Impact des résistances du SARS-CoV-2 sur la prise en charge de la COVID-19 (focus sur le traitement de l'immunodéprimé)

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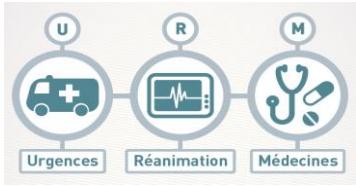
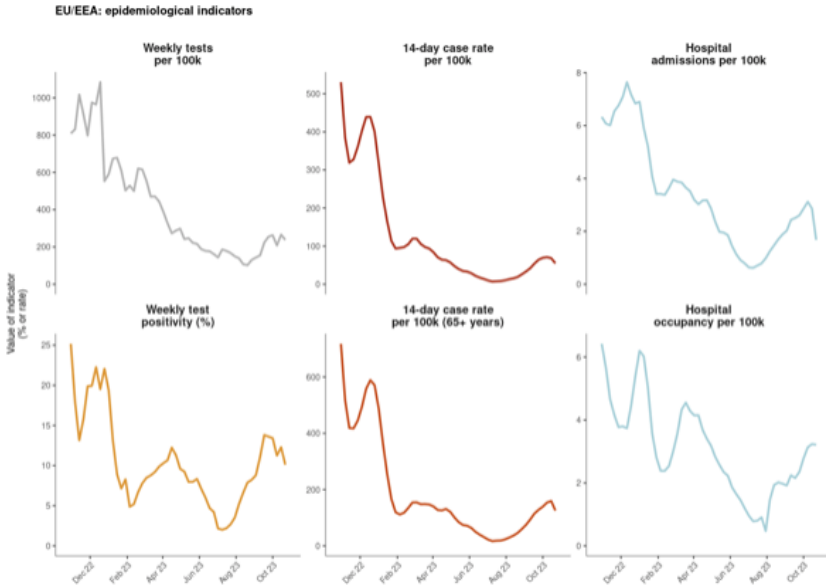


Cours d'Automne en Infectiologie, 14/11/2023

Liens d’intérêts

- Intérêts financiers : aucun
- Liens durables ou permanents : aucun
- Interventions ponctuelles : BMS, MSD, Janssen, Abbvie, Sanofi, Gilead, Lilly, Pfizer, SPIKIMM
- Intérêts indirects : aucun

Evolution de l'épidémie
Incidence et populations



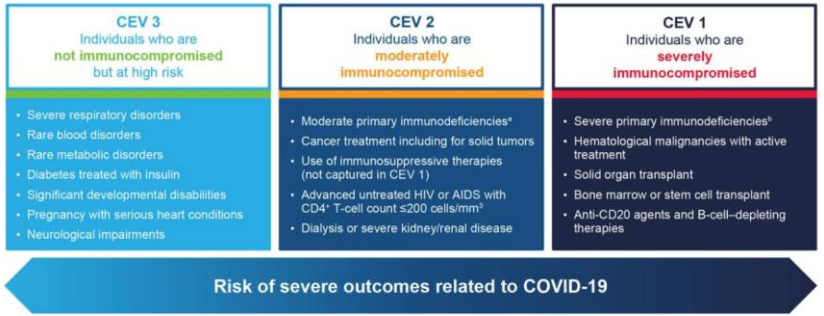
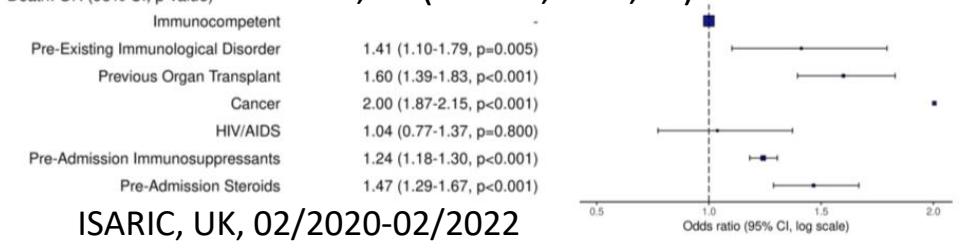


Figure 1. Spectrum of COVID-19 risk continuum for the clinically extremely vulnerable immunocompromised population. [a]Moderate primary immunodeficiencies include conditions that require ongoing immunoglobulin replacement therapy or primary immunodeficiencies that have confirmed genetic causes (eg, DiGeorge syndrome and Wiskott-Aldrich syndrome). [b]Severe primary immunodeficiencies include combined immunodeficiencies affecting T cells, immune dysregulation (particularly familial hemophagocytic lymphohistiocytosis), and type I interferon defects. Abbreviations: CEV, clinically extremely vulnerable.

aOR 1,44 (IC95 1,39-1,50)



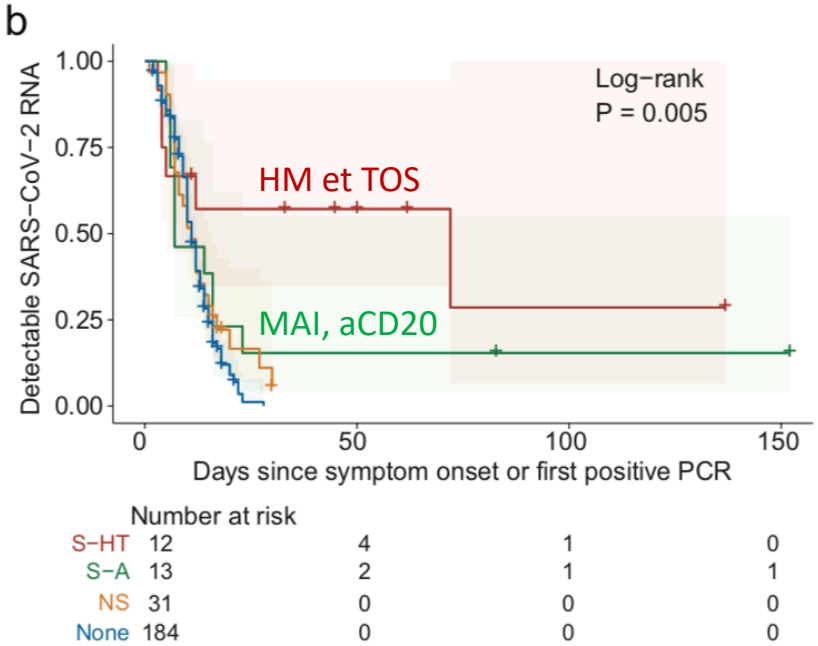
ISARIC, UK, 02/2020-02/2022

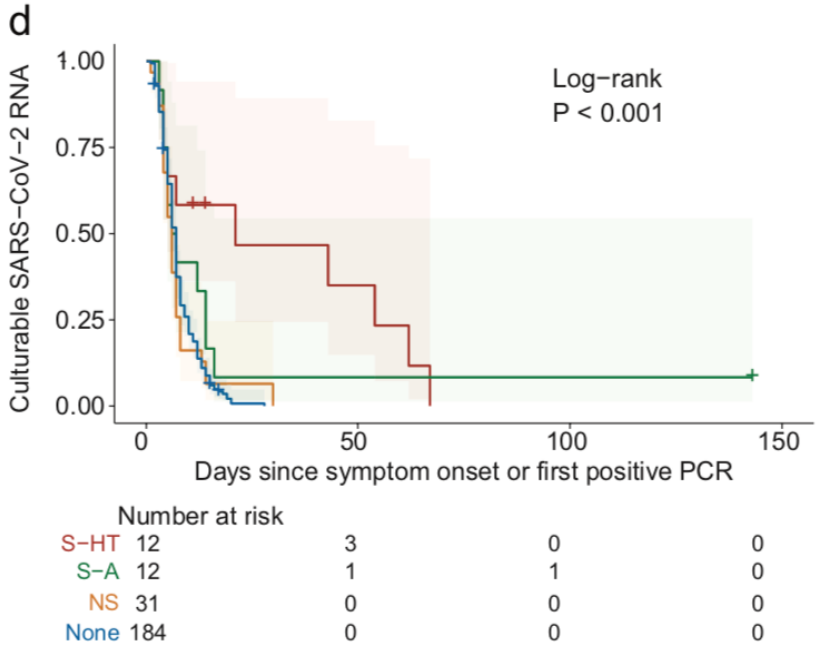
Fig 3. Outcomes of hospitalised immunocompromised patients, compared with immunocompetent patients. Odds ratios (ORs) from multivariable logistic regression and 95% confidence intervals (CIs) for outcomes of death, critical care admission, noninvasive and invasive ventilation, adjusted for age, sex, ethnicity, socioeconomic deprivation, chronic cardiac, pulmonary and renal disease, and vaccination status.

Epidémie subintrante dans les populations fragiles qui ne peuvent pas « vivre avec »

https://www.ecdc.europa.eu/en/covid-19/country-overviews; Antinori, JID 2023, 228; Turtle, PLoS Med 2023, e1004086

Immunodéprimés

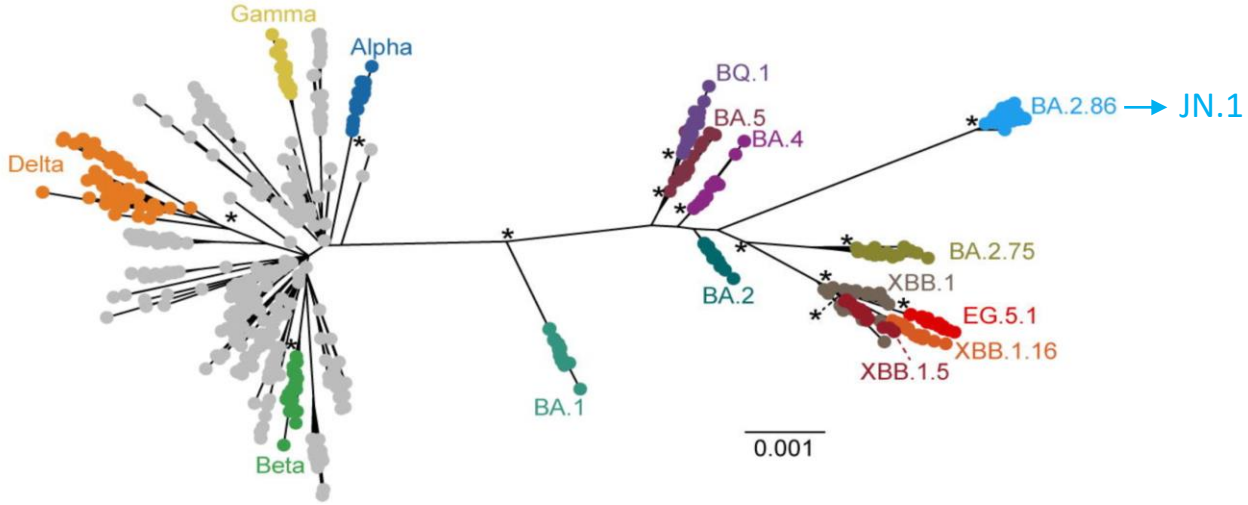




Réplication prolongée ➔ impact sur la durée des PC

Li, medRxiv, doi.org/10.1101/2023.07.31.23293441

Evolution virale

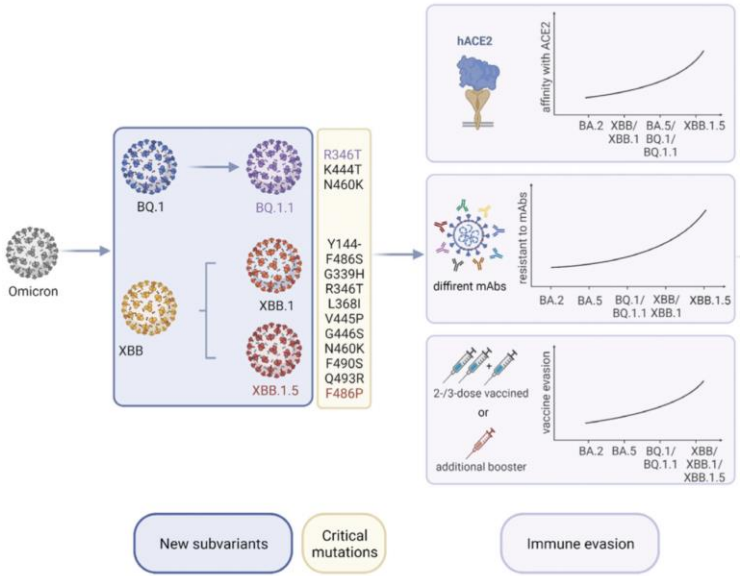


Variant	Classement	Flash S36 (04/09/2023)		Flash S37 (11/09/2023)		Flash S38 (18/09/2023)		Flash S39 (25/09/2023)		Flash S40 (02/10/2023)		Tendance
		N	%	N	%	N	%	N	%	N	%	
XBB.1.5 (23A)	VOI	112	8,6	111	8,7	118	9,0	112	10,1	97	13,1	↗
XBB.1.16 (23B)	VOI	198	15,3	182	14,2	163	12,4	154	13,8	73	9,9	↘
EG.5 (22F-23F) [2]	VOI	521	40,2	481	37,6	531	40,4	413	37,1	276	37,4	→
BA.2.75 (22D)	VUM	32	2,5	21	1,6	36	2,7	35	3,1	15	2,0	→
XBB (22F) [1]	VUM	58	4,5	72	5,6	68	5,2	43	3,9	26	3,5	↘
XBB.1.9 (22F)	VUM	140	10,8	146	11,4	110	8,4	113	10,2	91	12,3	→
XBB.2.3 (22F)	VUM	230	17,7	256	20,0	270	20,6	224	20,1	126	17,1	→
BA.2.86 (21L)	VUM	3	0,2	5	0,4	11	0,8	15	1,3	29	3,9	↗
Autres	0	2	0,2	5	0,4	6	0,5	3	0,3	5	0,6	→

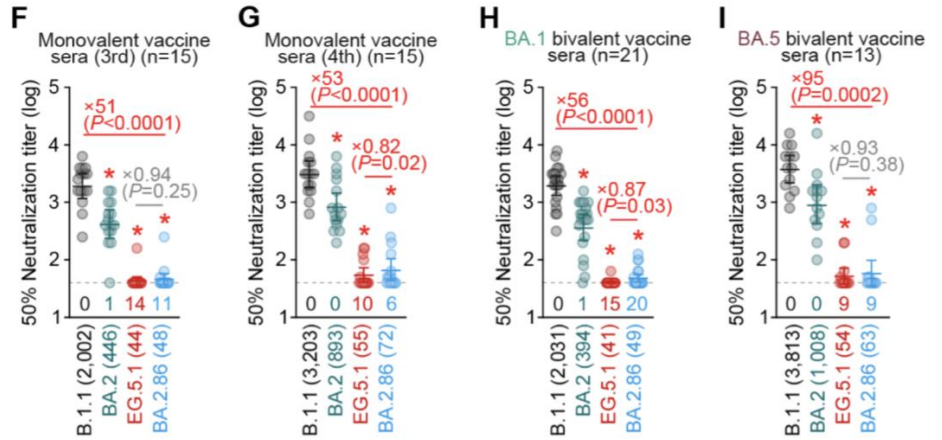
- Diversification génétique avec co-circulation de sous-lignages XBB
- Lente progression BA.2.86

Tamura, bioRxiv preprint doi: https://doi.org/10.1101/2023.11.02.565304 ; SPF/CNR, analyse de risque 23/10/2023

Evolution virale



Transmissibilité accrue; sévérité faible



Fold decrease vs D614G	BAM	ETE	BAM/ ETE	CAS	IMD	CAS/ IMD	CIL	TIX	CIL/ TIX	SOT	BEB	ADI
Alpha	1	13	1.3	1	0.6	0.9	0.6	1.5	0.8	1.8	0.9	1.3
Delta	1000	0.4	1	0.7	1.5	1.3	2.4	1.0	1	1.1	1	1.5
XBB	1000	1000	-	589	588	200	1000	1000	738	14	1000	1000
XBB.1	1000	1000	1000	880	1000	887	1000	1000	1000	15	900	-
XBB.1.5	-	-	-	650	572	751	433	1000	867	18	475	-
XBB.1.16	-	-	-	420	143	615	127	448	488	5.3	149	-
BA.2.86										X		

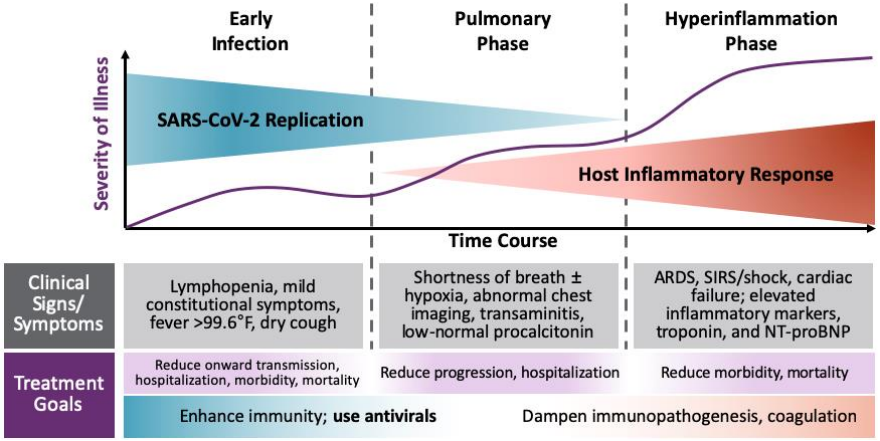
<10 | 10-100 | > 100

Pas d'impact sur les antiviraux directs

Variants d'échappement immunitaire

Ao, MedComm 2023, e239; Uriu, TLID 2023, e460-e461; https://covdb.stanford.edu/susceptibility-data/table-mab-susc/; Imai, NEJM 2022, 89

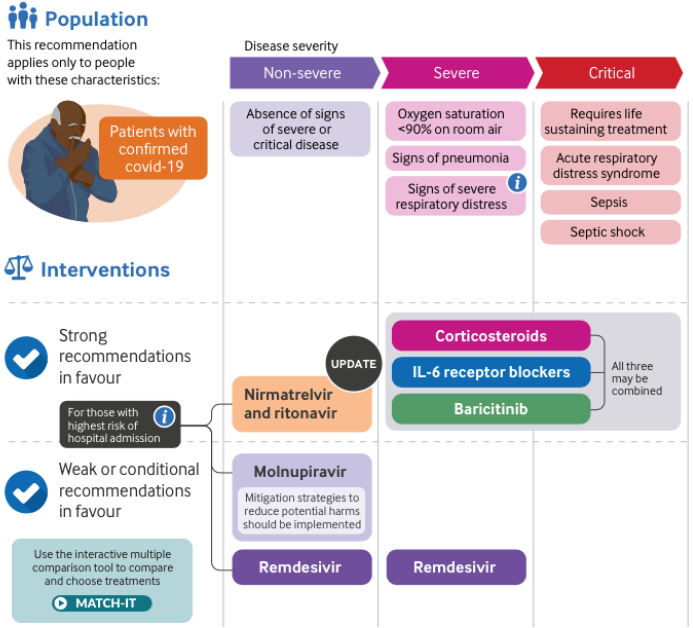
Paradigme et recommandations



Diagnostic criteria of persistent inflammatory sero-negative COVID[a]

A patient is defined as having persistent inflammatory sero-negative COVID if they fulfil the following criteria and no alternative diagnosis:	
1. Host criterion	B-cell depleting disease or therapy, including the following: • Primary immunodeficiency causing hypogammaglobinaemia (X-linked agammaglobulinaemia, common variable immunodeficiency, other primary hypogammaglobinaemia). • Secondary immunodeficiency - anti-CD20 treatment in the past year; chronic lymphoblastic leukaemia, non-Hodgkin lymphoma, multiple myeloma accompanied by hypogammaglobinaemia or receiving immunotherapy directed against B cells (bi-specific antibodies or antibody-drug conjugates against CD19, CD20 or BCMA); chimeric antigen receptor T-cell therapy or allogeneic or autologous haematopoietic stem cell transplantation within 1 y.
2. Clinical criterion	Prolonged or remitting fever (total >7 d) with elevated CRP levels plus either one of the following: prostration, non-resolving cough and dyspnea (total >14 d), abnormal chest imaging showing pneumonitis (bilateral ground glass opacities).
3. Virological criterion, defined as either of the following	• Persistent or intermittent positive SARS-CoV-2 RT-PCR result over >21 d.[b] • Positive SARS-CoV-2 RT-PCR result in the last 90 d + sero-negativity for SARS-CoV-2 14 d after the initial infection in monoclonal antibody-naïve patients.[c]

A living WHO guideline on drugs for covid-19



Aucun focus sur l'immunodéprimé
Reproductibilité des data de l'immunocompétent?

Siddiqi, J Heart Lung Transplant 2020, 405; Belkin, CMI 2023, 1
Agarwal, BMJ, update 13/01/2023 https://www.bmj.com/content/370/bmj.m3379

Typologie des patients à risque

- Patients à risque très élevé:
  - Quel que soit l'âge et l'état vaccinal: TOS, allo-CSH, cancers en cours chimiothérapie < 12 mois, immunosuppresseurs (dont corticoïdes et anti-CD20), PvVIH CD4 < 200/mm^3, déficits immunitaires primitifs, maladies rénales chroniques sévères (DFG < 30mL/min), poly-pathologies chroniques et présentant au moins deux insuffisances d'organe, maladies rares (Filières de Santé Maladies Rares 2020), trisomie 21
  - Age > 80 ans et rappel de vaccination datant de plus de 6 mois
- Risque élevé: Au moins 2 conditions parmi les suivantes:
  - Vaccination COVID : aucune ou rappel datant de plus de 6 mois
  - Age > 65ans
  - Diabète traité de type 1 ou 2, IMC > 30 kg/m^2, insuffisance respiratoire quel qu'en soit la cause, BPCO sévère, fibrose pulmonaire, insuffisance rénale chronique, cardiopathie ischémique, hypertensive et/ou insuffisance cardiaque, affection hépatique chronique ou cirrhose, antécédent d'accident vasculaire cérébral, démence, trouble psychiatrique, hémoglobinopathie sévère

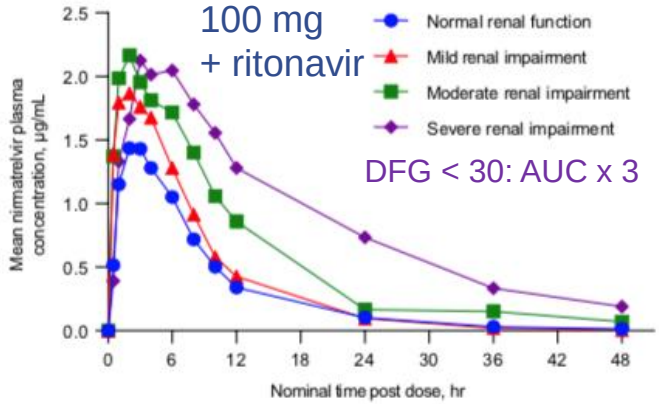
Position du groupe Avather ANRS-MIE, 19/10/2023

Nirmatrelvir ➔ 1ère intention COVID non sévère < SF5

Cohorte appariée exposé/non exposé, Colombie britannique, 02/2022-02/2023

Table 2. Risk of Death or COVID-19–Related Emergency Hospitalization (Primary End Point) by Cohort

Group	Nirmatrelvir and ritonavir exposed, No.	Event, No.	Nirmatrelvir and ritonavir unexposed, No.	Event, No.	Risk difference, % (95% CI)	No. needed to treat	Relative risk (95% CI)
CEV1	280	NA[a]	280	NA[a]	−2.5 (−4.8 to −0.2)	40	0.22 (05 to 12)
CEV2	1314	23	1314	45	−1.7 (−2.9 to −0.5)	60	0.51 (0.31 to 0.84)
CEV3	1050	25	1050	39	−1.3 (−2.8 to 0.1)	75	0.64 (0.39 to 15)
EXEL	789	35	789	27	1 (−0.9 to 2.9)	99[b]	1.30 (0.79 to 2.12)



Insuffisance rénale

DFG	Adaptation
> 60	300/100 x 2/j 5j
30-60	150/100 x 2/j 5j
< 30 ou HD	300/100 x 1 puis 150/100 x 1 4j

Hammond, NEJM 2022, 1397; Aggarwal, TLID 2023, 696; Lewnard, TLID 2023, 806; Dormuth, JAMA Open Network, 2023, e2336678; Kabore, CID 2023, 805; Toussi, Clin Pharmacol Ther 2022, 892; Hiremath, Clin J Am Soc Nephrol 2023, 485; Chun Kau Chan, CID 2023, 10.1093/cid/ciad287

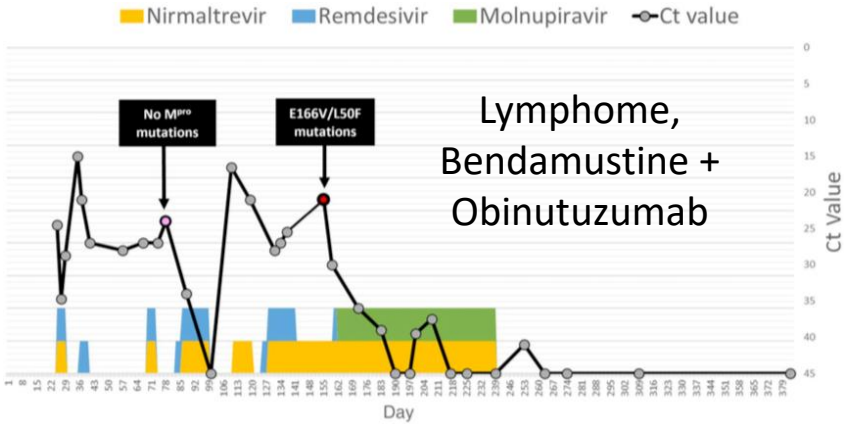
Rebond viral et résistance au Nirmatrelvir

Rebond viral post N/r

- Récurrence symptômes et/ou réversion test négatif 4 à 9j après arret N/r
  - Placebo ou non traité: 1,7% à 9,3%
  - N/r: 2,3% à 14,2%
- Immunodépression: OR 7 (IC95 2-21)
- Pas de lien avec émergence mutation 3CL^{Pro} ou survenue COVID sévère, mais transmission possible

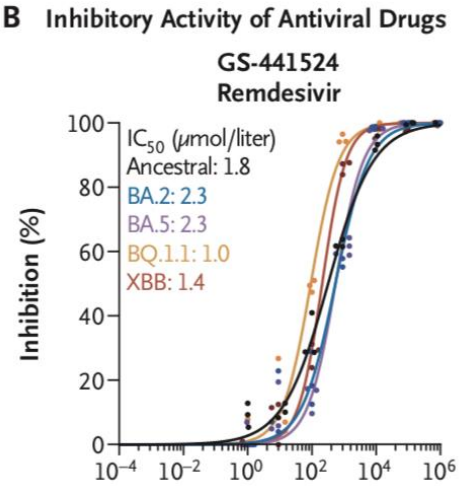
Résistance

- Mutations 3CL^{Pro}: 0,16% à 0,5% sans corrélation temporelle (G15S, T21I, L50F, E166A, L167F)
- Acquisition de résistance décrites:



Anderson, NEJM 2022,10.1056/NEJMc2205944; Pandit, CID 2023, 25; Tadmor, Leuk&Lymph 2023, 1054; Schilling, TLID 2023 epub; Wong, TLID 2023, 683; Carlin, CID 2023, e530; Sjaarda, JAMA Open Network, 2023, e2324963; Ip, eBioMed 2023, 104559; Zuckerman, CID 2023, 1; Duan, Nature 2023, 376

Remdesivir ➔ 2ème intention COVID non sévère < J7



Cohorte prospective 04/2022-05/2022 (BA.2), 192 TOS COVID < J7, 86 traités par RDV IV 3j

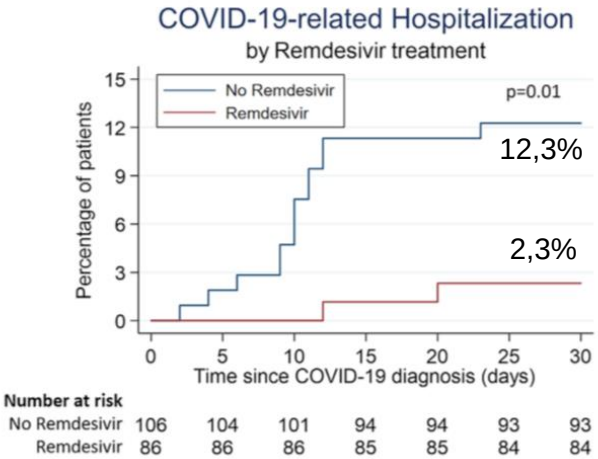
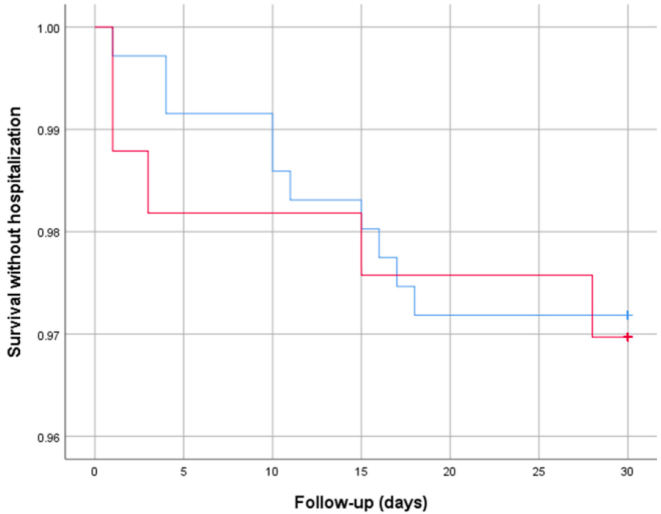


Figure 2. Kaplan–Meier curve of time to hospitalization through 30 days of follow-up by remdesivir treatment group. *p*-value estimated with the log-rank test.

Cohorte prospective 01/01/2022-15/03/2023, COVID non sévère < J5, Remdesivir (n=365), N/r (165)

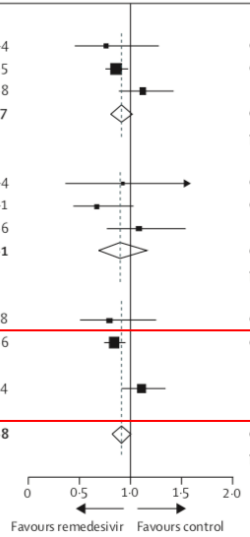


Gottlieb, NEJM 2022, 305; Imai, NEJM 2022, 89; Rajme-Lopez, OFID 2022, doi.org/10.1093/ofid/ofac502; Solera, Am J Transplant 2023, 78; Basoulis, Viruses 2023, 1515

Place du Remdesivir dans le COVID sévère?

Résultats définitifs de SOLIDARITY et méta-analyse

	Deaths reported/ number of patients (%)		Remdesivir deaths*		Mortality RR (95% CI), remdesivir vs control
	Remdesivir	Control	(O–E)	Var (O–E)	
Solidarity					
No oxygen	25/869 (2·9%)	33/861 (3·8%)	−3·9	14·4	0·76 (0·46–1·28)
Low-flow or high-flow oxygen	426/2918 (14·6%)	476/2921 (16·3%)	−32·0	223·5	0·87 (0·76–0·99)
Ventilation (any type)	151/359 (42·1%)	134/347 (38·6%)	8·3	69·8	1·13 (0·89–1·42)
Subtotal, with stratified analyses	**602/4146 (14·5%)**	**643/4129 (15·6%)**	**−27·6**	**307·7**	**0·91 (0·82–1·02)**
Trend: χ^2_1=3·9 ; p=0·05					p=0·12
Other randomised trials					
No oxygen	11/470 (2·3%)	12/473 (2·5%)	−0·3	4·4	0·93 (0·37–2·39)
Low-flow oxygen	45/598 (7·5%)	62/569 (10·9%)	−8·2	21·1	0·68 (0·44–1·04)
High-flow oxygen or ventilation	76/318 (23·9%)	70/326 (21·5%)	2·8	31·6	1·09 (0·77–1·55)
Subtotal, with stratified analyses	**132/1386 (9·5%)**	**144/1368 (10·5%)**	**−5·7**	**57·1**	**0·90 (0·70–1·17)**
Trend: χ^2_1=1·5 ; p=0·23					p=0·45
Meta-analysis of all trial results					
No oxygen	36/1339 (2·7%)	45/1334 (3·4%)	−4·2	18·8	0·80 (0·51–1·26)
On oxygen, but not ventilated; includes high-flow oxygen only in Solidarity*	471/3516 (13·4%)	538/3490 (15·4%)	−40·2	244·6	0·85 (0·75–0·96)
Ventilated; includes high-flow oxygen in studies other than Solidarity	227/677 (33·5%)	204/673 (30·3%)	11·0	101·4	1·11 (0·92–1·35)
Total (all trials), with stratified analyses	**734/5532 (13·3%)**	**787/5497 (14·3%)**	**−33·4**	**364·8**	**0·91 (0·82–1·01)**
Trend: χ^2_1=5·1 ; p=0·02					p=0·08



Pas de donnée spécifique chez l'immunodéprimé

Clinical Infectious Diseases

MAJOR ARTICLE

Real-World Effectiveness of Remdesivir in Adults Hospitalized With Coronavirus Disease 2019 (COVID-19): A Retrospective, Multicenter Comparative Effectiveness Study

Clinical Infectious Diseases

MAJOR ARTICLE

Optimal Timing of Remdesivir Initiation in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Administered With Dexamethasone

Clinical Infectious Diseases

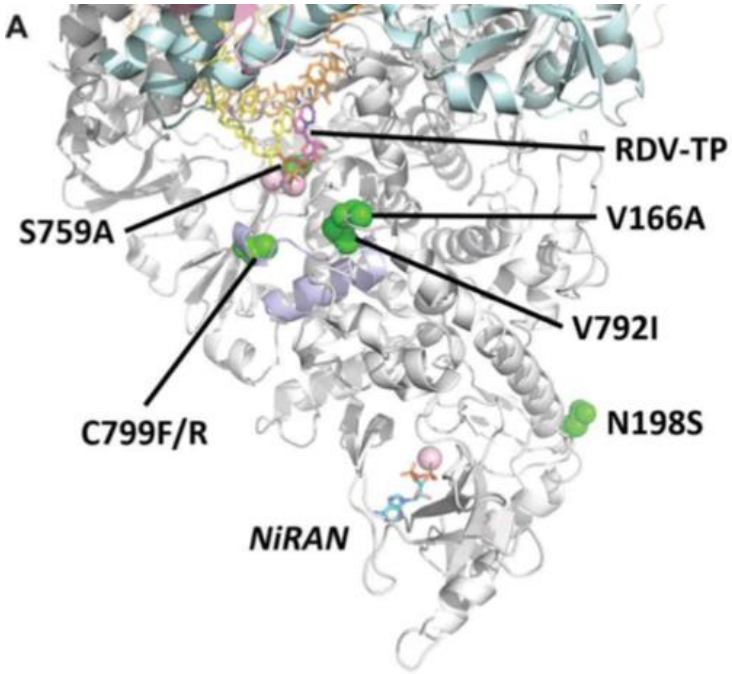
MAJOR ARTICLE

Remdesivir Reduced Mortality in Immunocompromised Patients Hospitalized for Coronavirus Disease 2019 Across Variant Waves: Findings From Routine Clinical Practice

WHO Solidarity trial consortium, Lancet 2022, 1941; Garibaldi, CID 2022, e516; Wong, CID 2022, e499; Mozaffari, CID 2023, epub

Résistance au Remdesivir

- Mutations RNA-dependent RNA polymerase (RdRp, *Nsp12*): 0,3%, sans corrélation temporelle avec utilisation Remdesivir
- Sous-étude ACTT-1: Substitution *Nsp12* 38% RDV, 40% placebo
  - Effet de la pression de sélection immunitaire
  - 2/31 patients fold-change EC_{50}: C799F 2,5 (± 0,3), V792I 2,2 (± 0,3)
  - Pas d'impact clinique, altération fitness viral
- Emergences de novo chez l'immunodéprimé (E802D, V792I, V166L)



Mari, Microorganisms, 2021, 1094; Stevens, STM 2022, eabo0718; Hedgskog, JID 2023, 1263; Ganghi, Nat Com 2022, 1547; Hogan, CID 2023, 342

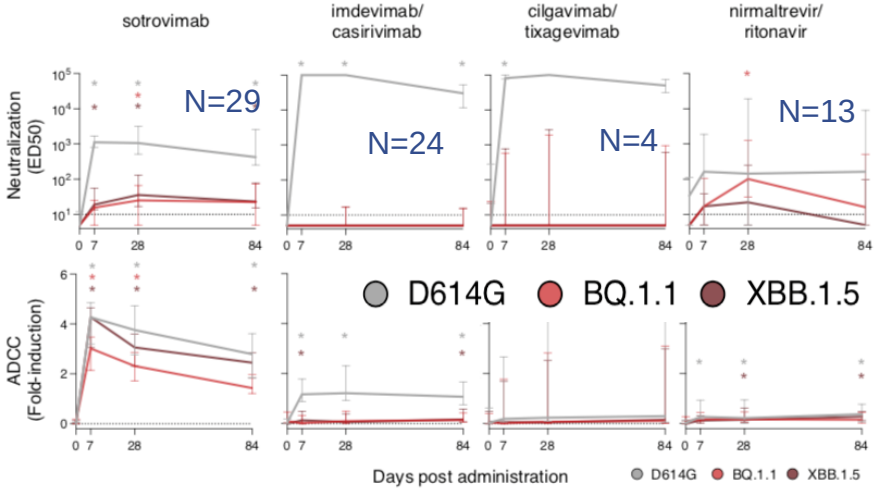
Sotrovimab ➔ 3ème intention, pas de donnée clinique avec XBB

Hamster, Sb J-3, challenge, Sac J+3

B

	Mean lung infectious titer reductions (%)					Mean mAb concentrations (µg/mL of serum)
	B.1	BA.1	BA.2	BQ.1.1	XBB.1	
Sotrovimab						
0.7mg/kg	82.33	84.58	96.47	*NA*	*NA*	3.8±2.5
2mg/kg	95.40	92.84	99.09	78.42	93.62	7.6±1.7
7mg/kg	99.99	99.65	99.79	98.28	99.74	21.1±4.0
14mg/kg	*NA*	99.78	99.86	98.07	97.74	40.4±9.2
Cilgavimab/Tixagévimab						
7mg/kg	*NA*	*NA*	*NA*	34.43	43.23	51.0±10.6

Analyse ex vivo des sérums de 80 patients immunodéprimés non répondeurs à la vaccination traités < SF5 pour COVID léger à modéré



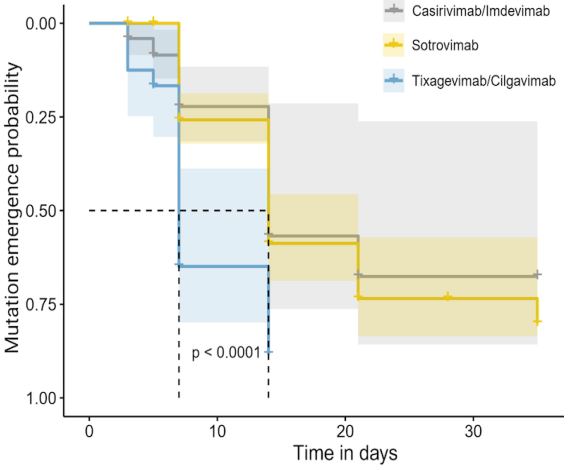
Activité antivirale polyfonctionnelle et potentiel effet-dose

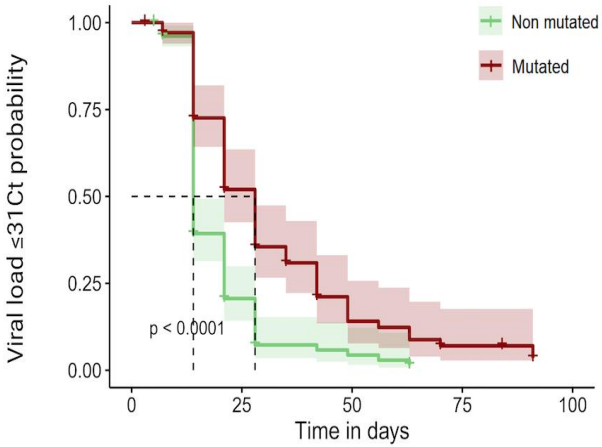
➔ Données cliniques en attente (RECOVERY, 1g; COMET-TAIL 2g)

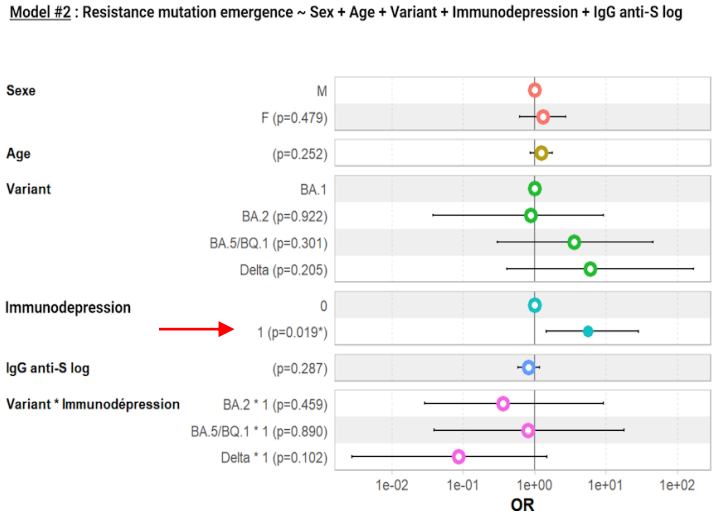
Driouich, Antivir Res 2023, doi.org/10.1016/j.antiviral.2023.105638; Bruel/Schwartz lab & CoCoPrev, Cell Med 2023; Moya, OFID 2023, doi.org/10.1093/ofid/ofad344

Emergence de mutations sous mAbs chez l'immunodéprimé

- Apparition mutations de novo avec prévalence > 5% chez 264 patients COVID léger/modéré < SF5, 78% ID, Casi-Imde (n=74), Sotro (n=166), Cilga-Tixa (n=24)



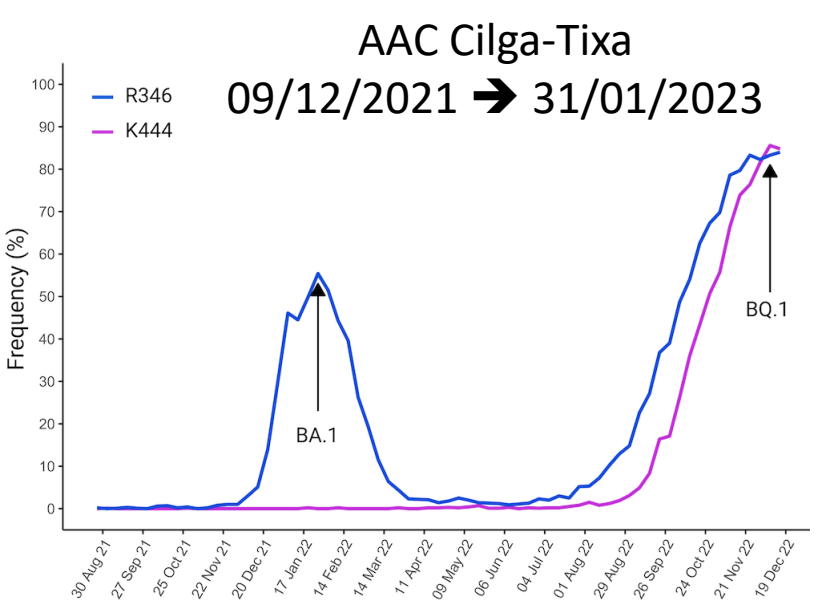




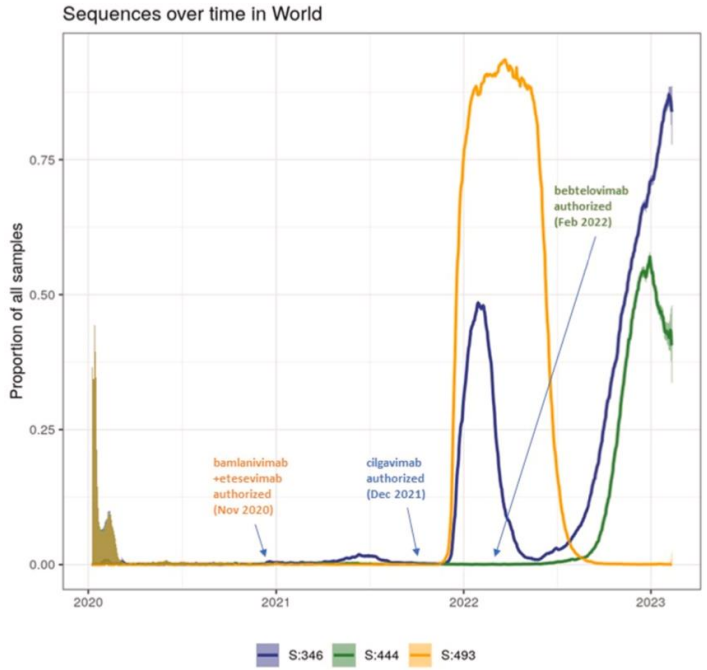
Emergence rapide de mutations de novo spécifiques ➔ Vulnérabilité mAbs

Leducq, CoCoPrev study group, En révision dans JID; Gupta, JCI 2023, 133(6):e166032

Rôle des mAbs dans l'émergence de sous-lignages?



L1186, E340, K356, P337: < 1%



Corrélation temporelle

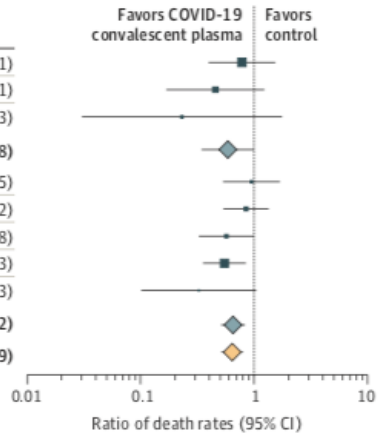
Leducq, CoCoPrev study group, En révision dans JID; Focosi, Drug Resistance Updates, 2023, 100991

Plasma de convalescent COVID ➔ Ac polyclonaux

PCC / Immunodéprimés

Figure 2. Forest Plot of Mortality Among Randomized Clinical Trials and Matched Cohort Studies

Source	Deaths/patients (%) CCP group	Usual care group	RR (95% CI)
Denkinger et al,[30] 2022	12/68 (18)	15/65 (23)	0.77 (0.39-1.51)
Lacombe et al,[31] 2022	4/22 (18)	11/27 (41)	0.45 (0.17-1.21)
Bar et al,[29] 2021	1/15 (7)	5/17 (29)	0.23 (0.03-1.73)
RCT total	**17/105 (16)**	**31/109 (28)**	**0.58 (0.34-0.98)**
Cristell et al,[33] 2021	13/58 (22)	28/116 (24)	0.93 (0.52-1.65)
Lanza et al,[36] 2022	19/79 (24)	46/159 (29)	0.83 (0.52-1.32)
Hueso et al,[35] 2022	13/61 (21)	29/76 (38)	0.56 (0.32-0.98)
Thompson et al,[34] 2021	19/143 (13)	204/823 (25)	0.54 (0.35-0.83)
Biernat et al,[32] 2021	3/23 (13)	9/22 (41)	0.32 (0.10-1.03)
MCT total	**67/364 (18)**	**316/1196 (26)**	**0.64 (0.50-0.82)**
Overall	**84/469 (18)**	**347/1305 (27)**	**0.63 (0.50-0.79)**



PCC vacciné < 6 mois

GMT(GMT$_{50}$) of plasma from three different sources against recent Omicron sublineages.

Neutralization virus	WA-1	BQ.1.1	BA.4/5	BA.4.6	BA.2.75	XBB	BF.7
Post COVID-19/vaccine (study cohorts)	9	9	9	9	9	6	7
GMT(GMT$_{50}$)	4983*	201	719	352	303	52	204
Fold reduction from WA-1	ref	25	7	14	16	96	24
Samples tested	231	231	231	106	231	62	148
Samples neutralizing	231	103**	230	106**	230	60	146
Percent neutralizing	100	97	100	100	100	97	99

COVIC-19

A Randomised Open-Label Trial of Early, Very High-Titre Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19 - NCT05271929

Besoin d'études contrôlées +++
Maintien d'une filière d'approvisionnement

Senefeld, JAMA Open Network 2023, e2250647; Sullivan, J Gen Virol 2023, 001854; Lacombe, BMJMed 2023

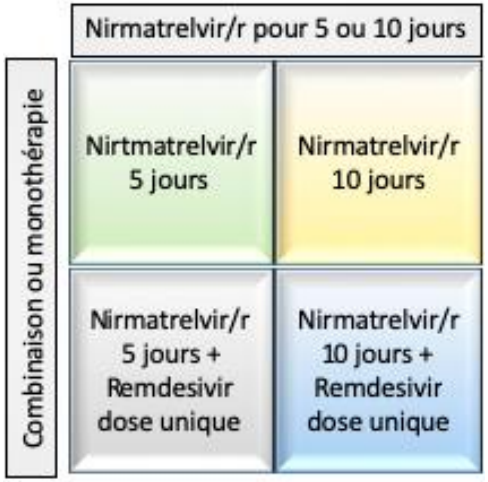
Perspective des traitements optimisés/combinés chez l'ID

ID avec COVID persistant/prolongé		
Lanzafame, J Chemother 2023	N/r + Sb	Clairance virale 4/4
Mikulska, CID 2023	RDV 10j + N/r ou Molnu. +/- mAbs	Clairance virale 16/22 à J30
Aiello, JAC 2023	RDV 10j + PCC ou Sb	4/60 ICU, 3/60 décès
Huygens, JAC 2023	PCC + N/r	Clairance virale 4/5
Breeden, OFID 2023	N/r 15 à 21 jours après RDV ou mAbs	Guérison 4/4
Pasquini, Haematological Oncology, 2023	N/r + RDV 10 jours	Guérison 14/14 J6 Clairance virale 14/10 J9

Besoin d'études contrôlées +++

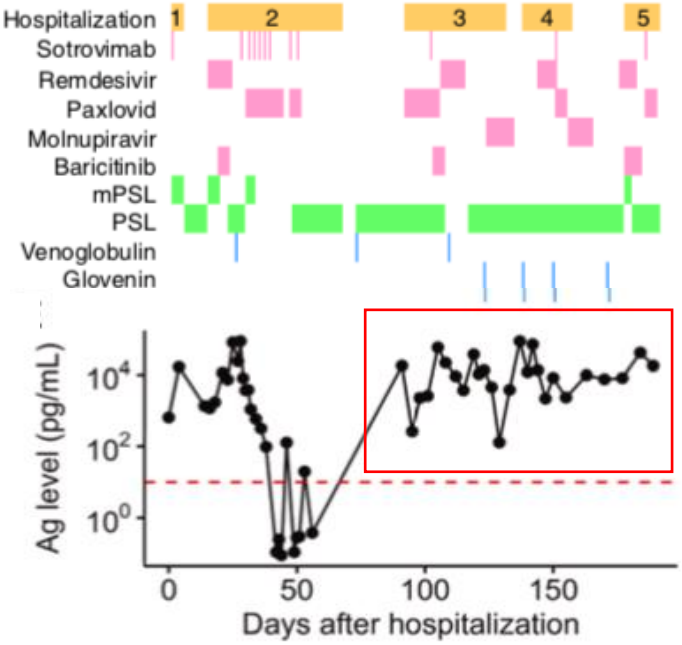
OPTICOV
Optimizing COVID-19 antiviral therapy
anrs MALADIES INFECTIEUSES ÉMERGENTES Inserm
HUG Hôpitaux Universitaires Genève

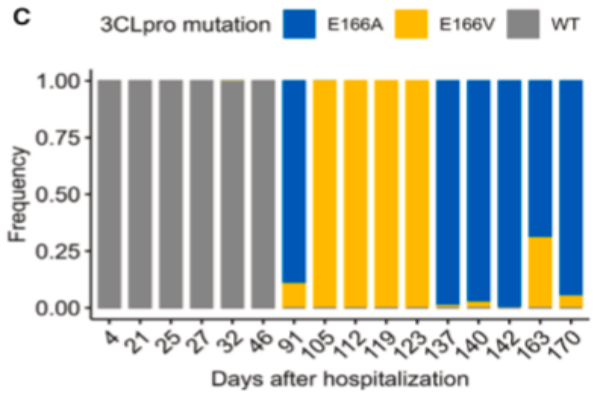
ID avec COVID non sévère



Multidrug-resistant mutations to antiviral and antibody therapy in an immunocompromised patient infected with SARS-CoV-2

M65, lymphome/Rituximab, 5 hospitalisations





P377L et E340K

Sotrovimab

		Codon	337	340	796
		Amino acid	P	E	D
Cluster 1	1	D4	·	·	Y
	1	D21	L	·	Y
	1	D25	L	·	Y
	2	D27	L	·	Y
	4	D32	L	·	Y
	8	D46	L	·	Y
Cluster 2	9	D91	·	K	Y
	10	D105	·	K	Y
	10	D112	·	K	Y
	10	D119	·	K	Y
Cluster 3	10	D123	·	K	Y
	10	D137	·	K	Y
	10	D140	·	K	Y
	10	D142	·	K	Y
	11	D163	·	K	Y
	11	D170	·	K	Y

V166L

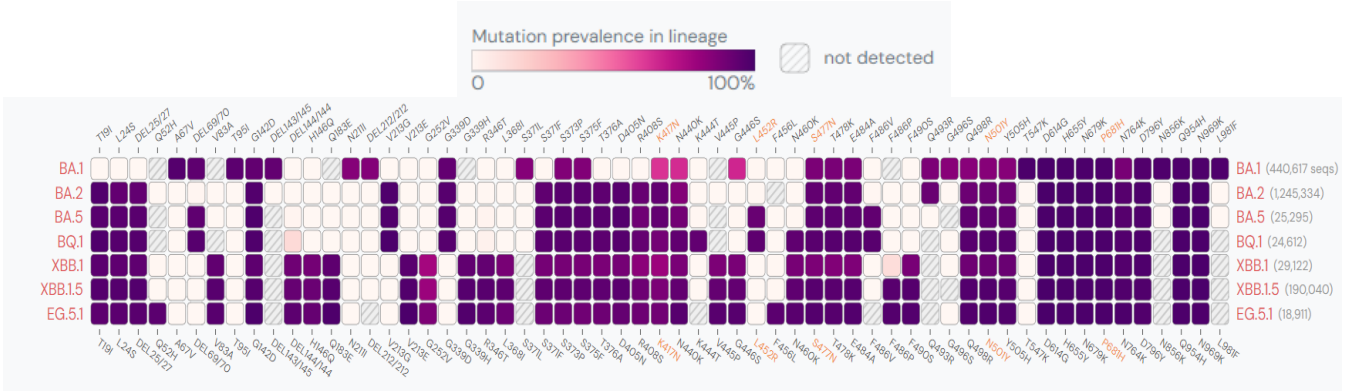
Remdesivir

		Codon	166	198	536	759	792	799	802
		Amino acid	V	N	I	S	V	C	E
Cluster 1	0	D4	·	·	·	·	·	·	·
	1	D21	·	·	·	·	·	·	·
	1	D25	·	·	·	·	·	·	·
	1	D27	·	·	·	·	·	·	·
	1	D32	·	·	·	·	·	·	·
	1	D46	·	·	·	·	·	·	·
Cluster 2	1	D91	L	·	·	·	·	·	·
	2	D105	L	·	·	·	·	·	·
	2	D112	L	·	·	·	·	·	·
	2	D119	L	·	·	·	·	·	·
Cluster 3	2	D123	L	·	·	·	·	·	·
	2	D137	L	·	·	·	·	·	·
	2	D140	L	·	·	·	·	·	·
	2	D142	L	·	·	·	·	·	·
	3	D163	L	·	·	·	·	·	·
	3	D170	L	·	·	·	·	·	·

Pression de sélection médiée par les antiviraux

Hirotsu, Med 2023, 1

En pratique



- Criblage ➔ identification des variants (dont certaines mutations signent polymorphisme résistance)
- Séquençage génome complet et séquençage ciblé sur Spike par NGS ➔ identification polymorphismes associés à une moindre neutralisation in vitro
  - Pas d'algorithme disponible
  - Impact sur la prise en charge?

Merci à Pauline Tremeaux, virologie, CHU de Toulouse

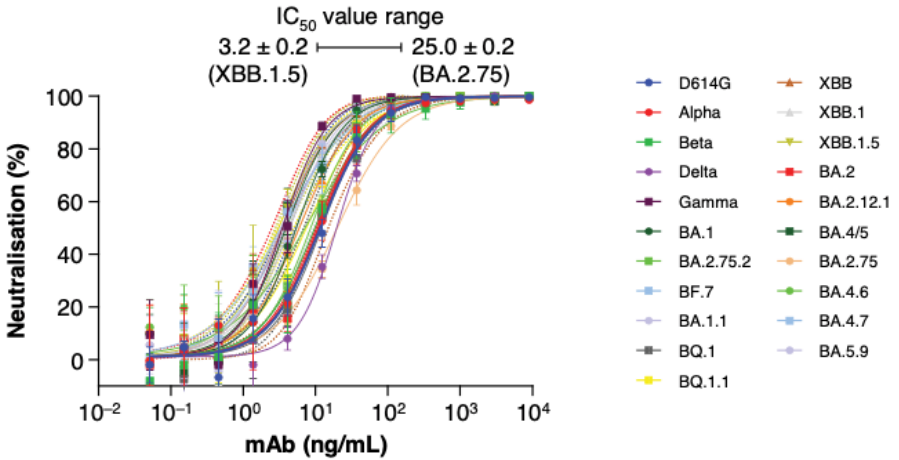
Principaux antiviraux directs en développement

Molécule	Données cliniques
VV116 / Analogue nucléotidique prodrogue du RDV/ PO	Phase 3: COVID léger/modéré < SF5, BA.2, population vaccinée: non infériorité délai avant guérison clinique vs N/r (0 hospitalisation ou décès à J28); délai avant conversion PCR similaire; dysgueusie 3,6% vs 25,8% ➔2 autres études de phase 3 en cours Autres en développement: Obeldesivir, GS-621763, GS-441524
Ensitrelvir / M^{pro} / PO	Phase 2b SCORPIO-SR: COVID léger/modéré < SF5, BA.1: bénéfice virologique vs placebo: J4 −0.41 log_{10}; délai avant conversion PCR: – 29 à 40h ➔ Phases 3 vs placebo en cours SCORPIO-HR & STRIVE Autres en développement: PF-07817883, Tollovir, Pomotrelvir, EDP-235, ALG-097558

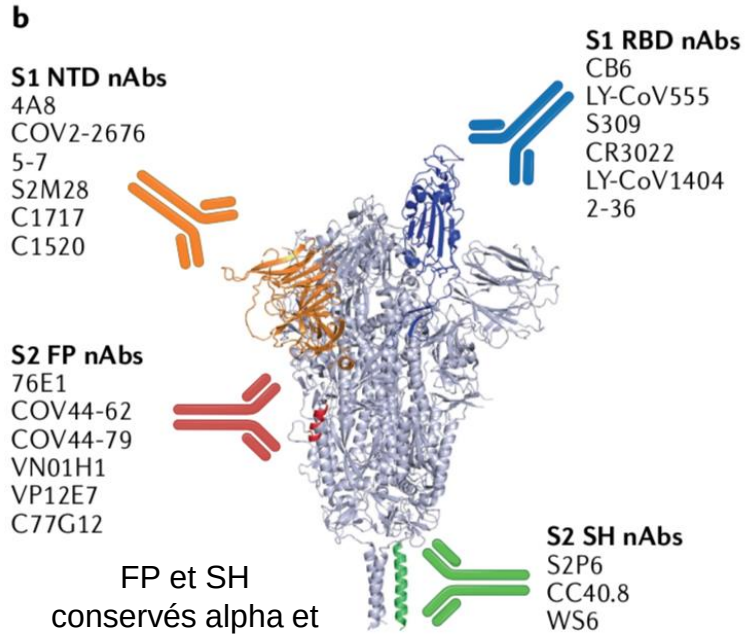
Cao, NEJM 2023, 406; Mukae, CID 2023, 1403

Autres mAbs en développement

AZD5156: Cilgavimab + AZD3152



Trial in progress: a Phase I/III, randomised, modified double-blind, placebo-and active-controlled pre-exposure prophylaxis study of the SARS-CoV-2–neutralising antibody AZD3152 (SUPERNOVA)



FP et SH conservés alpha et beta-CoVs

Francica, Poster P2636 ECCMID 2023 & Webber, Poster LB021 ECCMID 2023; Chen, Nat Rev Immunol 2023, 189

Corticothérapie

Essai plateforme RECOVERY, « low O2 »
DEXA 20 mg/j 5 jours puis 10 mg/j 5 jours
vs DEXA 6 mg/j

	Higher dose steroids (n=659)	Usual care (n=613)	RR (95% CI)
Primary outcome			
28-day mortality	123 (19%)	75 (12%)	1·59 (1·20–2·10)
Secondary and subsidiary outcomes			
Median (IQR) duration of hospitalisation, days	9 (5–17)	9 (5–16)	..
Discharged from hospital alive within 28 days	526 (80%)	504 (82%)	0·92 (0·81–1·05)
Invasive mechanical ventilation or death within 28 days	131 (20%)	80 (13%)	1·52 (1·18–1·97)
Use of ventilation	119 (18%)	85 (14%)	1·30 (1·01–1·68)
Non-invasive ventilation	108 (16%)	83 (14%)	1·21 (0·93–1·58)
Invasive mechanical ventilation	22 (3%)	14 (2%)	1·46 (0·75–2·83)
Renal replacement therapy*	11/658 (2%)	8/613 (1%)	1·28 (0·52–3·16)

Data are n (%) or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for other outcomes. *Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: **Effect of allocation to higher dose corticosteroid on key study outcomes**

Bénéfice de la corticothérapie chez l'ID?
No data

NIH: Patients who are immunocompromised may experience delayed development of favorable adaptive responses and a prolonged period of viral replication, as discussed above. For patients who are immunocompromised, are receiving minimal levels of conventional oxygen, and are earlier in the course of COVID-19 (e.g., those with <10 days of symptoms), the preferred approach may be emphasizing supportive care, using antiviral therapy, and avoiding corticosteroids. This strategy may reduce the duration of viral replication and the risk of secondary infections. Dexamethasone should be added if the patient has escalating oxygen requirements.

RECOVERY, Lancet 2023, 1499; https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/?utm_source=site&utm_medium=home&utm_campaign=highlights

Conclusion

- Améliorer le parcours de soins des patients à risque
- Personnaliser le traitement chez les immunodéprimés en tenant de compte du risque d'acquisition de résistances
  - Besoin d'études contrôlées dans cette population

		Antiviraux	Antiinflammatoires
COVID léger à modéré	< SF5 chez les patients à haut risque	1- OPTICOV chez l'immunodéprimé 2- Nirmatrelvir 3-Remdesivir	Non
	COVID persistant de l'immunodéprimé	1- OPTICOV 2- Bithérapie (RDV + N/r 10j?) 3- +/- PCC	Non
COVID sévère de l'immunodéprimé		1- Bithérapie (RDV + N/r 10j?) 2- +/- PCC	1- DEXA 6 mg 2- +/- Toci ou Bari

- Prévention chez les patients immunodéprimés
  - Poursuite des mesures barrières
  - Rappel de vaccin monovalent XBB.1.5