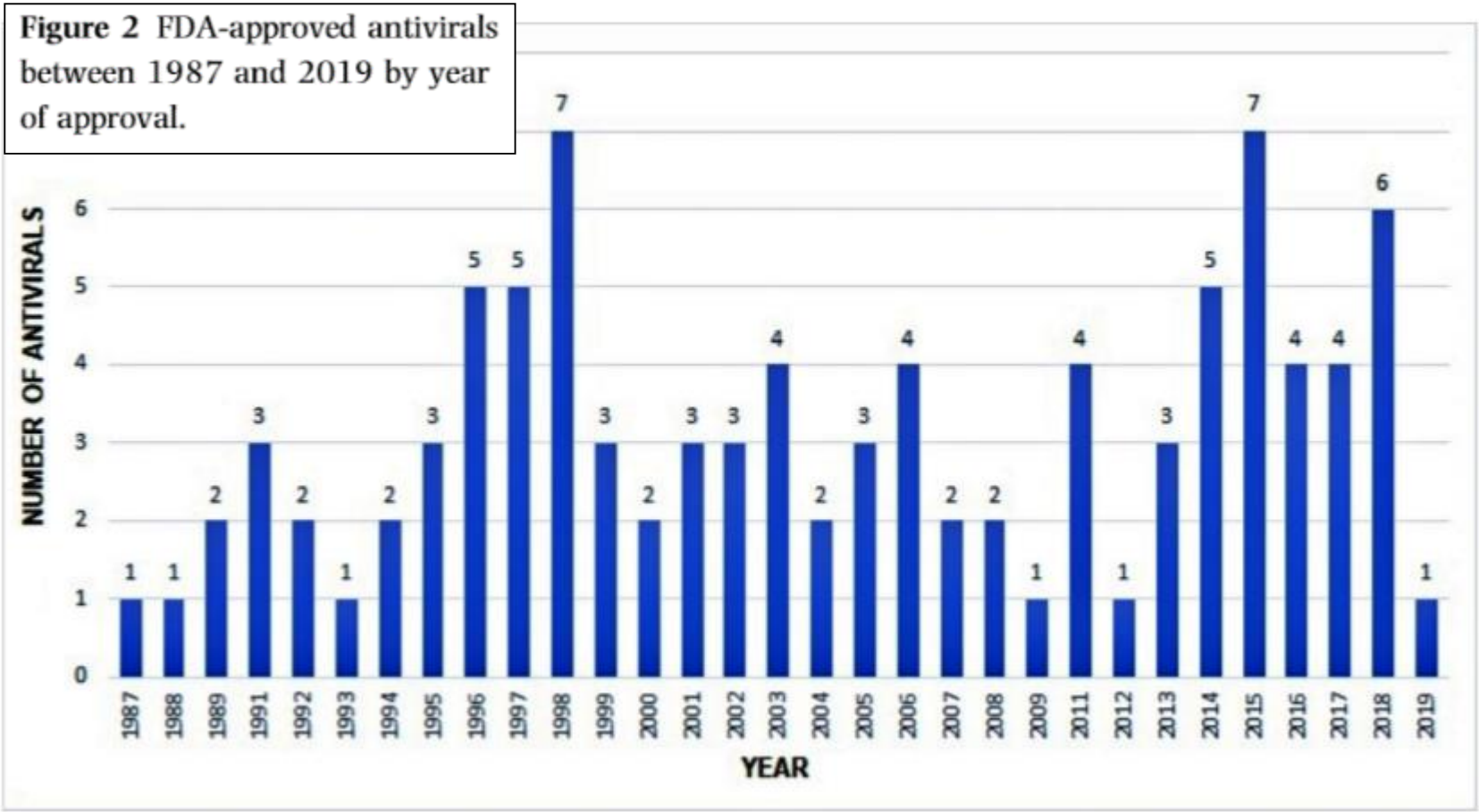
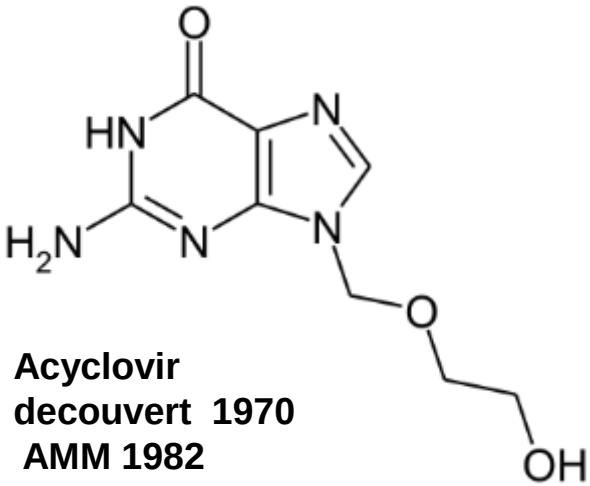


Figure 2 FDA-approved antivirals between 1987 and 2019 by year of approval.

96 FDA-approved antivirals between 1987 and 2019,
of which 49 are anti-HIV, followed by 17 anti-HCV,
five anti-influenza, one anti-RSV, six anti-CMV, eight anti-HBV, four anti-HPV and six anti-HSV drugs.

Goncalves B et al Fundamental & Clinical Pharmacology 2020

Antiviraux : les belles histoires



Acyclovir
decouvert 1970
AMM 1982

Gertrude Elion
Nobel Médecine1988

International Journal of
Molecular Sciences

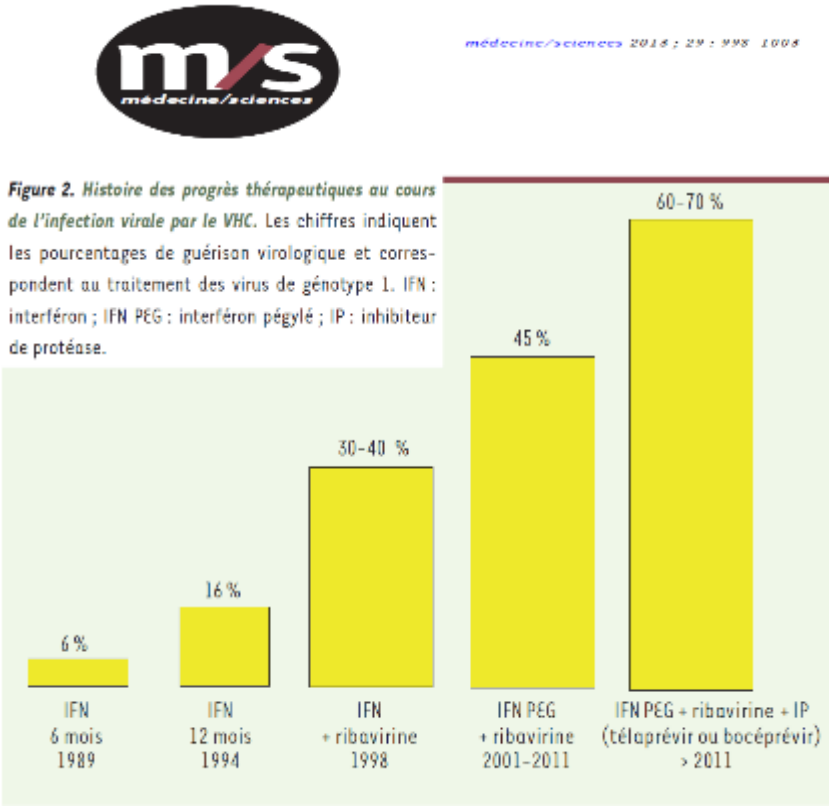
MDPI

Review

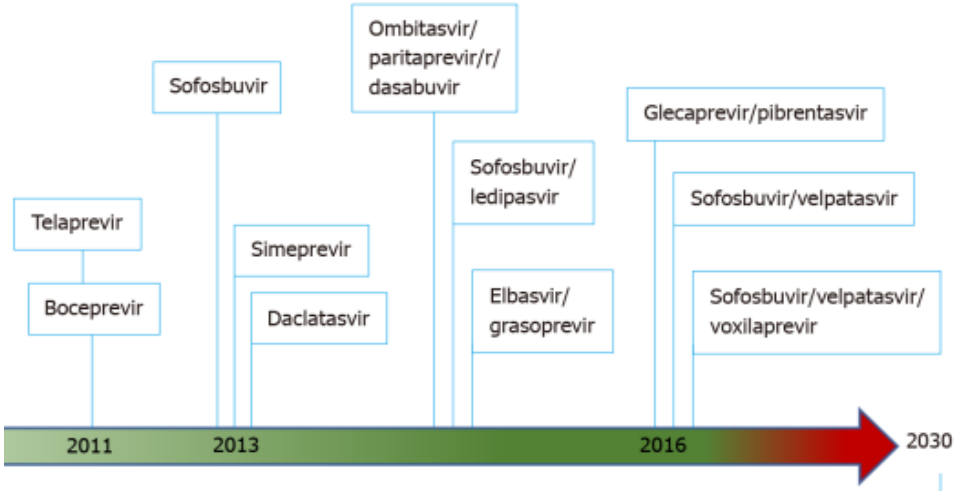
40 Years after the Registration of Acyclovir: Do We Need New Anti-Herpetic Drugs?

Anna Majewska [1,†] and Beata Mlynarczyk-Bonikowska [2,*,†]

Antiviraux : les belles victoires



Antiviraux à action directe
~ 95 -100 % de guérison en 2020
…previr : anti protéase
…asvir : anti NS5A
…buvir : anti NS5B (polymérase)



González Grande R et al World
World J Gastro Enterol 2021

Objectif OMS : éradication HCV en 2030

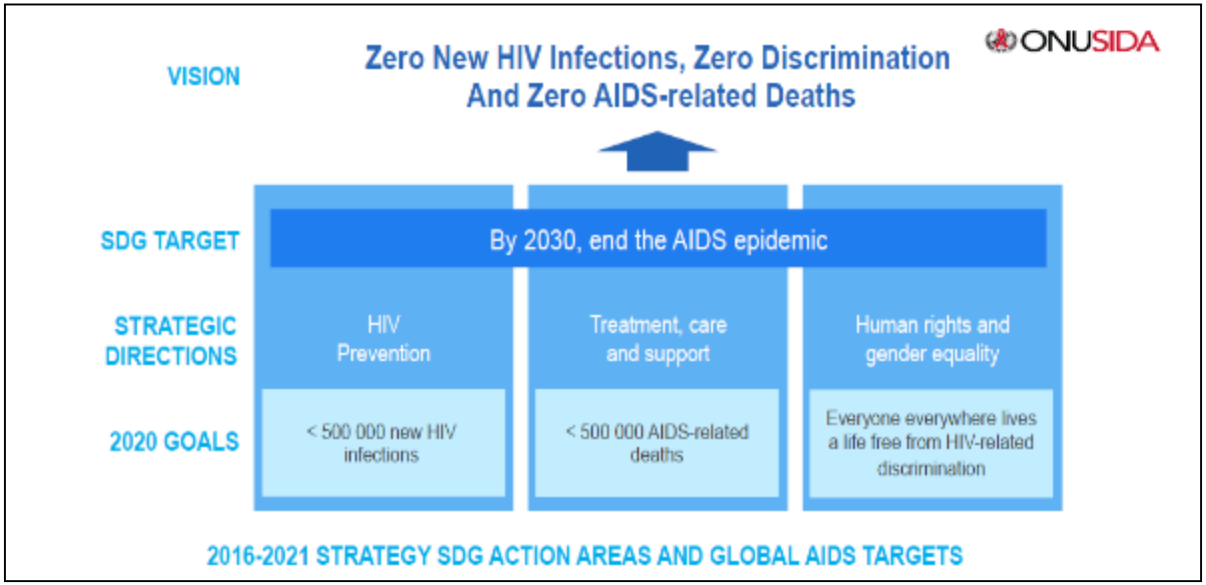
Antiviraux : les belles victoires

Conférence de Washington

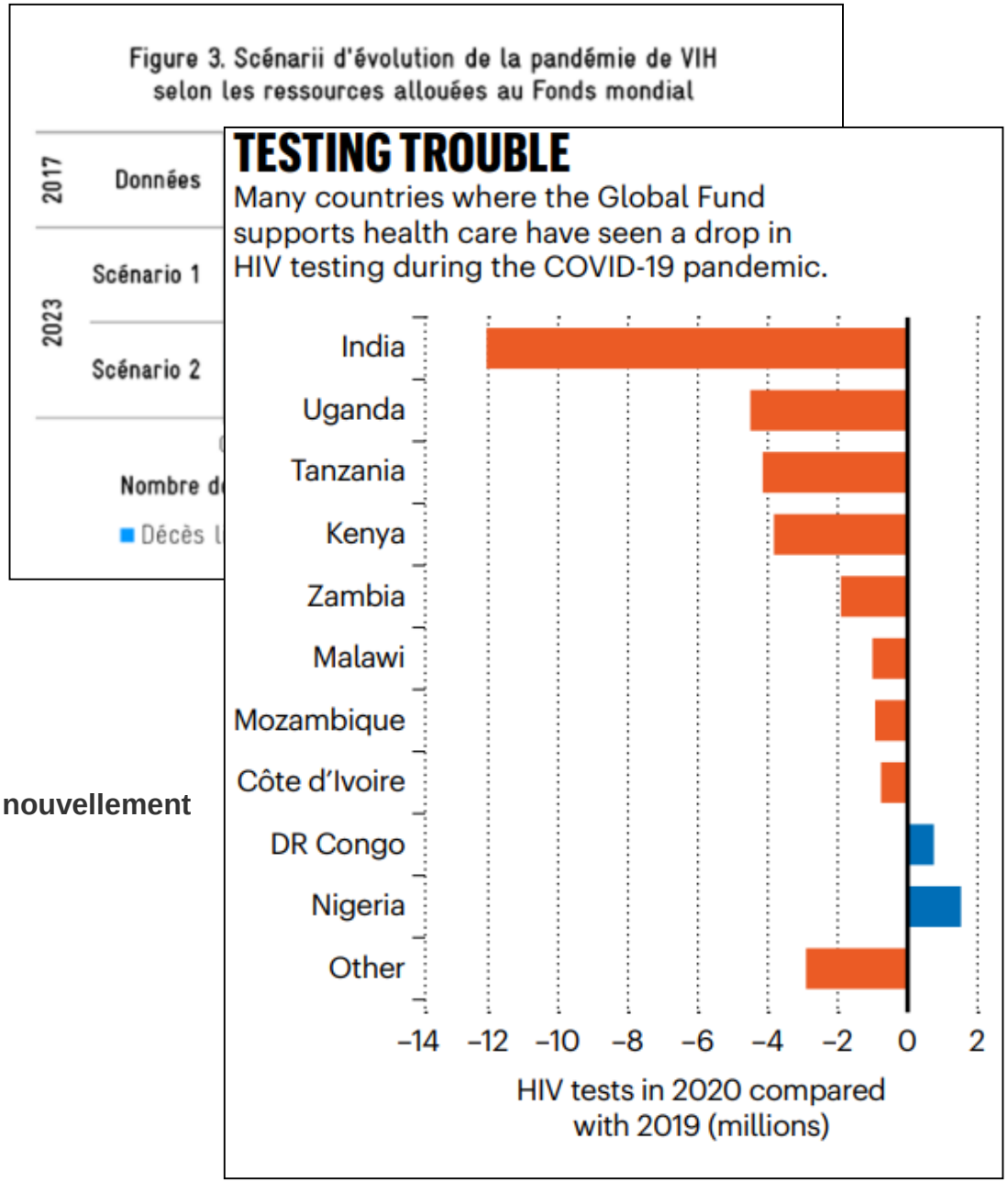
LA FIN DU SIDA?

L'éradication de l'épidémie est désormais possible, encore faudrait-il que l'aide internationale, première victime de la crise, soit maintenue.

Long-term retention in care and maintenance of successful antiretroviral therapy allow persons with HIV infection to have a near-normal life span and virtually eliminate transmission of HIV to others
Saag MS New Engl J Med 2021



Antiviraux : les belles victoires … qui tardent



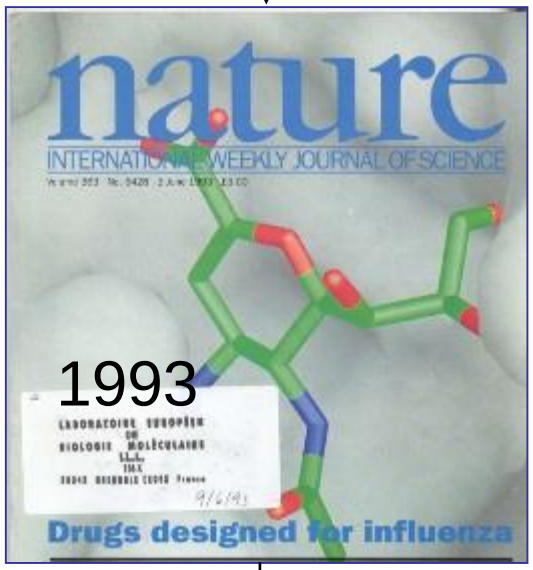
En 2021,

1,5 million [1,1 –2 millions] personnes étaient nouvellement infectées par le VIH

650 000 [510 000-860 000] décès

Antiviraux : l'histoire qui s'accélère

Structure de la neuraminidase
(Colman PM. Nature 1983)



Essais Phase I / II /III

AMM TAMIFLU 2002

How Pfizer scientists transformed an old drug lead into a COVID-19 antiviral

Behind the scenes of the medicinal chemistry campaign that led to the pill Paxlovid

by Bethany Halford

January 14, 2022 | A version of this story appeared in Volume 100, Issue 3

Antiviraux : l'histoire qui s'accélère

Anno 2021: Which antivirals for the coming decade?

Elisabetta Groaz[a,b,*], Erik De Clercq[c], and Piet Herdewijn[a]

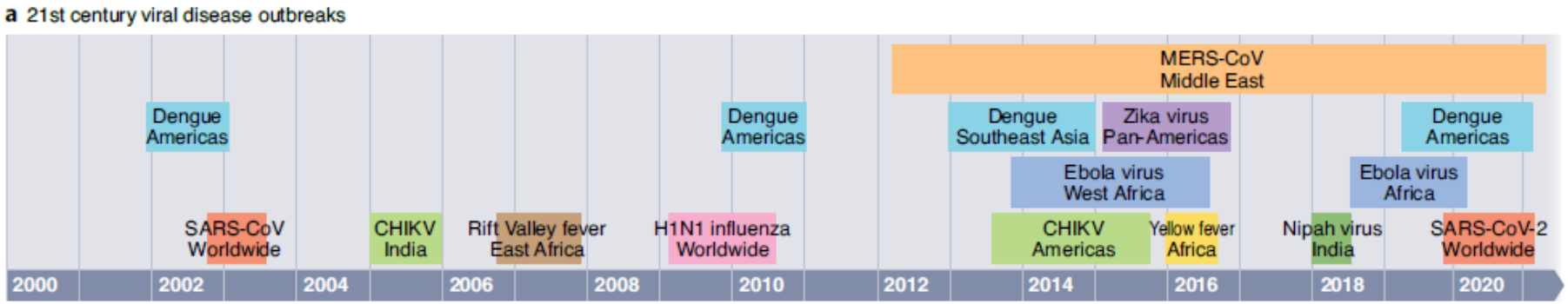
Contents

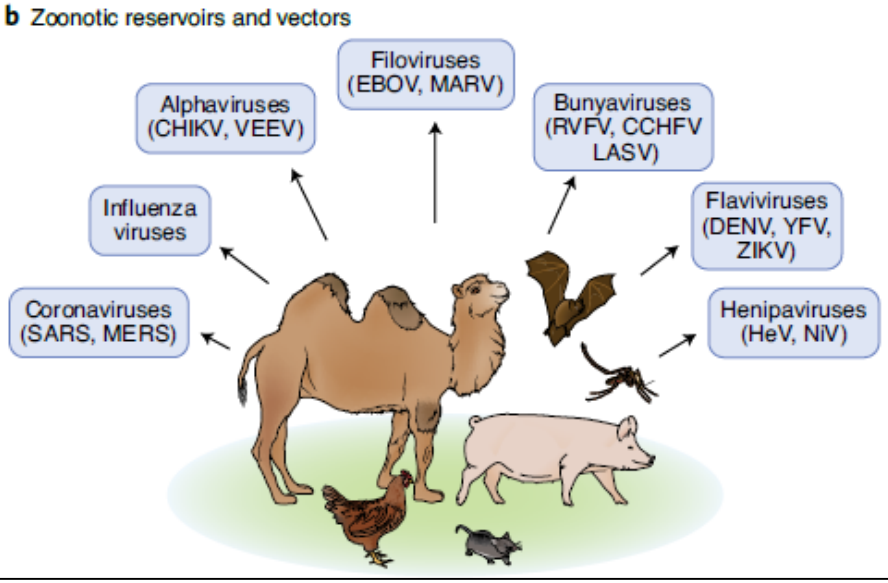
Groaz et al Annuals Reports in Medical Chemistry 2021

Antiviraux : l'histoire qui s'accélère

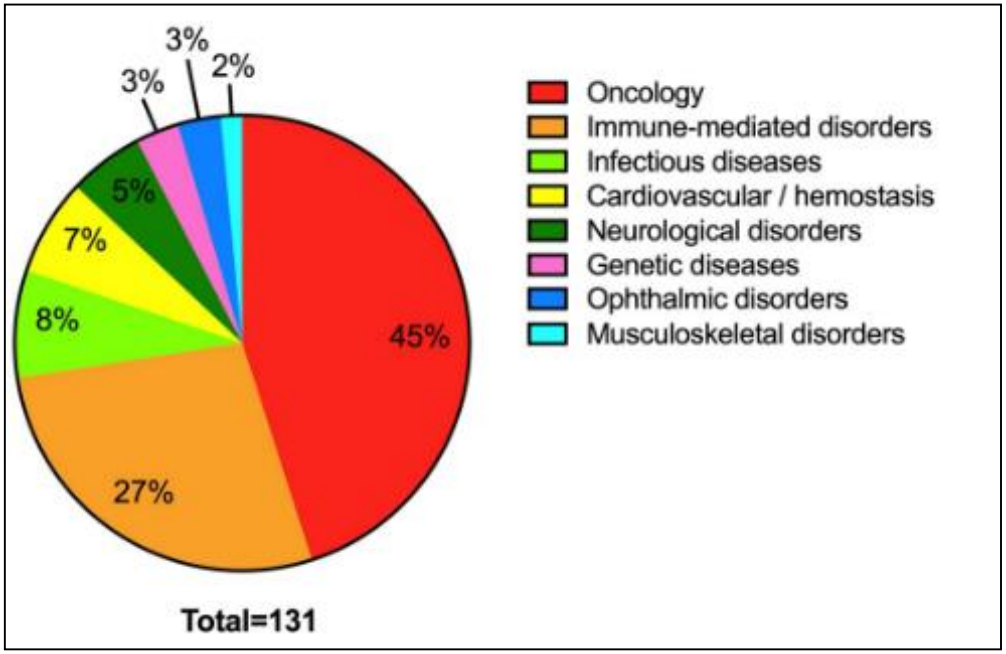
Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases

Meganck RM and Baric RS Nature Med 2021





Antiviraux : l'histoire qui s'accélère :
La révolution des Ac monoclonaux neutralisant

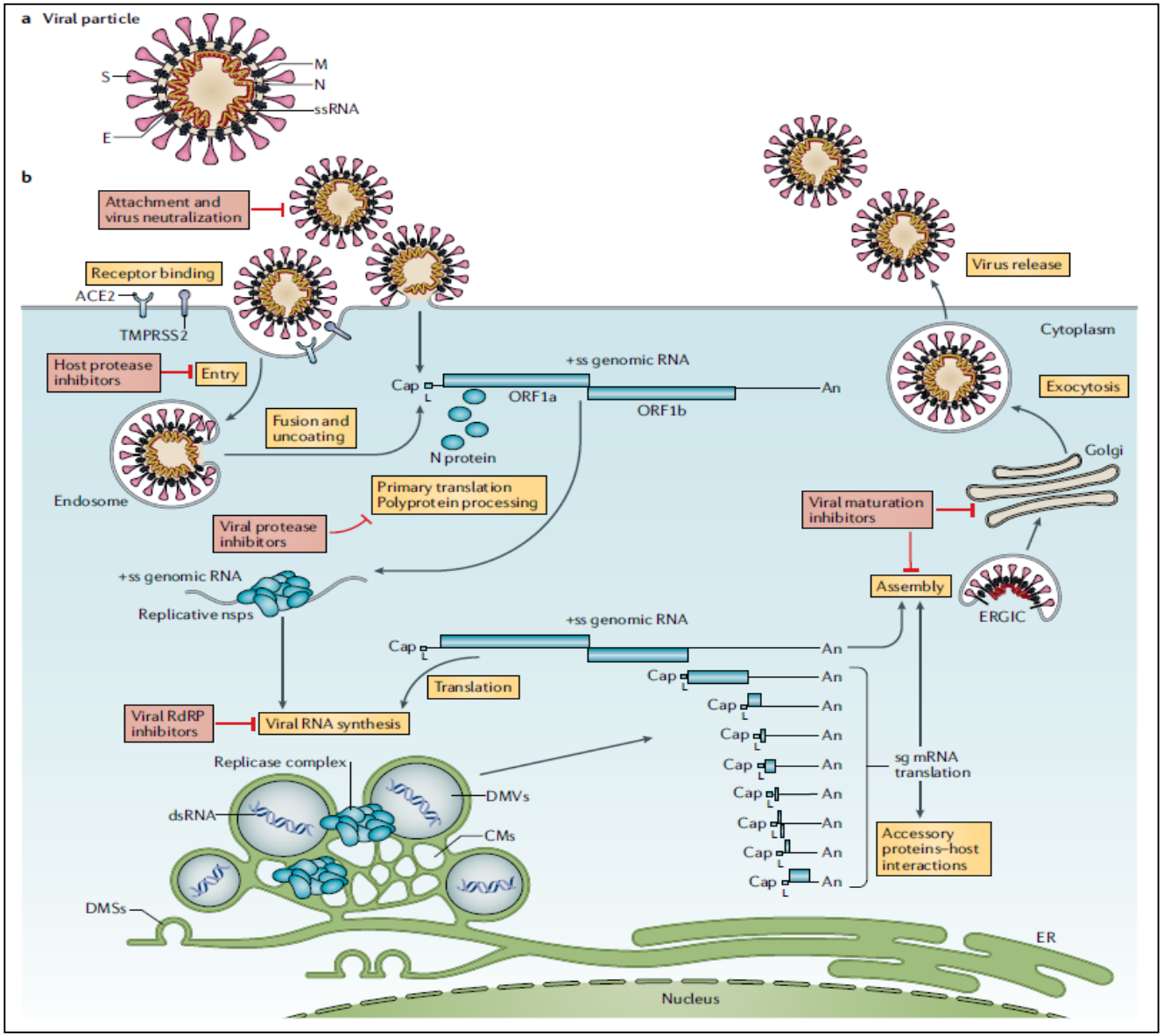


Primary indications for antibody therapeutics
Approved or in regulatory review in the United States
or European Union .
Kaplon H et al, Mabs 2022

Q Wang et al **Current Opin Virol 2022** ***: Développement of mAbs against***

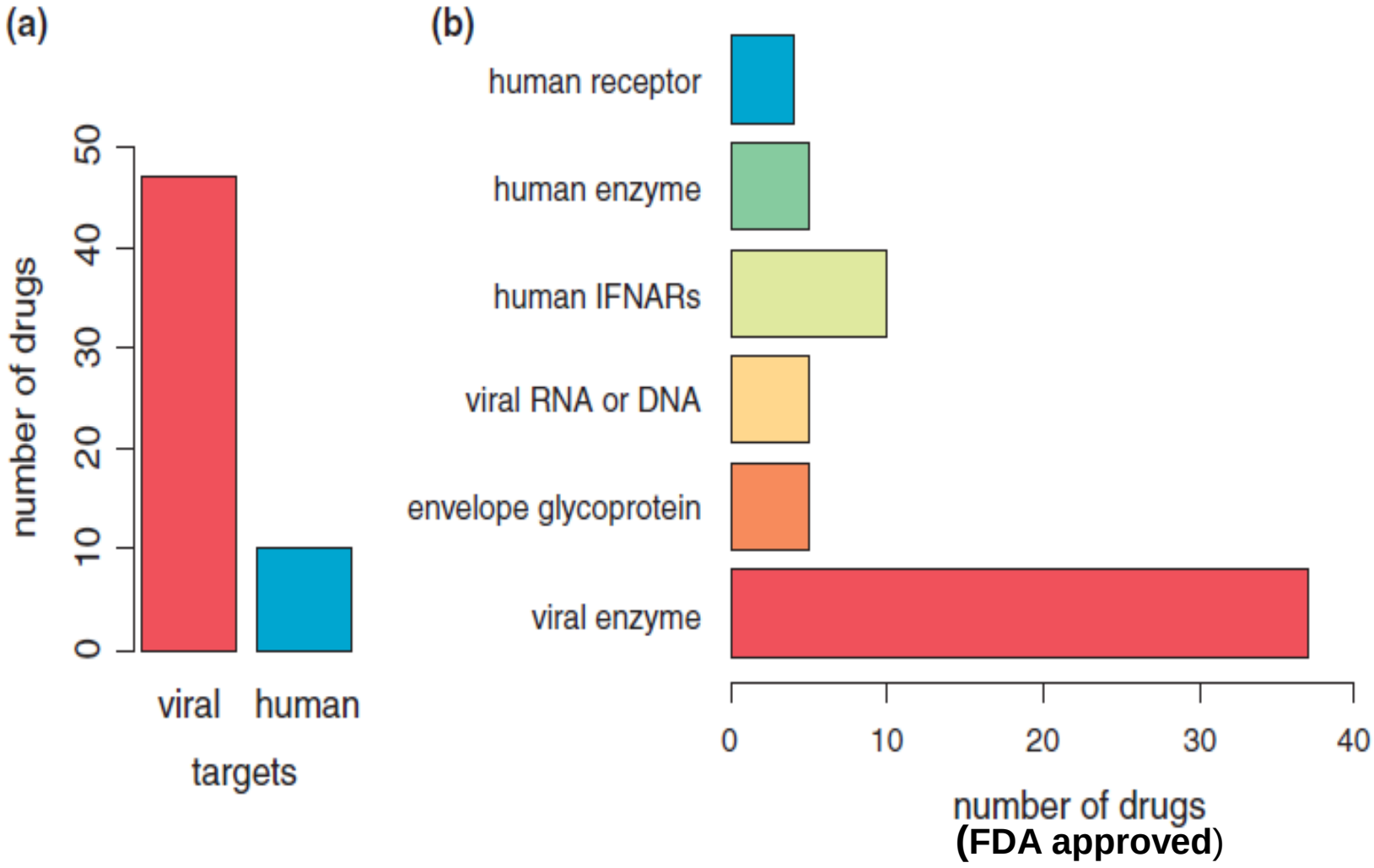
HIV,
Ebola virus
Hepatitis B virus
influenza virus
coronavirus
CMV
rabies virus

Virus = parasites cellulaires obligatoires : les différentes étapes du cycle de réplication virale sont toutes des cibles antivirales potentielles:



V'kovski P et Nature Rev Microbiol 2020

Virus = parasites cellulaires obligatoires : les cibles antivirales sont principalement virales (enzymes +++) et plus rarement cellulaires



De Chassey B. Curr Opi Virol 2012

Virus Respiratoire Syncytial : Problème de santé publique

. Principale cause de bronchiolite chez le nourrisson (sévérité 1ère année++)

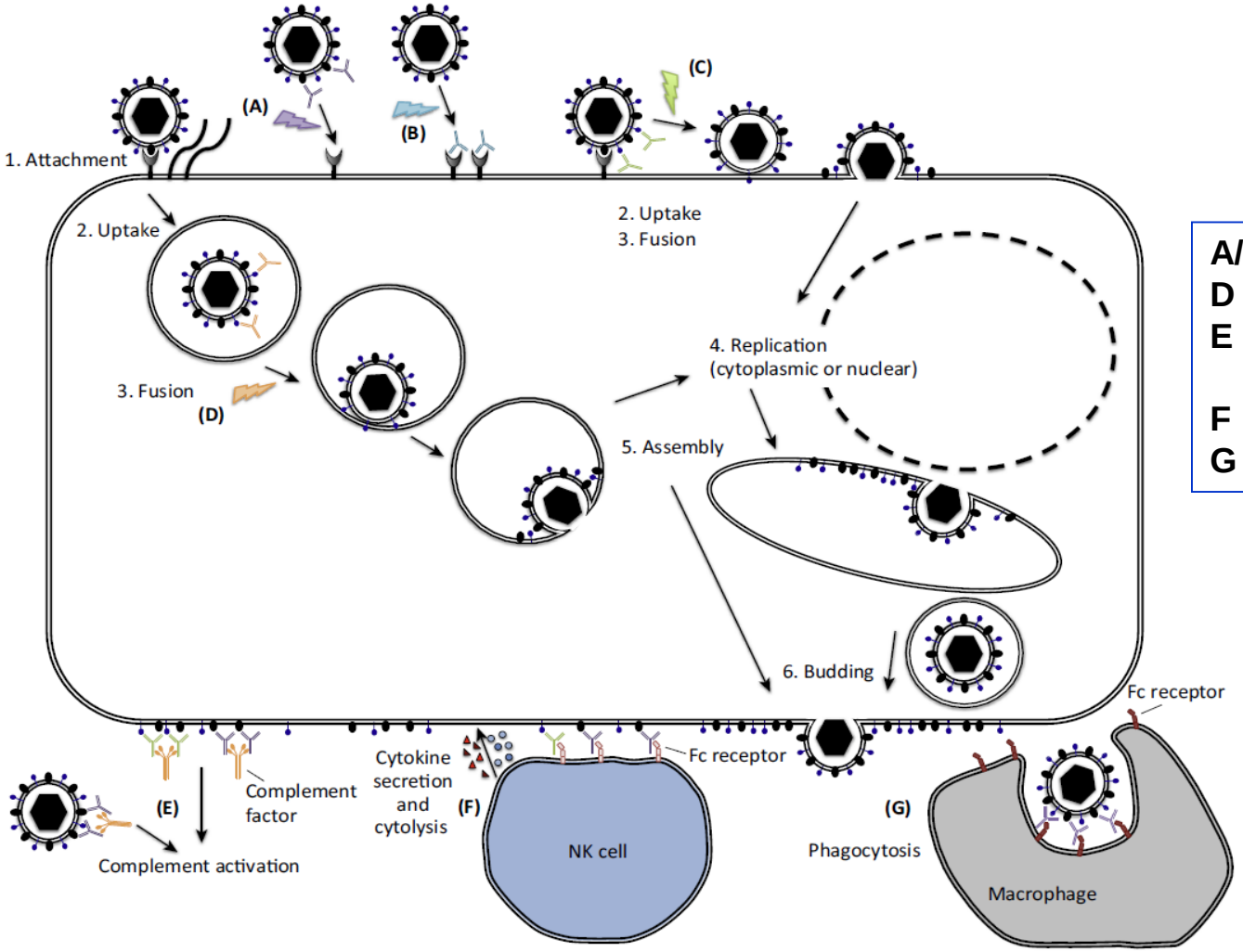
3 millions hospitalisations et > 50 000 morts /an chez les < 5 ans
2% des décès des enfants de moins de 5 ans (3,6% des < 6 mois)

. Adulte > 60 ans : Morbi-mortalité associée similaire à Influenza

Rate of Hospitalizations and Mortality of Respiratory Syncytial Virus Infection Compared to Influenza in Older People: A Systematic Review and Meta-Analysis.
Maggi S et al *Vaccines* . 2022

. Sévérité chez Greffes (CSH, poumons)

Antiviraux : l'histoire en marche :
La révolution des Ac monoclonaux neutralisant



A/B/C : entrée du virus
D : décapsidation
E : opsonisation et activation complément
F : ADCC
G : phagocytose

Wisskirchen K. Trends Pharmacol Sci 2014

Actualités sur les nouveaux antiviraux Virus Respiratoire Syncytial

institutmondor
de recherche biomédicale

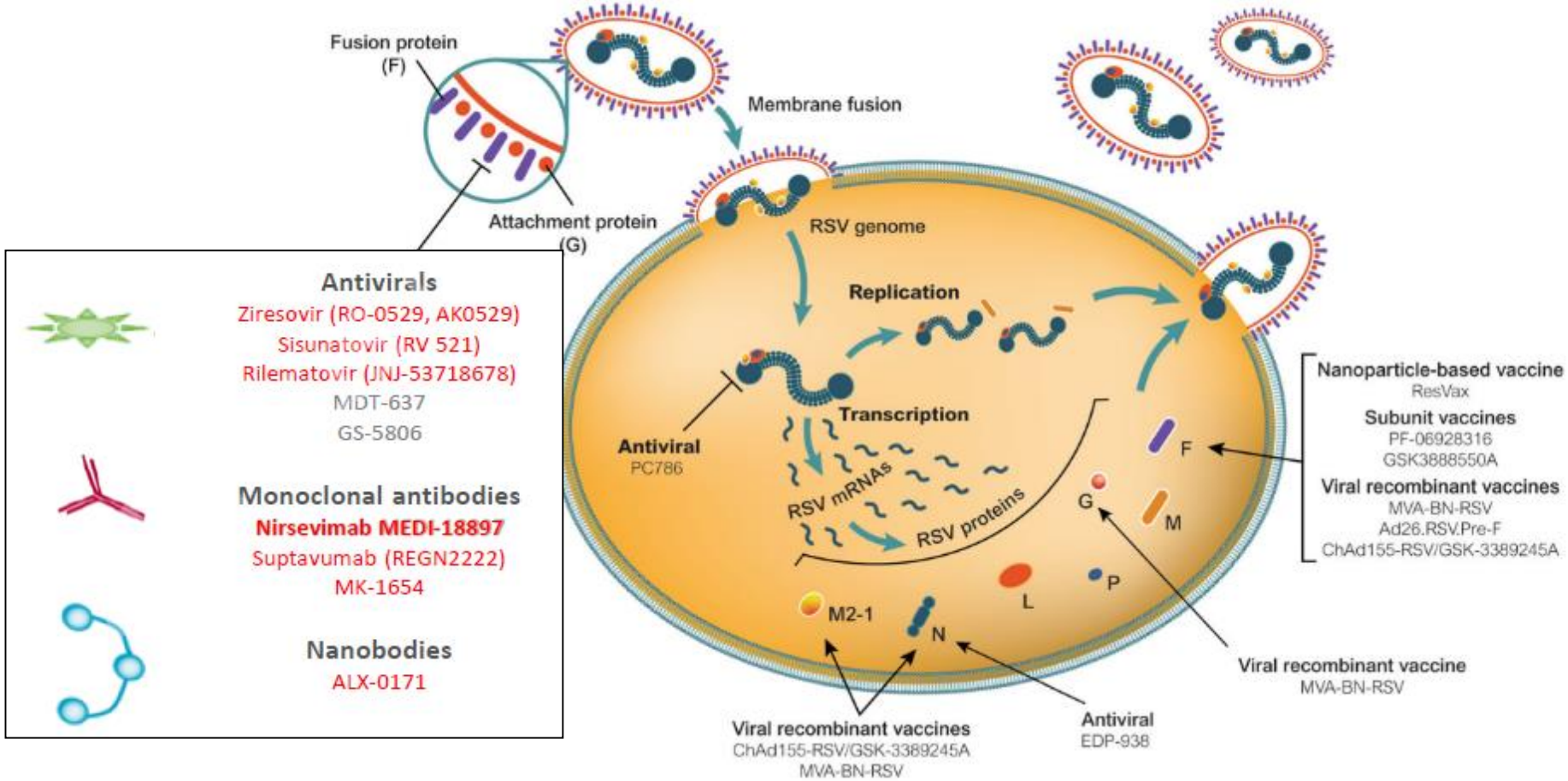
Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

AP-HP. Hôpitaux universitaires Henri-Mondor

SLIM FOURATI
HÔPITAL HENRI MONDOR
LABORATOIRE DE VIROLOGIE
INSERM U955

UPEC
Connaissance - Action
UNIVERSITÉ PARIS EST CRÉTEIL DE MARNE

Virus Respiratoire Syncytial



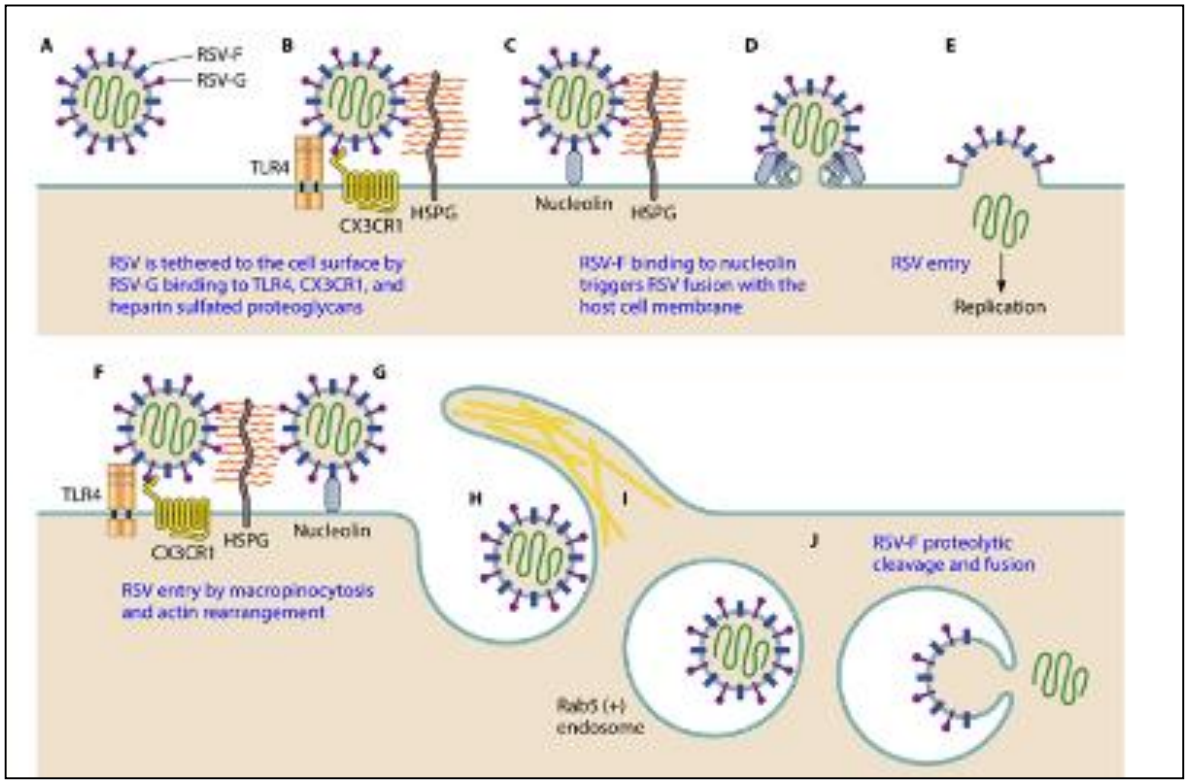
Domachowske JB et al Infect Dis The 2021
S Fourati RICAI 2022

Virus Respiratoire Syncytial : plusieurs cibles antivirales

. Protéine F de fusion :

. Ziresovir
. Rilematovir
. Sisunatovir

Agissent sur la même cible : poche formé par le trimère F (prefusion)
→ résistance croisée



Virus Respiratoire Syncytial : plusieurs cibles antivirales

. Protéine L de l'ARN polymérase :

porte la sous unité catalytique de la polymerase + impliqué ds la coiffe des ARN m
inhibiteur non nucléosidique (PC 786)
voie inhalée

. Nucléoprotéine (protéine N)

interagit avec la polymérase : rôle ds la transcription et réplication
EDP 938 : puissante activité in vitro/ barrière génétique élevée

→ **Anti F/L/ N/ Essais phase II / III:**

.adultes sains («human challenge») infectés par une souche VRS
.enfants et adultes infectés
. greffe CSH

Virus Respiratoire Syncytial : antiviraux anti F

Données cliniques. Patients infectés (Phase II/III)

Ziresovir (AIRFLO study):

311 NRS hospitalisés pour bronchiolite à VRS :

↘ CV (77% vs placebo) à J5

↘ la symptomatologie à J3: 30% et 55% (<6 mois) vs placebo

↘ la durée d'hospitalisation en réanimation (3J vs 8J)

ArkBio
爱科百发

Ark Biopharmaceutical Presents Positive Results in Phase 3 AIRFLO Study of Ziresovir in RSV-Infected Hospitalized Infants at 12th International RSV Symposium

[illegible] 2022 23h39 HE | Source: Shanghai Ark Biopharmaceutical Co., Ltd.

Rilematovir (JNJ-53718678) : essais de phase II (traitement enfants et adultes hospitalisés) terminés. Résultats non disponibles

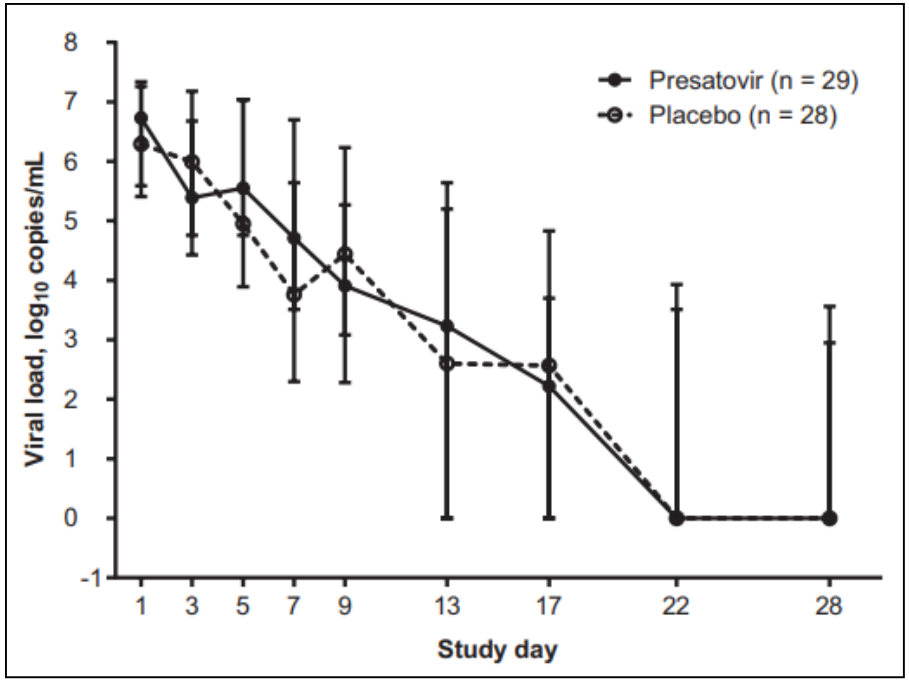
Sisunatovir (RV521) : essais de phase II en cours de recrutement (NRS bronchiolite à VRS sévère nécessitant hospitalisation) ; NCT04225897

S Fourati RICAI 2022

A Phase 2b, Randomized, Double-blind, Placebo-Controlled Multicenter Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of Presatovir in Hematopoietic Cell Transplant Recipients with Respiratory Syncytial Virus Infection of the Lower Respiratory Tract

Francisco M. Marty,[1] Roy F. Chemaly,[2] Kathleen M. Mullane,[3] Dong-Gun Lee,[4] Hans H. Hirsch,[5] Catherine B. Small,[6] Anne Bergeron,[7] Shmuel Shoham,[8] Per Ljungman,[9] Alpana Waghmare,[10,11] Elodie Blanchard,[12] Yae-Jean Kim,[13] Matt McKevitt,[14] Danielle P. Porter,[14] Robert Jordan,[14] Ying Guo,[14] Polina German,[14] Michael Boeckh,[10,11] Timothy R. Watkins,[14] Jason W. Chien,[14] and Sanjeet S. Dadwal[15]

Clinical Infect Dis 2019



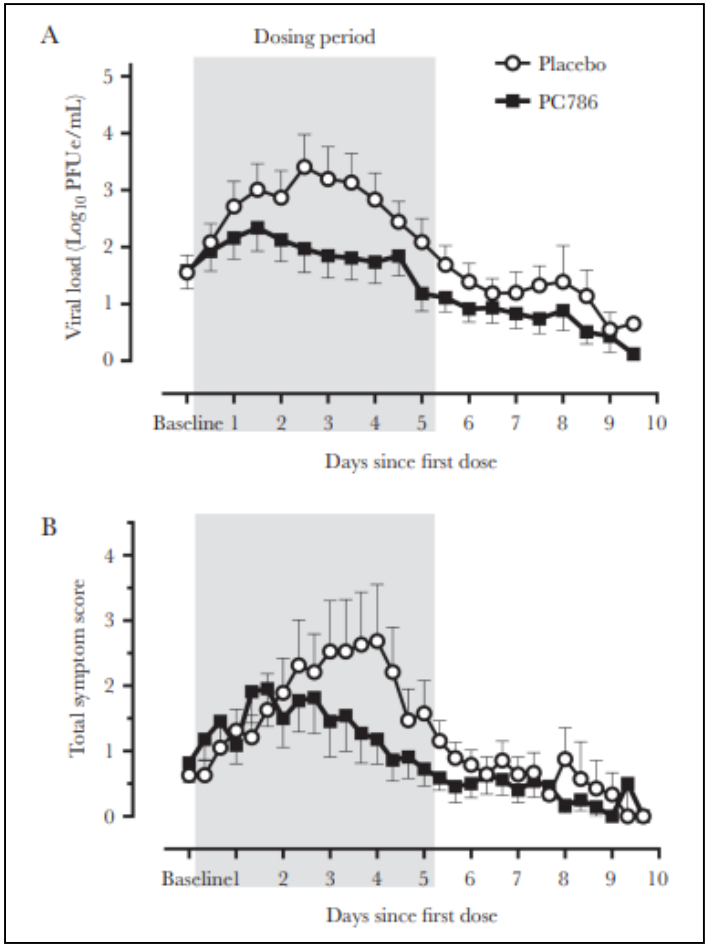
Well tolerated in HCT patients with RSV LRTI but did not improve virologic or clinical outcomes versus placebo.

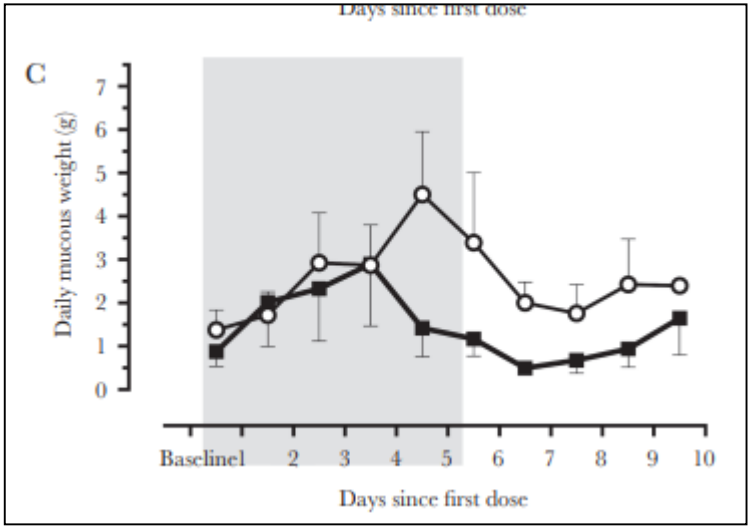
The Journal of Infectious Diseases
MAJOR ARTICLE

Safety and Antiviral Effects of Nebulized PC786 in a Respiratory Syncytial Virus Challenge Study

John DeVincenzo,[1,2,3] Lindsey Cass,[4] Alison Murray,[4] Kathy Woodward,[4] Elizabeth Meals,[1,2] Matthew Coates,[4] Leah Daly,[4] Vicky Wheeler,[5] Julie Mori,[5] Charlie Brindley,[6] Amanda Davis,[6] Meabh McCurdy,[7] Kazuhiro Ito,[4,8] Bryan Murray,[5] Pete Strong,[4] and Garth Rapeport[4]

inhibiteur non nucléosidique de la protéine L





DeVincenzo et al. J. Inf. Dis 2022

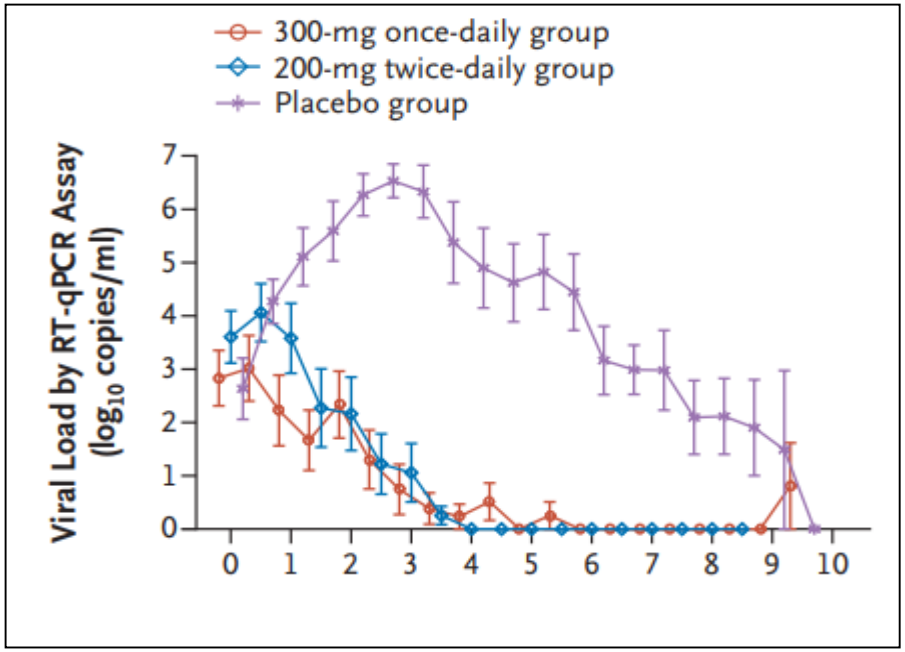
The NEW ENGLAND JOURNAL of MEDICINE

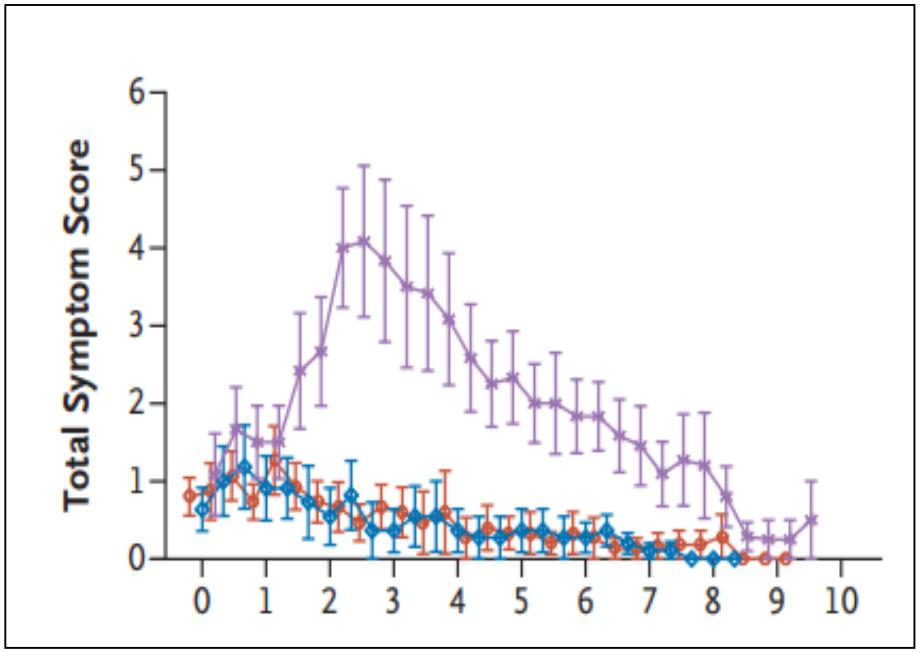
ORIGINAL ARTICLE

EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge

Alaa Ahmad, Ph.D., Kingsley Eze, B.Sc., Nicolas Noulin, Ph.D., Veronika Horvathova, M.B., Ch.B., Bryan Murray, M.B., B.S., Mark Baillet, B.Sc., C.Stat., Laura Grey, Ph.D., Julie Mori, Ph.D., and Nathalie Adda, M.D.

Inhibiteur de la nucleoprotéine N

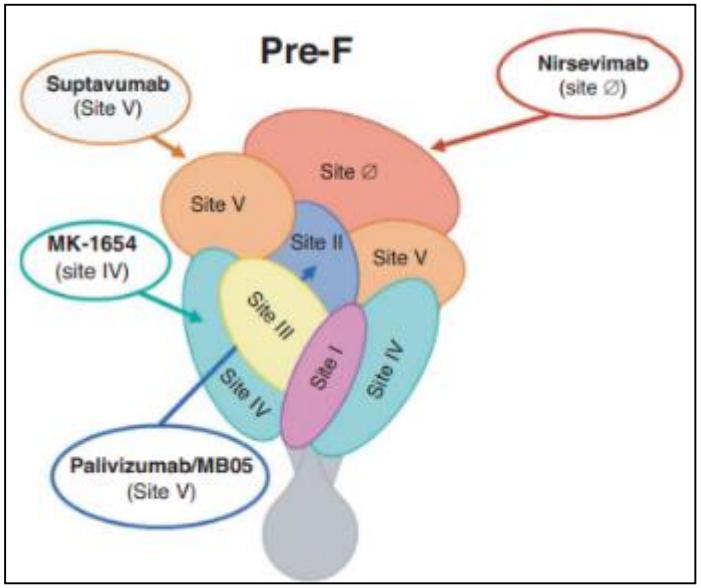




Ahmad A et al .NEJM 2022

Virus Respiratoire Syncytial : nouveaux Ac monoclonaux

. Ac monoclonaux anti F bloquant la fusion :



. **Palivuzumab** (Synagis)

seul Ac monoclonal AMM (2006) :
prévention des IR sévères des nourrissons fragiles
(prématurés, malformations cardio pulmonaires)

. **Nirsevimab**:

½ vie prolongée
dose unique chez les nourrissons prématurés pour la prévention d'infection sévère
essais phase III achevés ou en cours (Harmonie)
autorisation du Nirevimab (Beyfortus) par EMA en septembre 2022 pour prevention des infections vRS chez les nourisson (première saison hivernale)

. **Suptuvumab**

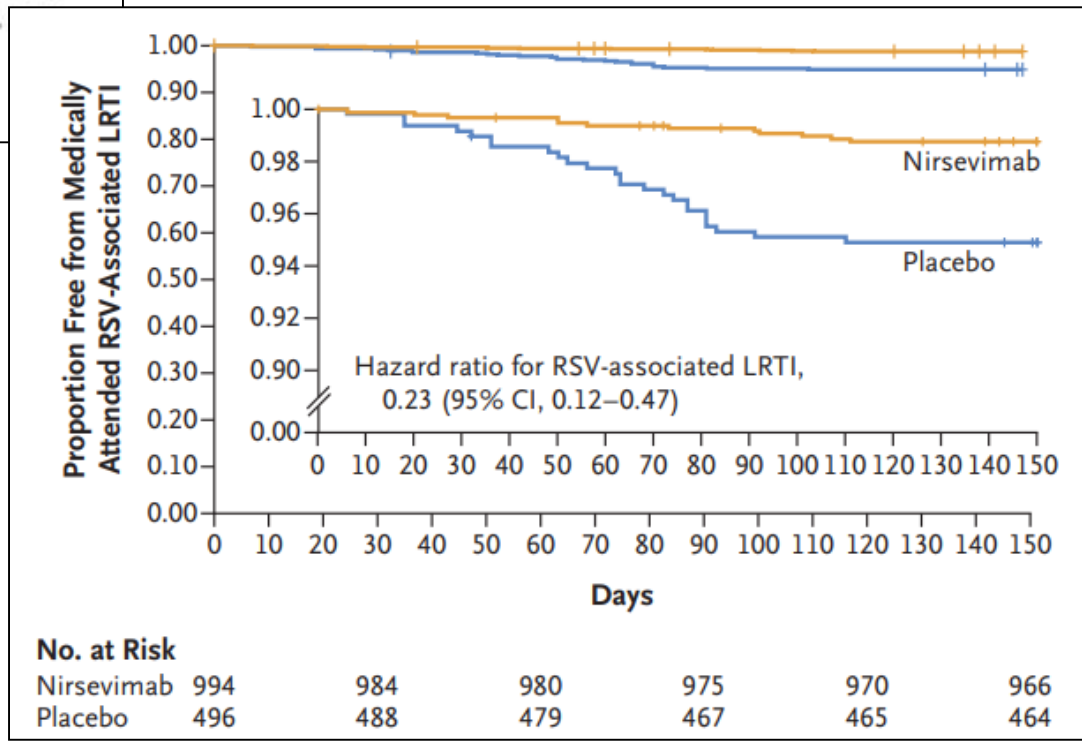
The NEW ENGLAND JOURNAL of MEDICINE

2022

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, Pin Ren, Ph.D., Therese Takas, B.Sc., Michael E. Abram, Ph.D., Amanda Leach, M.R.C.P.C.H., M. Pamela Griffin, M.D., and Tonya Villafana, Ph.D., for the MELODY Study Group*



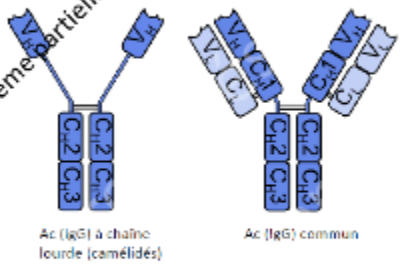
CONCLUSIONS : A single injection of nirsevimab administered before the RSV season protected healthy late-preterm and term infants from medically attended RSV-associated lower respiratory tract infection.

Hammitt LL et al NEJM 2022

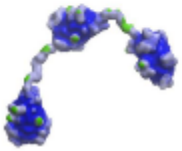
Nanobody : ALX 0171

Anticorps à domaine unique

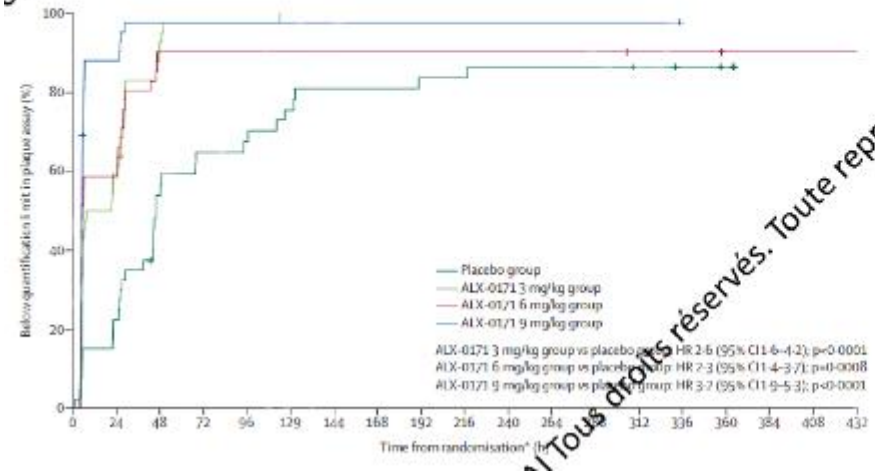
- stabilité
  - Affinité de l'ordre du nM voire pM
  - reconnaissance d'épitopes enfouis, inaccessibles aux anticorps monoclonaux conventionnels.



- **ALX-0171 (trivalent)**
  voie intranasale
  Cible le site antigénique II de la protéine F



Essai clinique (randomisé/ double aveugle) : traitement de **nourrissons** (1 -24 m) par ALX 0171 *vs* placebo **hospitalisés pour bronchiolite sévère à VRS**



Négativation rapide de la réplication virale (NP) mais pas d'amélioration clinique significative *versus* placebo

-> nécessité de reconsidérer les essais cliniques par l'évaluation d'une intervention plus précoce +++

Cunningham S et al. Lancet Respir Med 2021; 9:21-32

S Fourati RICAI 2022

Virus Respiratoire Syncytial : conclusion Slim Fourati Ricai 2022

Plusieurs nouveaux antiviraux avec différents mécanismes d'action, prometteurs :

inhibiteurs de fusion,
inhibiteurs de la polymérase,
inhibiteurs de N

Intervention précoce +++ :

plusieurs antiviraux (nanobody, inhibiteur de fusion) n'ont pas montré d'efficacité significative lorsque initiés à un stade tardif.

Prophylaxie :

Place des anticorps monoclonaux chez les NRS (nirsevimab) et les immunodéprimés (post-exposition ?) en complément des nouveaux candidats vaccins prometteurs

Protein vaccines in clinical trial

Name	Target	Target population	Route of administration	Clinical development phase	Advantages	Disadvantages
Nucleic acid (mRNA 1345, 1172, 1777)[a]	pre-F	Pediatric, adult	Systemic	Phase I	Can multiplex with other respiratory viruses, rapid production, Robust T-cell responses [57]	Instability of pre-F, novel technology with few approved examples
Particle based						
V-306[b]	PreF and PostF (site II)	Maternal	Systemic	Phase I	Safe, immunogenic, safe for immunosuppressed	Post-F antibodies might increase the risk of ERD
IVX- 121[c]	Prefusion F	Elderly	Systemic	Phase I		
Subunit						
DS-Cav1[d]	pre-F	Maternal, elderly	Systemic	Phase I		
GSK RSV F[e]	pre-F	Maternal, elderly	Systemic	Phase III, Phase III		
DPX-RSV[f]	SH	Elderly	Systemic	Phase I	Safe for immunosuppressed	Less immunogenic than live-attenuated, risk of ERD
RSV-F[g]	pre-F	Maternal, elderly	Systemic	Phase III, Phase III		
RSV-G[h]	G	Pediatric and elderly	Systemic	Phase II		
VN-0200[i]		Elderly	Systemic	Phase I		

Abbreviations: ERD enhanced RSV disease; F fusion proteinG attachment; NIAID National Institute of Allergy and Infectious Diseases; NIH National Institutes of Health; pre-F prefusion; post-F post fusion; SH small hydrophobic.
Vaccine developers: [a]Moderna (Cambrige, MA); [b]virometrix (Schlieren, Switzerland); [c]Icosavax (Seattle, WA); [d]NIH/NIAID (Bethesda, MD); [e]GlaxoSmithKline (Brentford, United Kingdom); [f]Immunovaccine (Dartmouth, Nova Scotia, Canada); [g]Pfizer (New York, NY); [h]Advaccine Biotech (Beijing, China); [i]Daiichi-Sankyo (Tokyo, Japan).

New preventive strategies for respiratory syncytial virus infection in children

Rebecca Glowinski[1], Asuncion Mejias[1,2,3] and Octavio Ramilo[1,2]

Current Opinion in Virology 2021,

Table 2

Live vaccines currently in clinical trials

Name	Target	Target population	Route of administration	Clinical development phase	Advantages	Disadvantages
Live-attenuated/ chimeric						
rBCG/N-hRSV[a]	N	Newborn	Systemic	Phase I	Induces Th1 responses [58]	
RSV/ΔG[b]	Lacking G	Pediatric	Mucosal	Phase I		Potential to mutate back to WT, stability needed for mass production, cannot be given to immunosuppressed patients
RSV ΔNS2 1313/ I1314L						
RSV 276; RSV 6120/ΔNS2/ 1030_S[c,d]	pre-F, post-F	Pediatric	Mucosal	Phase II	Low risk of ERD, broad stimulation of immune response against all antigens	
SeV/RSV[e]	F	Pediatric	Mucosal	Phase I		
MV-012-968[f]		Pediatric	Mucosal	Phase Ic/II		
CDX-RSV[g]		Pediatric	Mucosal	Phase I		
Vector based						
AdV26 RSV[h]	pre-F	Elderly, Pediatric	Systemic	Phase III, Phase II	Maternal antibodies will not interfere with immunogenicity, low ERD risk	Anti-vector immunity
MVA-BN RSV[i]	F, GA/GB, N, M2	Elderly	Systemic	Phase II		

Abbreviations: AdV, adenovirus; BCG, Bacille Calmette Guerin; ERD, enhanced RSV disease; G, attachment; NS2, non-structural 2; NIH, National Institutes of Health; MVA, modified vaccinia Ankara virus; M2-2, matrix 2-2; NS1, non-structural 1; pre-F, prefusion ; post-F, postfusion; SeV, Sendai Virus; Th, T helper cell; WT, wild-type.

Vaccine developers [a]Universidad de Chile (Santiago, Chile); [b]Intravac (Bilthoven, Netherlands); [c]Sanofi Pasteur (Lyon, France), [d]NIH/NIAID (Bethesda, MD); [e]St. Jude Hospital (Atlanta, GA); [f]Meissa Vaccines; [g]Codagenix (New York, NY); [h]Janssen (Beerse, Belgium); [i]Bavarian Nordic (Kvistgaard, Denmark).

New preventive strategies for respiratory syncytial virus infection in children

Rebecca Glowinski[1], Asuncion Mejias[1,2,3] and Octavio Ramilo[1,2]

Current Opinion in Virology 2021,

Stuart ASV et al
Phase 1/2a Safety and Immunogenicity of an Adenovirus 26 Vector Respiratory Syncytial Virus (RSV) Vaccine Encoding Prefusion F in Adults 18-50 Years and RSV-Seropositive Children 12-24 Months.
J Infect Dis. 2022

Cunningham CK et al,
Evaluation of Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV/ΔNS2/Δ1313/I1314L and RSV/276 in RSV-Seronegative Children.
J Infect Dis. 2022

Schmoele-Thoma B et al.
Vaccine Efficacy in Adults in a Respiratory Syncytial Virus Challenge Study.
N Engl J Med. 2022

Baber J, Arya M, Moodley Y, et al.
A Phase 1/2 Study of a Respiratory Syncytial Virus Prefusion F Vaccine With and Without Adjuvant in Healthy Older Adults.
J Infect Dis. 2022

Lewnard JA, Fries LF, Cho I, Chen J, Laxminarayan R.
Prevention of antimicrobial prescribing among infants following maternal vaccination against respiratory syncytial virus.
Proc Natl Acad Sci U S A. 2022

Grippe

Bruno Lina RICAI 2022 :

Dans le domaine des virus respiratoires, ce sont les virus influenza qui ont la plus grande pharmacopée

•Deux cibles majeures sont utilisées : la neuraminidase et la polymérase

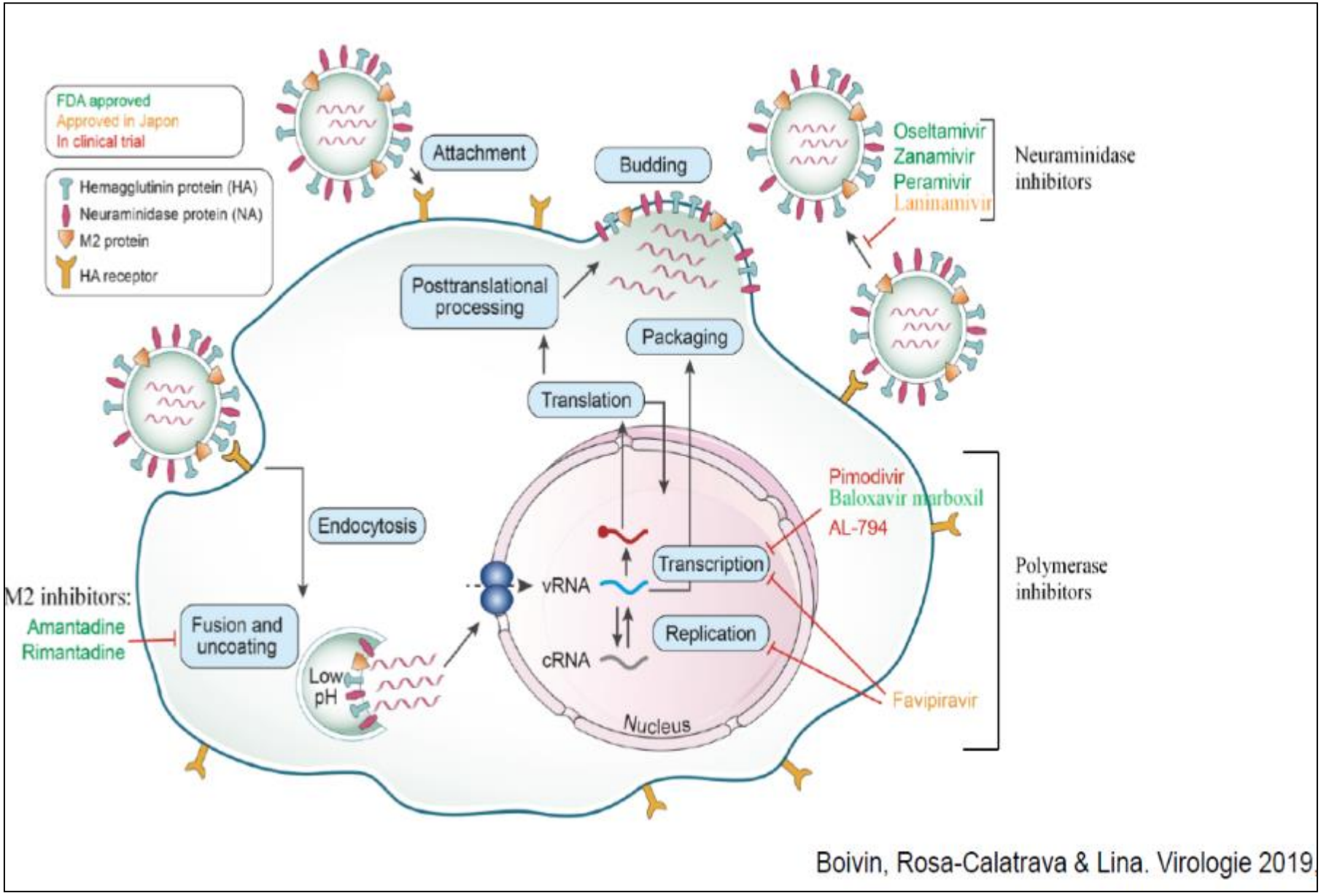
•Il existe des «profils de résistance» spécifique de certains virus ou antiviraux, ou commun pour l'ensemble d'une classe

•Des résistances apparaissent rapidement (notamment chez les enfants), mais ces virus sont peu transmissibles (sauf en 2007)

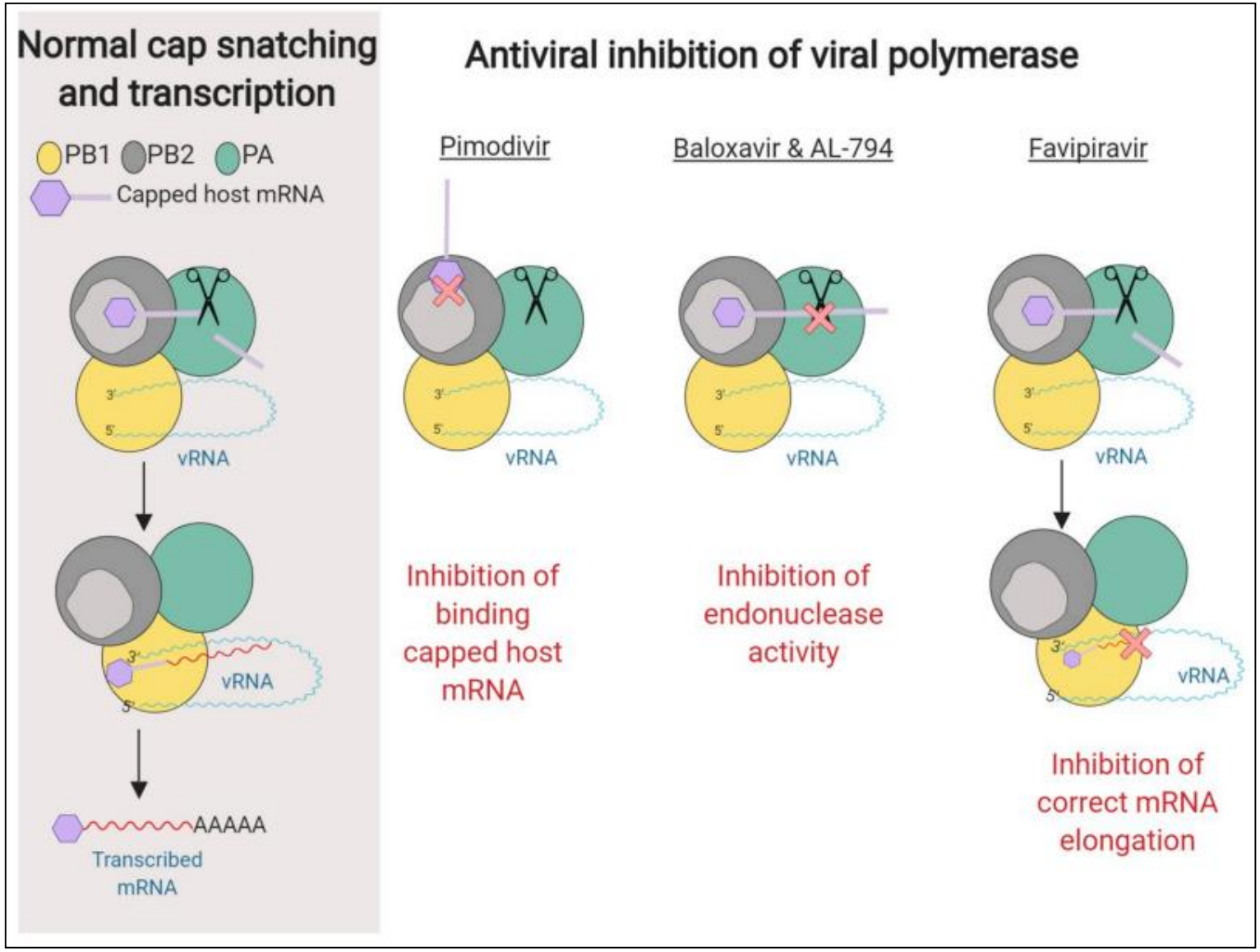
•Des associations efficaces sont possibles, mais pas dans la même classe d'antiviral

• L'épidémie de grippe commençant, utilisons ces produits en complément de la vaccination

Grippe (Influenza)



Boivin, Rosa-Calatrava & Lina. Virologie 2019

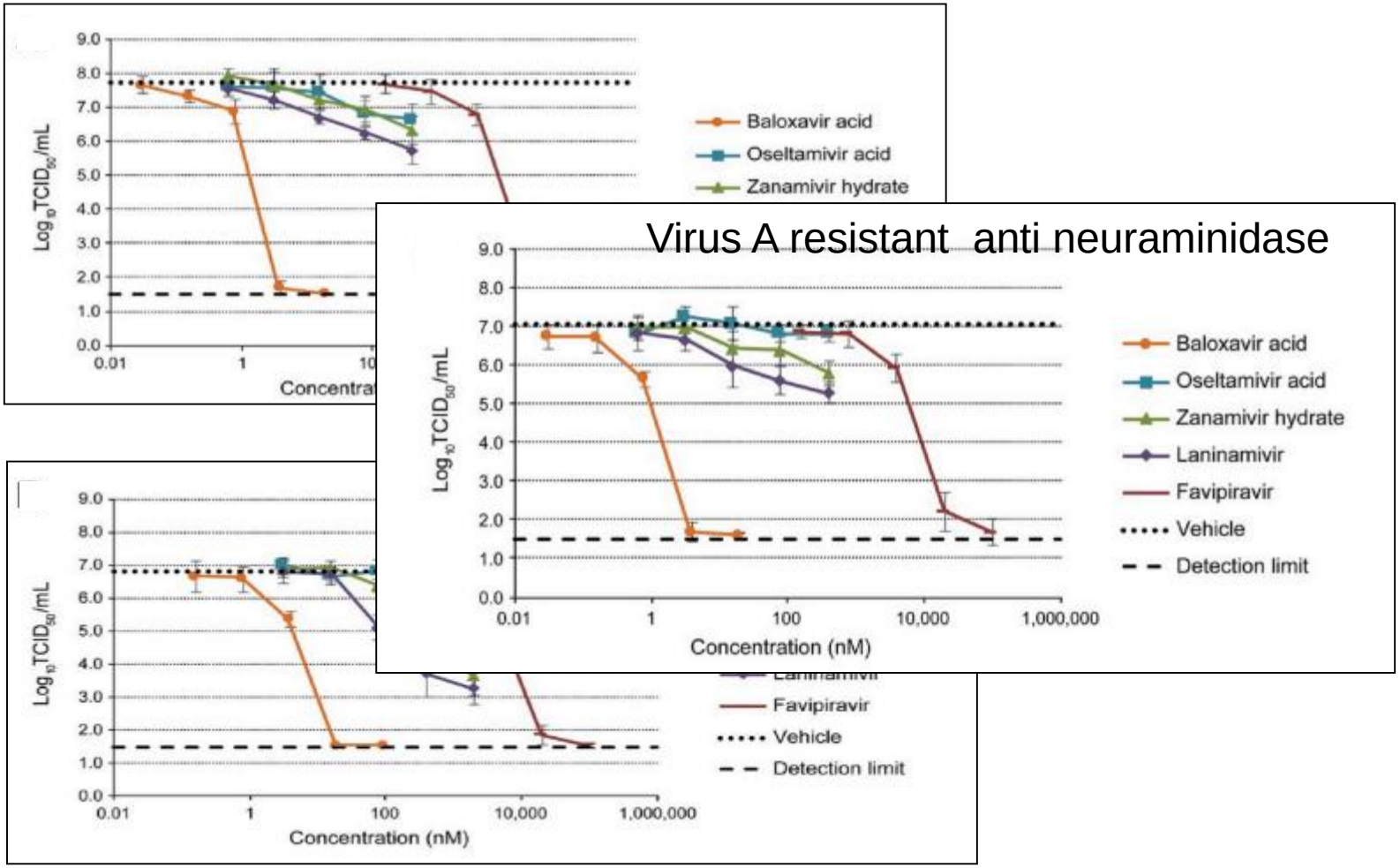


Mifsud EJ et al Antivir Res 2019

In vitro characterization of baloxavir acid, a first-in-class cap-dependent endonuclease inhibitor of the influenza virus polymerase PA subunit

Takeshi Noshi[a], Mitsutaka Kitano[a], Keiichi Taniguchi[a,b], Atsuko Yamamoto[a], Shinya Omoto[a], Keiko Baba[a], Takashi Hashimoto[a], Kayo Ishida[a], Yukihiro Kushima[a], Kazunari Hattori[a], Makoto Kawai[a], Ryu Yoshida[a], Masanori Kobayashi[a,1], Tomokazu Yoshinaga[a], Akihiko Sato[a,c], Masatoshi Okamatsu[b], Yoshihiro Sakoda[b], Hiroshi Kida[c], Takao Shishido[a,*], Akira Naito[a]

Noshi T et al, Antivir Res 2018



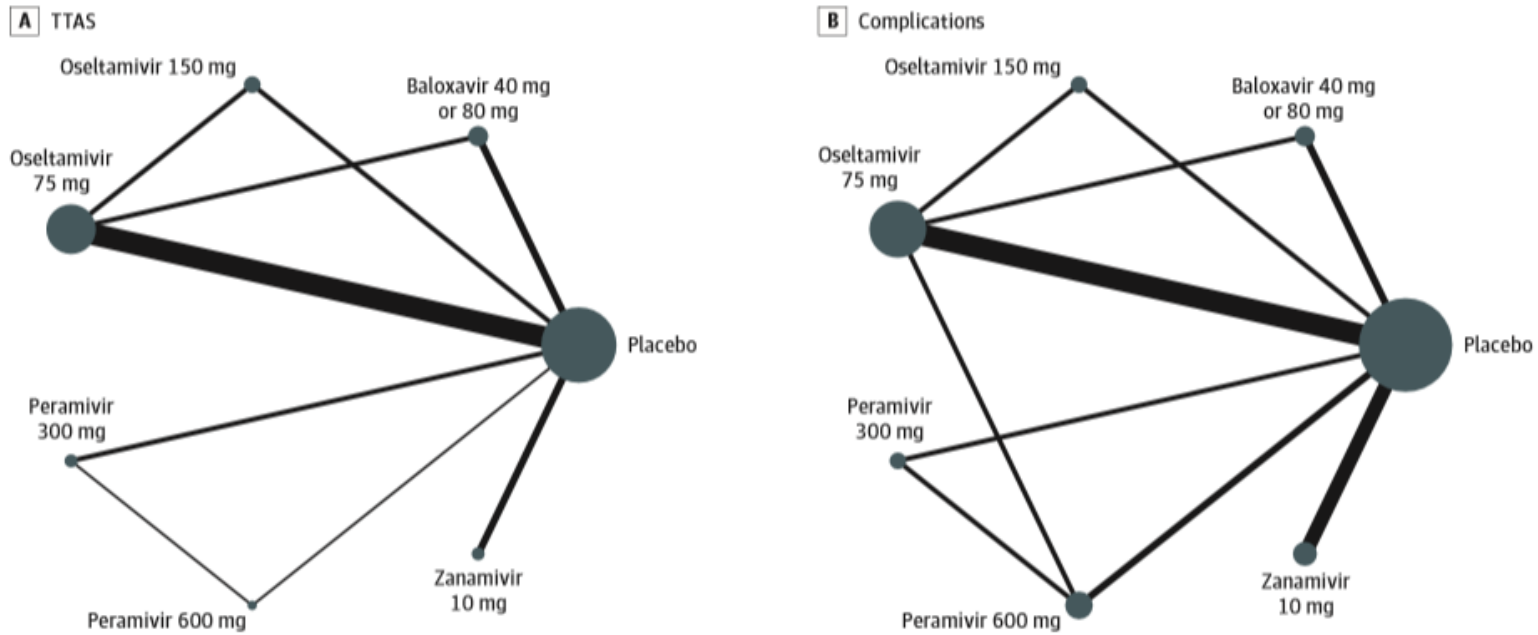
Comparison of Antiviral Agents for Seasonal Influenza Outcomes in Healthy Adults and Children A Systematic Review and Network Meta-analysis

Liu JW et al *JAMA Network Open.* 2021

CONCLUSIONS AND RELEVANCE In this systematic review and network meta-analysis, all 4 antiviral agents assessed were associated with shortening TTAS; zanamivir was associated with the shortest TTAS, and baloxavir was associated with reduced rate of influenza-related complications.

TTAS = Time To Alleviation of influenza Symptoms

Figure 2. Network Graphs of Treatment Comparisons for Time to Alleviation of Influenza Symptoms and Complications

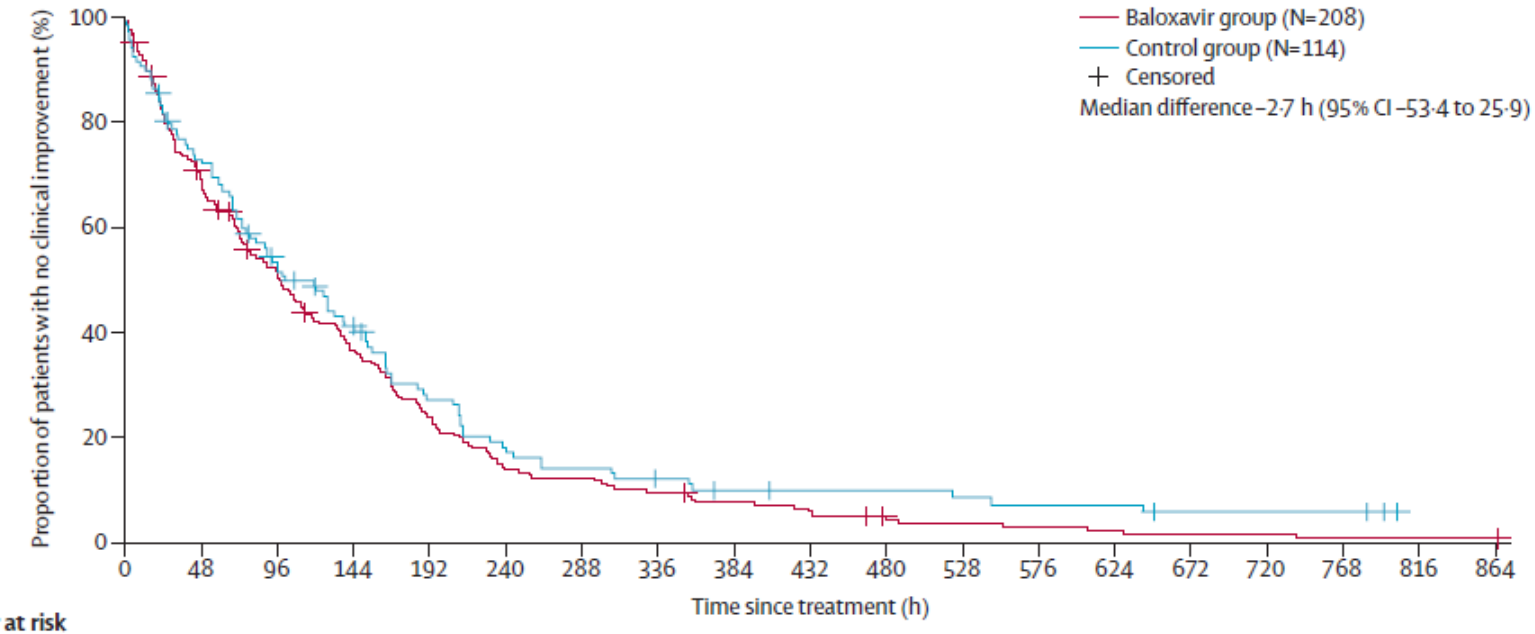


Nodes indicate different active interventions or placebo; size of nodes, number of studies; thickness of lines between nodes, number of randomized participants contributing to direct comparisons.

Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial

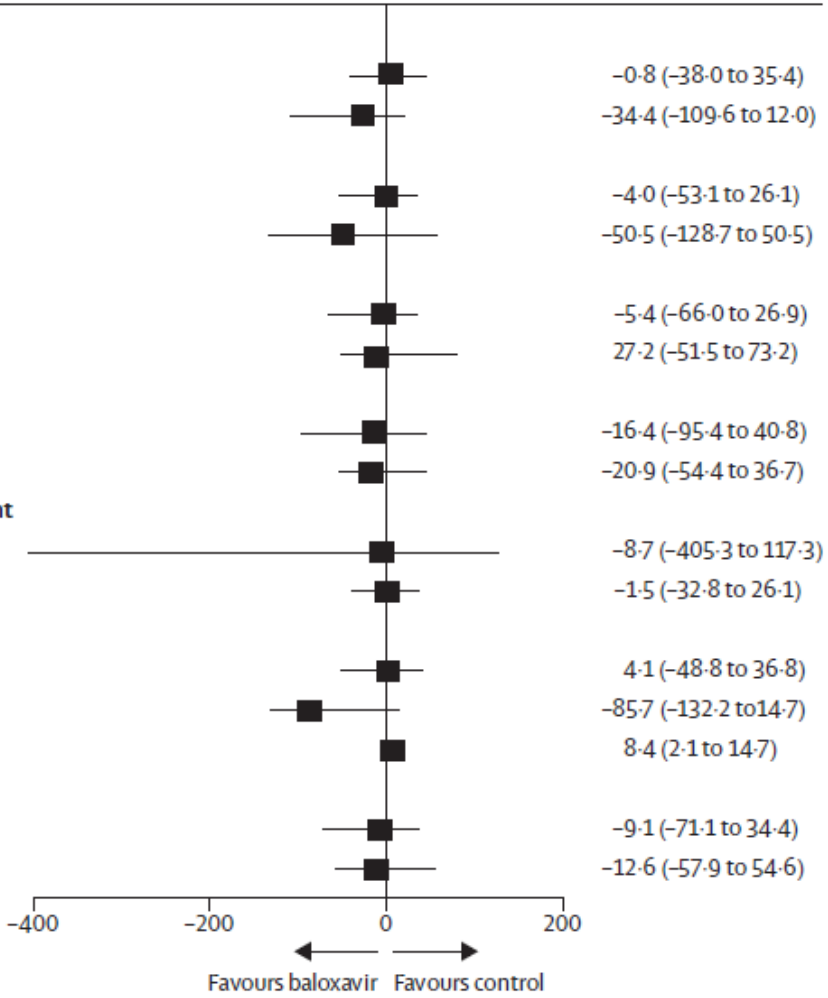
Deepali Kumar, Michael G Ison, Jean-Paul Mira, Tobias Welte, Jick Hwan Ha, David S Hui, Nanshan Zhong, Takefumi Saito, Laurie Katugampola, Neil Collinson, Sarah Williams, Steffen Wildum, Andrew Ackrill, Barry Clinch, Nelson Lee

Kumar D et al. Lancet Infect Dis. 2022



Number at risk (number censored)																		
Baloxavir group	208 (0)	140 (3)	100 (7)	72 (8)	47 (8)	27 (8)	24 (8)	18 (8)	14 (9)	11 (9)	6 (11)	5 (11)	4 (11)	3 (11)	2 (11)	2 (11)	1 (11)	1 (11)	1 (11)
Control group	114 (0)	81 (2)	56 (4)	43 (6)	27 (8)	17 (8)	14 (8)	11 (9)	8 (10)	7 (11)	7 (11)	6 (11)	5 (11)	5 (11)	3 (12)	3 (12)	3 (12)	NE (NE)	NE (NE)

	Median TTCI in h, (95% CI; n)		Difference (95% CI)
	Baloxavir group (N=208)*	Control group (N=114)*	
Age group 1			
<65 years	72·0 (48·3 to 102·9; 115)	72·8 (47·9 to 98·2; 54)	−0·8 (−38·0 to 35·4)
≥65 years	132·9 (95·5 to 145·8; 93)	167·3 (120·0 to 212·8; 60)	−34·4 (−109·6 to 12·0)
Age group 2			
<80 years	88·3 (68·8 to 107·4; 175)	92·3 (70·0 to 127·4; 91)	−4·0 (−53·1 to 26·1)
≥80 years	138·1 (95·0 to 164·0; 33)	188·6 (65·2 to 243·5; 23)	−50·5 (−128·7 to 50·5)
Baseline NEWS2 score†			
≤7	72·0 (51·6 to 97·5; 140)	77·4 (55·5 to 136·9; 75)	−5·4 (−66·0 to 26·9)
>7	154·6 (112·7 to 192·7; 66)	127·4 (92·3 to 210·7; 38)	27·2 (−51·5 to 73·2)
Time from symptom onset to study treatment			
≤48 h	75·9 (49·9 to 134·6; 80)	92·3 (60·5 to 162·8; 47)	−16·4 (−95·4 to 40·8)
>48 h	106·3 (88·4 to 135·3; 170)	127·2 (72·8 to 152·8; 91)	−20·9 (−54·4 to 36·7)
ICU or mechanical intervention at baseline or any point before clinical improvement			
Yes	228·7 (164·0 to 328·0; 38)	237·4 (136·9 to 642·4; 23)	−8·7 (−405·3 to 117·3)
No	75·9 (57·5 to 96·5; 170)	77·4 (60·7 to 100·2; 91)	−1·5 (−32·8 to 26·1)
Baseline influenza type (PCR)‡			
Type A	102·3 (78·2 to 132·0; 194)	98·2 (75·0 to 144·4; 103)	4·1 (−48·8 to 36·8)
Type B	33·5 (20·2 to 49·0; 16)	119·2 (15·3 to 164·5; 11)	−85·7 (−132·2 to14·7)
Type A and B	37·4 (31·1 to 43·7; 2)	29·0 (NE to NE; 1)	8·4 (2·1 to 14·7)
High and low baseline viral titre (split at median§)¶			
High	86·8 (56·8 to 118·2; 114)	95·9 (67·5 to 156·3; 67)	−9·1 (−71·1 to 34·4)
No	107·4 (78·2 to 135·4; 94)	120·0 (67·7 to 152·8; 45)	−12·6 (−57·9 to 54·6)



Kumar D et al. Lancet Infect Dis. 2022

Hayden FG, Lenk RP, Stonis L, Oldham-Creamer C, Kang LL, Epstein C. Favipiravir Treatment of Uncomplicated Influenza in Adults: Results of Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials. *J Infect Dis*. 2022;226(10):1790-1799. doi:10.1093/infdis/jiac135

Bruyndonckx R, Bilcke J, van der Velden AW, et al. Impact of Adding Oseltamivir to Usual Care on Quality-Adjusted Life-Years During Influenza-Like Illness. *Value Health*. 2022;25(2):178-184. doi:10.1016/j.jval.2021.08.001

Kumar D, Ison MG, Mira JP, et al. Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial. *Lancet Infect Dis*. 2022;22(5):718-730. doi:10.1016/S1473-3099(21)00469-2

Portsmouth S, Hayden FG, Kawaguchi K, et al. Baloxavir Treatment in Adolescents With Acute Influenza: Subgroup Analysis From the CAPSTONE-1 Trial. *J Pediatric Infect Dis Soc*. 2021;10(4):477-484. doi:10.1093/jpids/piaa145

Han A, Czajkowski L, Rosas LA, et al. Safety and Efficacy of CR6261 in an Influenza A H1N1 Healthy Human Challenge Model. *Clin Infect Dis*. 2021;73(11):e4260-e4268. doi:10.1093/cid/ciaa1725

Hsieh YH, Dugas AF, LoVecchio F, et al. Intravenous peramivir vs oral oseltamivir in high-risk emergency department patients with influenza: Results from a pilot randomized controlled study. *Influenza Other Respir Viruses*. 2021;15(1):121-131. doi:10.1111/irv.12794

Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. *N Engl J Med*. 2020;383(4):309-320. doi:10.1056/NEJMoa1915341

O'Neil B, Ison MG, Hallouin-Bernard MC, et al. A Phase 2 Study of Pimodivir (JNJ-63623872) in Combination With Oseltamivir in Elderly and Nonelderly Adults Hospitalized With Influenza A Infection: OPAL Study. *J Infect Dis*. 2022;226(1):109-118. doi:10.1093/infdis/jiaa376

Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;20(10):1204-1214. doi:10.1016/S1473-3099(20)30004-9

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

2020

ANTIVIRAL AGENTS

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of MHAA4549A, a Monoclonal Antibody, plus Oseltamivir in Patients Hospitalized with Severe Influenza A Virus Infection

Jeremy J. Lim,[a] Anna C. Nilsson,[b] Michael Silverman,[c] Nimer Assy,[d] Priya Kulkarni,[a] Jacqueline M. McBride,[a] Rong Deng,[a] Chloe Li,[a] Xiaoying Yang,[a] Allen Nguyen,[a] Priscilla Horn,[a] Mauricio Maia,[a] Aide Castro,[a*] Melicent C. Peck,[a] Joshua Galanter,[a] Tom Chu,[a] Elizabeth M. Newton,[a] Jorge A. Tavel[a]

MHAA4549A binds to influenza A virus hemagglutinin (HA) blocking fusion

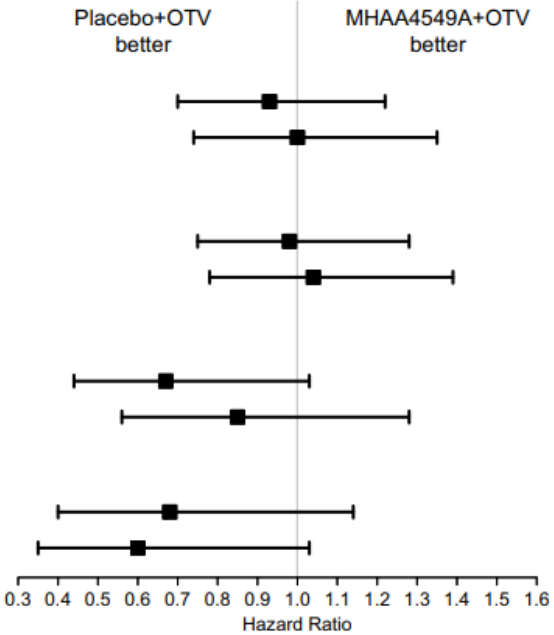
first published clinical trial of a monoclonal antibody to treat patients hospitalized with severe influenza.

Compared with placebo OTV, MHAA4549A OTV did not significantly reduce：

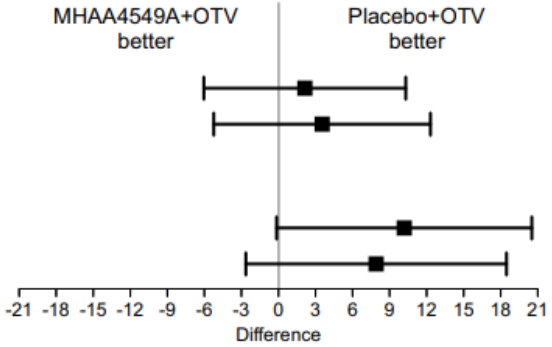
median time to removal of oxygen supplementation or positive-pressure ventilation
No significant improvements in secondary efficacy endpoints.

Lim JJ et a Antimicrob Agents Chemother 2020

Endpoint	Treatment+OTV	n	Median (days)	Hazard Ratio
Time to O_2/PPV removal (days)	Placebo	53	4.28	–
	3600-mg MHAA4549A	52	2.78	0.93
	8400-mg MHAA4549A	42	2.65	1.00
Time to hospital discharge (days)	Placebo	50	8.95	–
	3600-mg MHAA4549A	49	7.65	0.98
	8400-mg MHAA4549A	40	6.69	1.04
Time to ICU discharge (days)	Placebo	29	4.66	–
	3600-mg MHAA4549A	26	6.6	0.67
	8400-mg MHAA4549A	23	5.29	0.85
Time to ventilator removal (days)	Placebo	22	4.11	–
	3600-mg MHAA4549A	21	7.05	0.68
	8400-mg MHAA4549A	18	5.89	0.60



Endpoint	Treatment+OTV	n	Prop.	Diff.
30-day mortality (%)	Placebo	54	5.6	–
	3600-mg MHAA4549A	52	7.7	2.14
	8400-mg MHAA4549A	44	9.1	3.54
60-day clinical failure (%)	Placebo	54	14.8	–
	3600-mg MHAA4549A	52	25	10.19
	8400-mg MHAA4549A	44	22.7	7.91



Lim JJ et a Antimicrob Agents Chemother 2020

Clinical Infectious Diseases 2021

MAJOR ARTICLE

Safety and Efficacy of CR6261 in an Influenza A H1N1 Healthy Human Challenge Model

Alison Han,[1] Lindsay Czajkowski,[1] Luz Angela Rosas,[2] Adriana Cervantes-Medina,[1] Yongli Xiao,[2] Monica Gouzoulis,[1] Keith Lumbard,[3] Sally Hunsberger,[4] Susan Reed,[1] Rani Athota,[1] Holly Ann Baus,[1] Amy Lwin,[5] Jerald Sadoff,[6] Jeffery K. Taubenberger,[2] and Matthew J. Memoli[1]

. CR6261 monoclonal anti-HA antibody

. stabilizes the prefusion HA structure and prevents pH-dependent fusion of cellular and viral membranes in endosomes

. broad neutralization and protection in animals .

. When administered 24 hours after influenza challenge :

- . no effect on viral replication in healthy volunteers.
- . no meaningful efficacy in reducing influenza-induced disease
- . safe with no evidence of antibody-dependent enhancement

Han A et al Clin Infect Dis 2021

Herpes virus (HSV / VZV)

International Journal of
Molecular Sciences

MDPI

Review

40 Years after the Registration of Acyclovir: Do We Need New Anti-Herpetic Drugs?

Majewska Int. J. Mol. Sci. ***2022***

Les tt actuels anti HSV (aciclovir / valaciclovir /famciclovir) ne sont pas toujours suffisamment efficace

Rapid Viral Expansion and Short Drug Half-Life Explain the Incomplete Effectiveness of Current Herpes Simplex Virus 2-Directed Antiviral Agents

Schiffer J T , Antimicrob Agents Chemother 2013

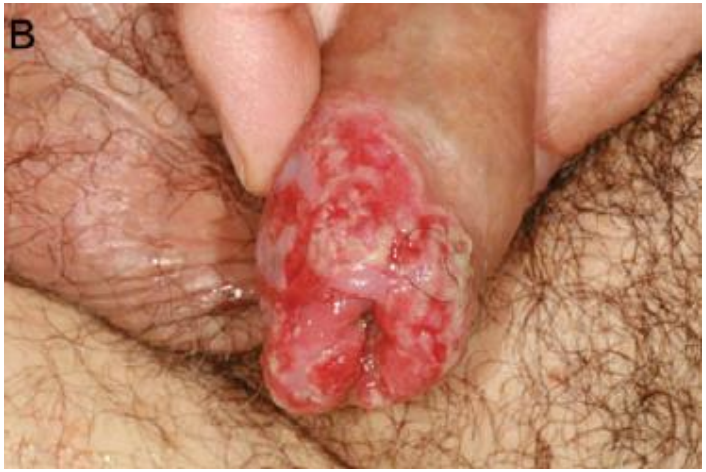
Neonatal Herpes Disease following Maternal Antenatal Antiviral Suppressive Therapy: A Multicenter Case Series

Pinninti, J Pediatrics, 2012

Le tt actuel (aciclovir / valaciclovir) n'est pas toujours suffisamment efficace

Recalcitrant Pseudotumoral Anogenital Herpes Simplex Virus Type 2 in HIV-Infected Patients:

Sbidian E, Clin infec Dis 2013



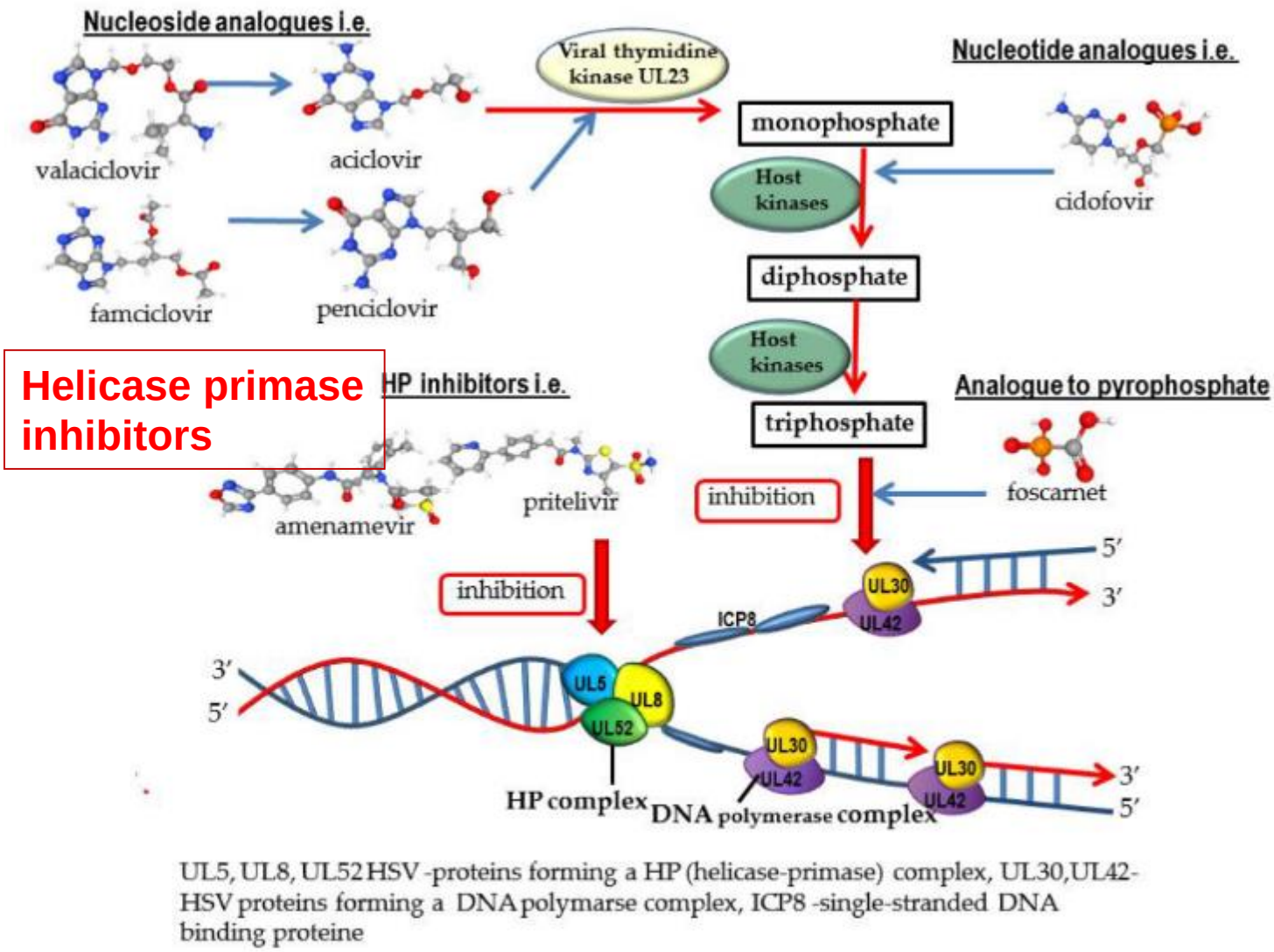


Figure 2. The mechanism of action of nucleoside analogues, nucleotide analogues, and analogues of pyrophosphate and HP-inhibitors on HSV-1.

JAMA | Original Investigation

Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences

A Randomized Clinical Trial

2016

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

Characteristic	Pritelivir (n = 75)	Valacyclovir (n = 76)	Relative Risk or Difference in Copy No., Pritelivir vs Valacyclovir (95% CI)	*P* Value
Virologic End Points				
Genital HSV shedding, No./total (%)				
Overall[a]	173/7276 (2.4)	392/7453 (5.3)	0.42 (0.21 to 0.82)	.01
Clinical End Points, No./Total (%)				
Days with lesions[d]	35/1855 (1.9)	75/1900 (3.9)	0.40 (0.17 to 0.96)	.04

Wald A et al JAMA 2016

Case Reports > Int J STD AIDS. 2021 Sep;32(10):978-980. doi: 10.1177/09564624211006568. Epub 2021 May 4.

Use of pritelivir in refractory aciclovir-resistant herpes simplex virus type 2

Luke Cannon [1], Eleni Tholouli [2], Chris Ward [1], Hamzah Farooq [3], Margaret Kingston [1]

Affiliations + expand

PMID: 33947276 DOI: 10.1177/09564624211006568

viruses MDPI

Review

Amenamevir, a Helicase-Primase Inhibitor, for the Optimal Treatment of Herpes Zoster

Kimiyasu Shiraki [1,*], Shinichiro Yasumoto [2], Nozomu Toyama [3] and Hiroaki Fukuda [4]

2021

Virus	Strains	EC50 (95% Confidence Interval) (μM) [a]		Susceptibility (Amenamevir/ Acyclovir) [d]
		Amenamevir (ASP2151)	Acyclovir	
HSV-1	KOS	0.010 (0.0082–0.012)	0.400 (0.32–0.50)	+/+
	A4-3	0.067 (0.049–0.091)	1.15 (98.8–133)	+/−
HSV-2	Genital isolate	0.012 (0.006–0.023)	1.34 (0.51–3.56)	+/+
	Whitlow 2	0.012 (0.006–0.022)	65.9 (31.9–136)	+/−
VZV	Kawaguchi [b]	0.064 (0.043–0.094)	1.61 (0.99–2.63)	+/+
	TK-deficient mutant	0.068 (0.052–0.088)	12.8 (9.5–17.3)	+/−
	A2 [c]	0.11 (0.078–0.16)	11.5 (6.5–20.3)	+/−
	A3 [c]	0.11 (0.049–0.26)	19.2 (11.1–33.1)	+/−
	A7 [c]	0.065 (0.045–0.093)	41.4 (21.6–79.2)	+/−
	A8 [c]	0.10 (0.062–0.162)	82.2 (72.7–92.9)	+/−

[a] Means of four independent experiments. [b] Parental strain of TK-deficient mutants, A2, A3, A7, and A8. [c] DNA polymerase mutant. [d] Susceptibility of virus strains to each compound: +, susceptible; -, resistant. The authors obtained permission from *Antiviral Research* to reuse this table [15].

KJP

Korean J Pain 2023;36(1):4-13
https://doi.org/10.3344/kjp.22381
pISSN 2005-9159, eISSN 2093-0569

Review Article

Current scenario and future applicability of antivirals against herpes zoster

Sang Hun Kim[1,2]

2023

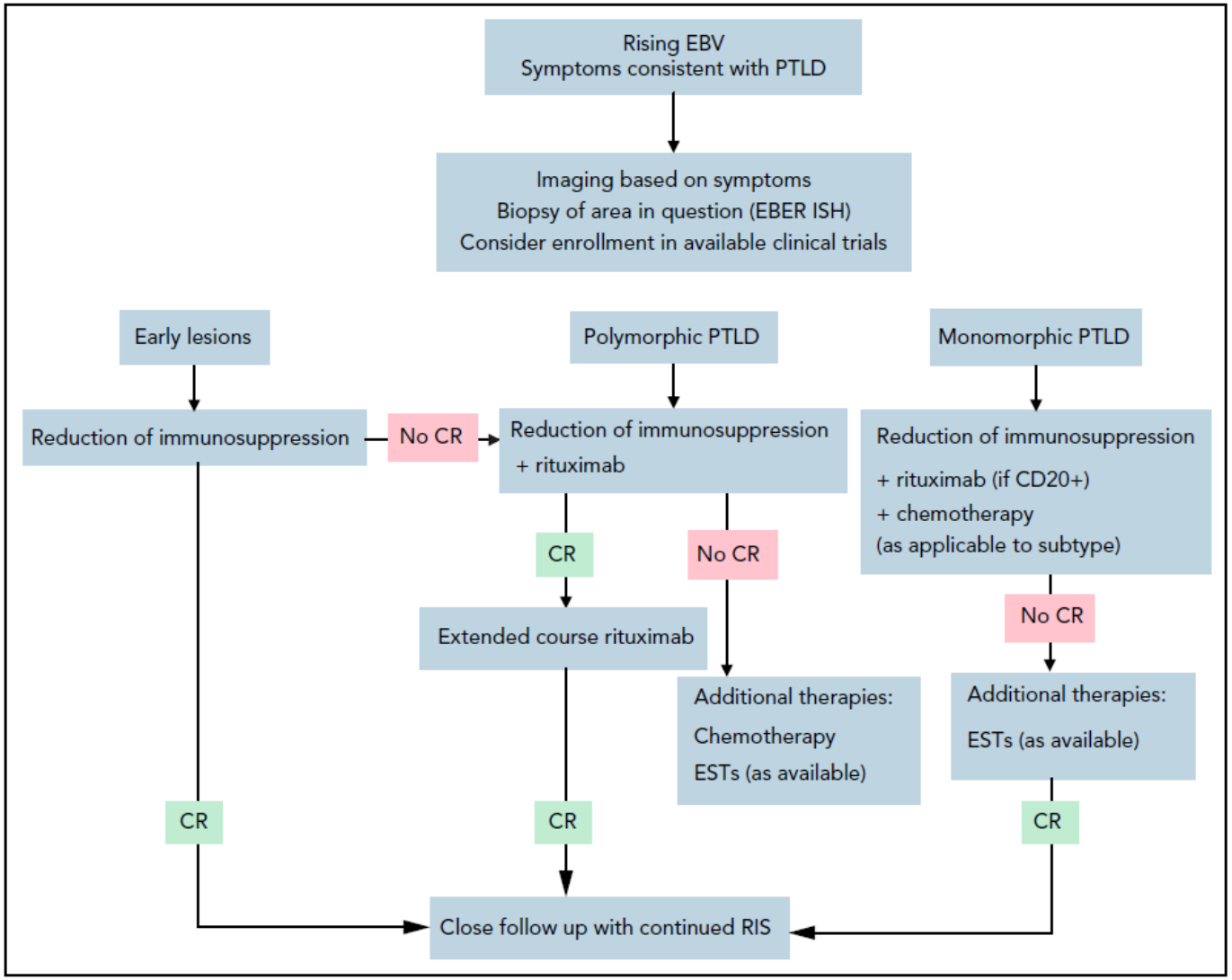
Table 1. Current licensed and off-labeled antivirals for HZ

Classification	Antivirals	Dosing schedule	Characteristics
Nucleoside analogs			
	Acyclovir	5 × 800 mg/day P.O.	Limited bioavailability FDA approval for HZ Nephropathy Usually for 5–7 days
		3 × 500 mg/day I.V. followed by oral regimens for 10–14 days	
	Valacyclovir	3 × 1,000 mg/day P.O.	Prodrug of acyclovir with 54% bioavailability FDA approval for HZ For 7 days
	Famciclovir	3 × 250–500 mg/day P.O.	Prodrug of penciclovir with 77% bioavailability FDA approval for HZ For 7 days
	Brivudine	1 × 125 mg/day P.O.	Some Europe approval for HZ No renal toxicity For 5 days
Pyrophosphate analogs			
	Foscarnet	I.V. only	FDA non-approval for HZ Off-label acyclovir resistance Nephrotoxicity, electrolyte imbalance, genital ulcer
Nucleotide analogs			
	Cidofovir	I.V. only	FDA non-approval for HZ Off-label acyclovir or foscarnet resistance Nephrotoxicity, neutropenia
Helicase-primase inhibitor			
	Amenamevir	1 × 400 mg/day P.O.	Japan approval for HZ For 7 days

« Brivudine and amenavir > famciclovir and Valacyclovir > acyclovir

EBV^{+} lymphoproliferative diseases: opportunities for leveraging EBV as a therapeutic target

K Toner and CM Bollard Blood 2022



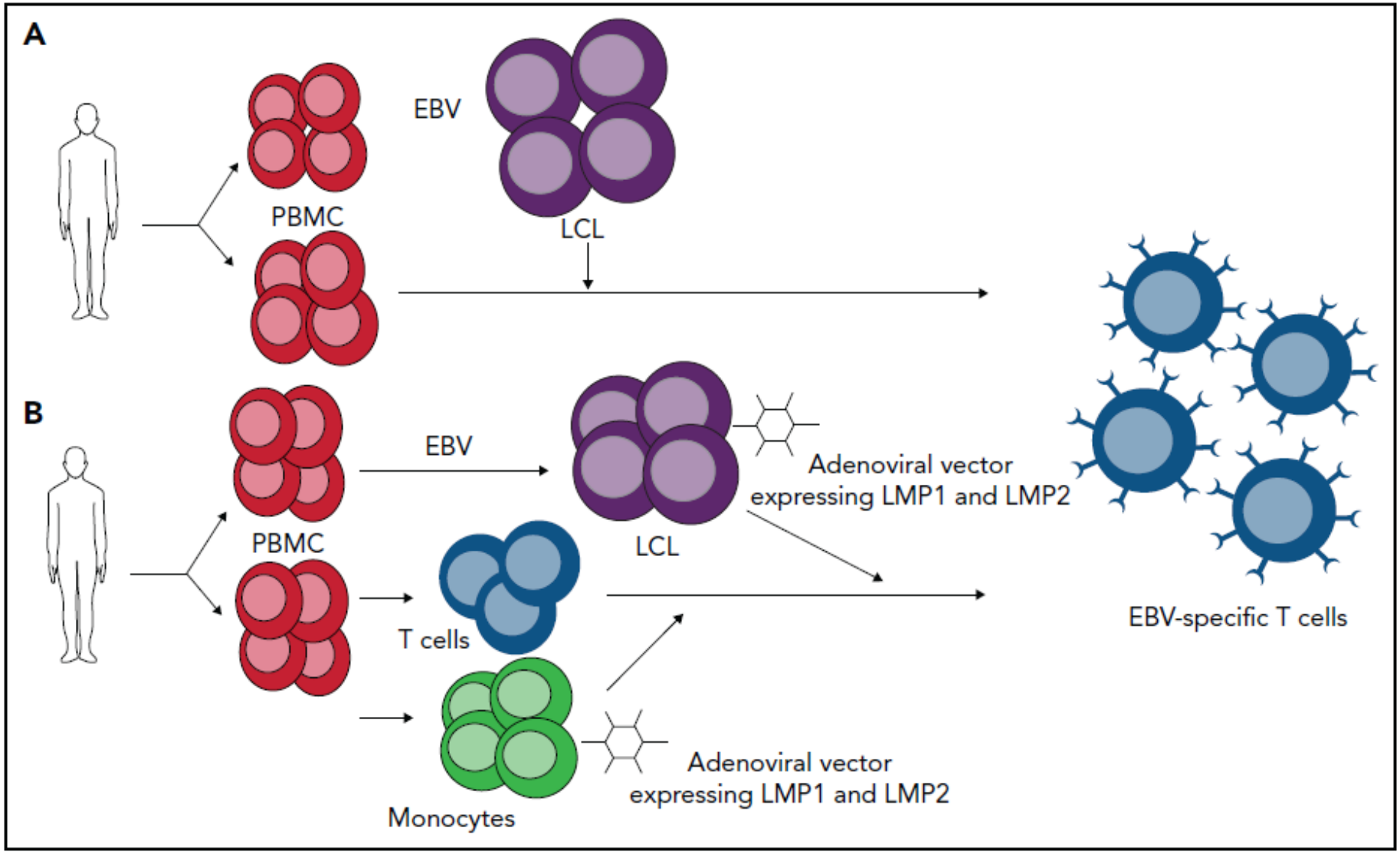


Figure 3. ESTs generated targeting latency type III vs latency type II EBV-associated lymphoproliferative disorders.

K Toner and CM Bollard Blood 2022

Table 2. Published third-party EST trials

Study	Year	Target	N	Serious adverse events	Clinical results
94	2007	EBV	33	None	52% CR/PR
81,95	2010, 2012	EBV	5	None	4/5 CR
97	2013	CMV, EBV, Adv	50	8 cases GVHD (2 de novo)	74% CR/PR
96	2017	CMV, EBV, Adv, BK, HHV6	38	2 cases of de novo GVHD (grade 1)	92% CR/PR
92	2018	CMV, EBV, Adv	30	2 cases of de novo GVHD	93% CR/PR
90	2020	EBV	46	None	68% CR/PR (BMT) 54% CR/PR (SOT)

K Toner and CM Bollard Blood 2022

Les défis de demain : Eradiquer les virus persistants dans l'organisme (VIH, VHB, HPV, Herpesvirus)

Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

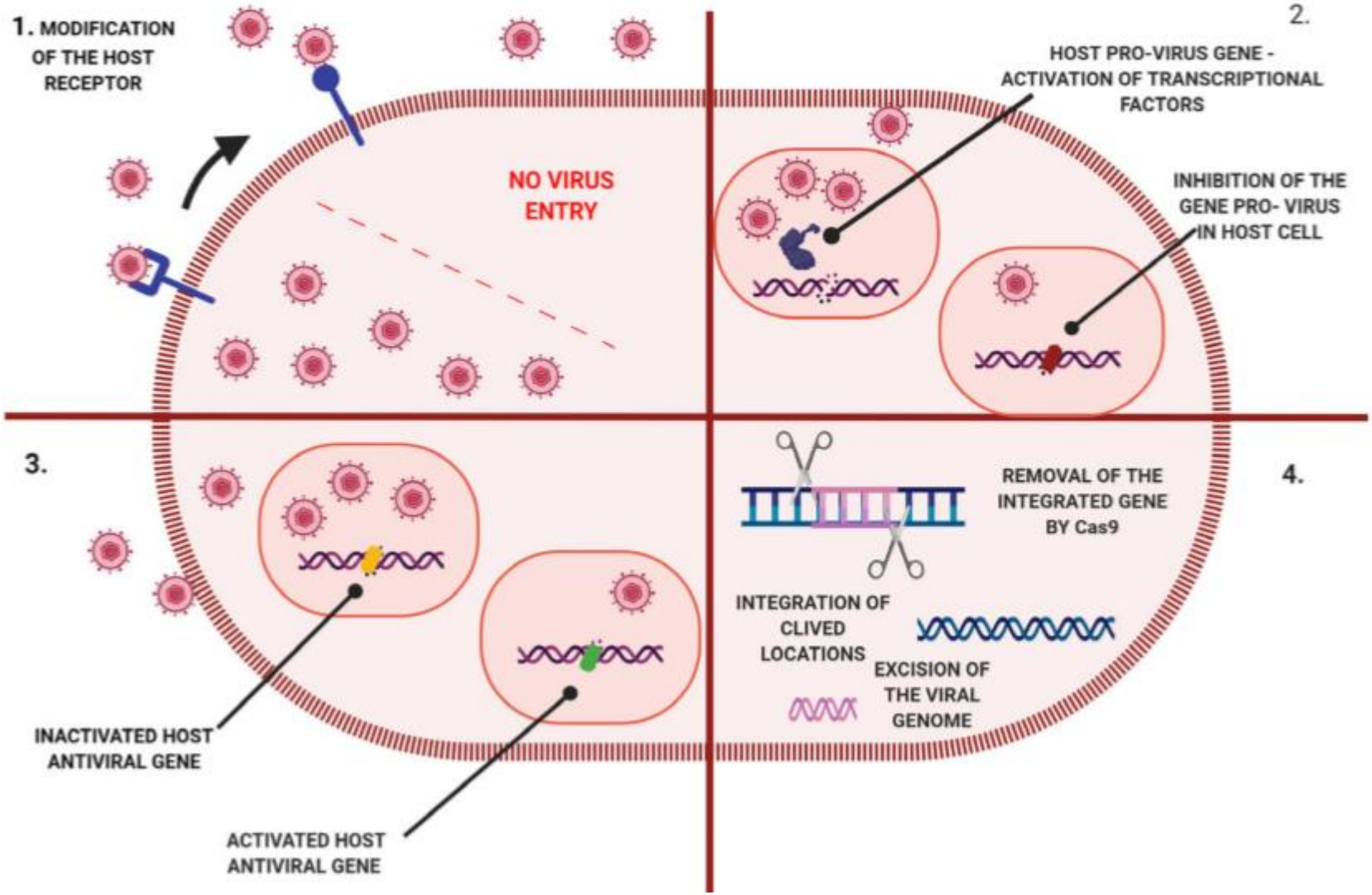
Steven G. Deeks[1], Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,17] and The International AIDS Society (IAS) Global Scientific Strategy working group*

Deek S G et al Nature Medicine 2021

"With a combination of immune activators, neutralizing antibodies, and therapeutic vaccines, some nonhuman primate models have been cured, providing optimism for these approaches now being evaluated in human clinical trials"

"In vivo delivery of gene-editing tools to either target the virus, boost immunity or protect cells from infection, also holds promise for future HIV cure strategies.".

CRISPR/ cas9
(Clustered Regularly Interspeced Short Palindromic Repeats)



Goncalvez BC et al Fundamental & Clinical Pharmacology 2020

The Perpetual Challenge of Infectious Diseases

Fauci A. N Eng J Med 2012

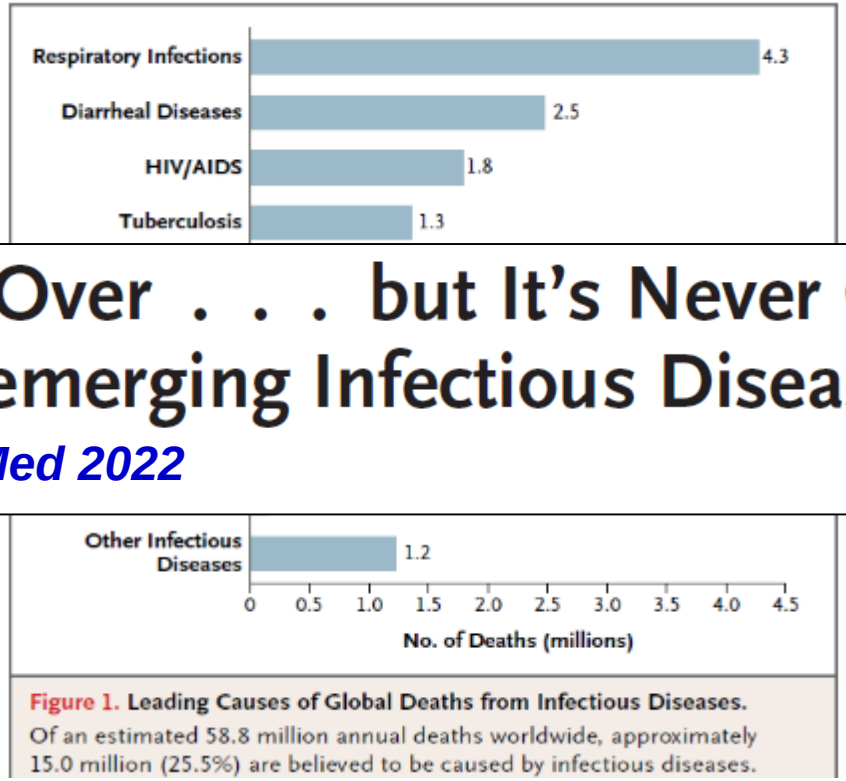


Figure 1. Leading Causes of Global Deaths from Infectious Diseases. Of an estimated 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are believed to be caused by infectious diseases.

It Ain't Over Till It's Over . . . but It's Never Over — Emerging and Reemerging Infectious Diseases

Anthony S. Fauci, M.D. ***N Eng J Med 2022***

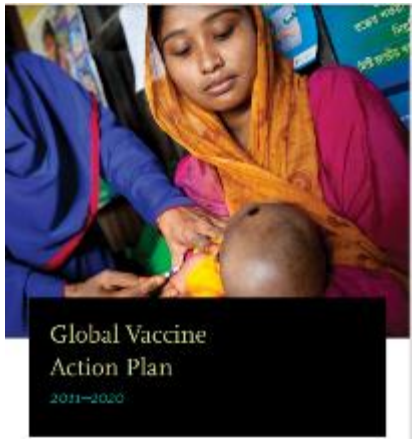
Nécessité d'augmenter l'arsenal antiviral :

- **Trouver de nouvelles cibles : biologie structurale / Interactome**
- **Repositionnement d'ancienne drogue**
- **immunothérapie (Ac neutralisant / CTL)**
- **nanotechnology**

Utilité du tt précoce, des associations d'antiviraux , associations AV+ immunomodula.

Possibilité d'éradication des infections virales persistantes ?

Antiviraux : l'histoire sans fin : les vaccins antiviraux



if the coverage targets for introduction and/or sustained use of 10 vaccines alone (HBV, haemophilus,HPV , Japanese encephalitis, measles, meningococcus A, pneumococcus, rotavirus, rubella and yellow fever) in 94 countries during the decade (2011-2020) are met, **between 24 and 26 million future deaths could be averted compared with a hypothetical scenario under which these vaccines have zero coverage**

18 janvier 2023 : arrêt prématuré du dernier essai de phase III anti VIH (HVTN 706 adenovirus-gp120 + booster gp120) pour inefficacité