COVID-19 aspects thérapeutiques
Les antiviraux

To see the good target from the good window
Is the virus only the trigger?
To be or not to be in the SOC?
From repurposing approach to innovating strategy

F-Xavier Lescure
Infectious diseases department, Bichat, APHP.Nord
Inserm UMR 1137, IAME Infection Antimicrobials Modeling and Evolution
Paris University, France

Disclosure of Potential Conflicts of Interest

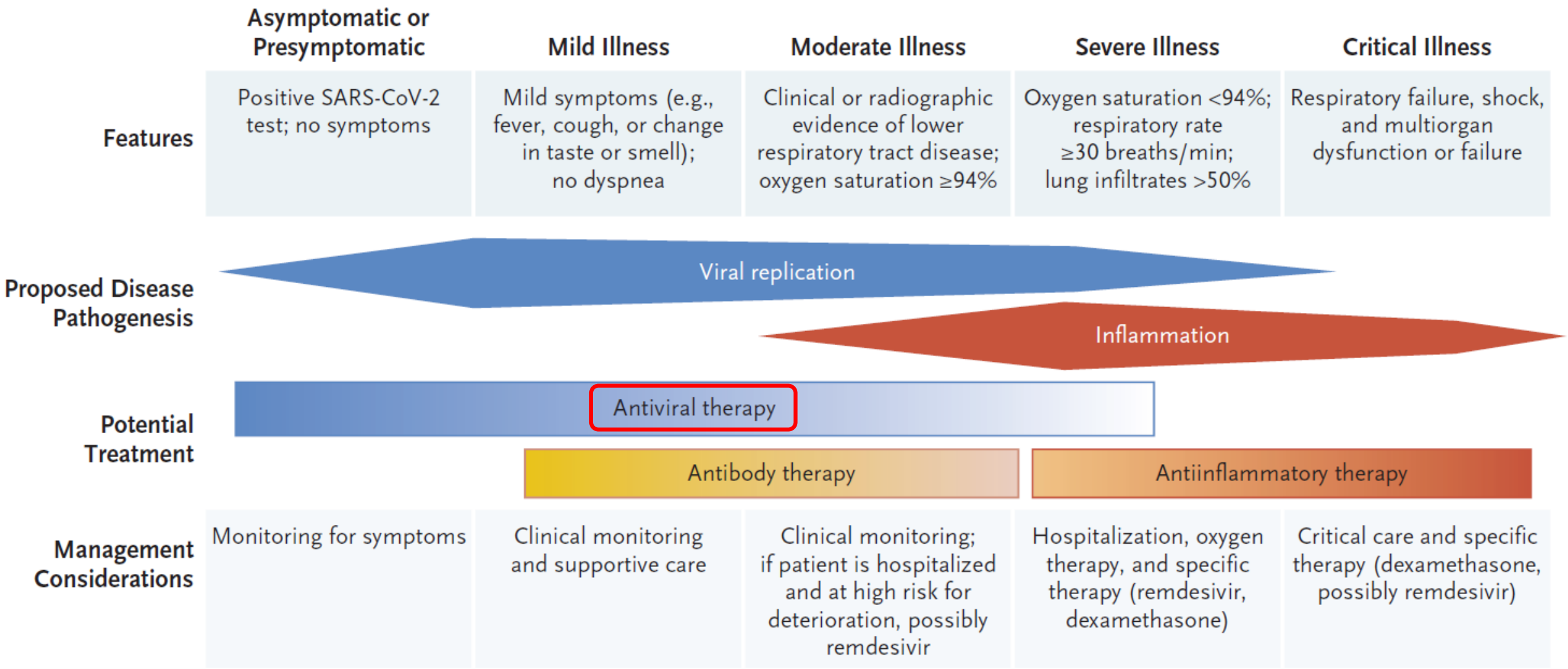
- General interest activities

- Investigator for academic research
  - CAMOMY (PHRC national), CLOCEBA (PHRC national), ADDAMAP (PHRC national), TEP STAR (PHRC national), SHASAR (PHRC national), RODEO (PHRC national), TEPvENDO (PHRC national), DISCOVERY (PHRC national), CORIMUNO (PHRC national), French COVID (ANR), DEEP covid (APHP), MicroCOVID (ANR), Aphroclic (ANRS)
- Investigator for industrial research
  - Posy TEICO (SANOFI), CONDUCT (MSD), OZAVIE (Pfizer), EFC16844 (SANOFI)
- Travel/accommodations/meeting expenses
  - JANSSEN-CILAG, GILEAD SCIENCES, SANOFI AVENTIS France, ViiV HEALTHCARE SAS, MSD France, bioMérieux, CORREVIO
- Payment for hospital unit
  - bioMérieux, SANOFI AVENTIS France, GUERBET, MSD France
- Payment for development of educational presentations (stop >2 years)
  - bioMérieux, GILEAD Sciences, MSD France

La COVID-19, une série sur deux ans

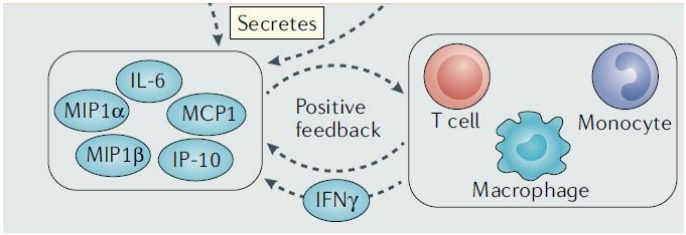
- La saison 2020
  - Episode 1 : quelques uns vs le reste du monde
  - Episode 2 : Gilead vs OMS
  - Episode 3 : les anticorps monoclonaux
  - etc.

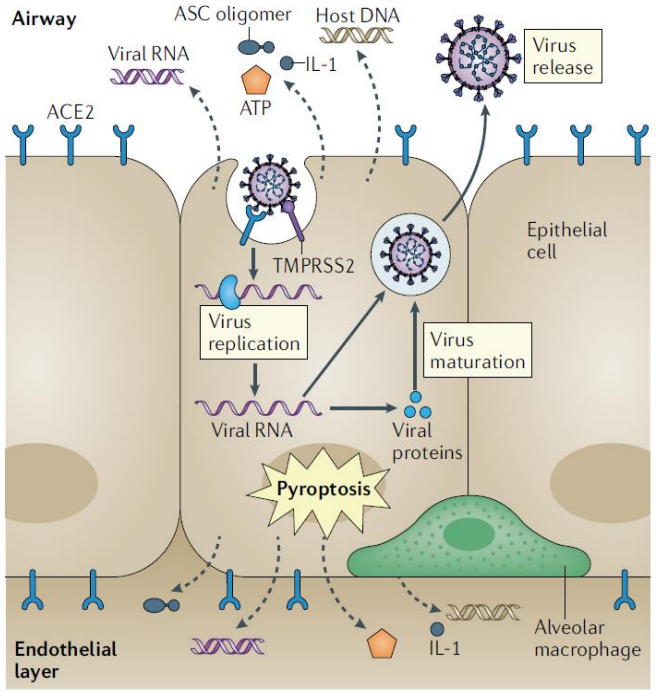
La « fenêtre d'opportunité virale »

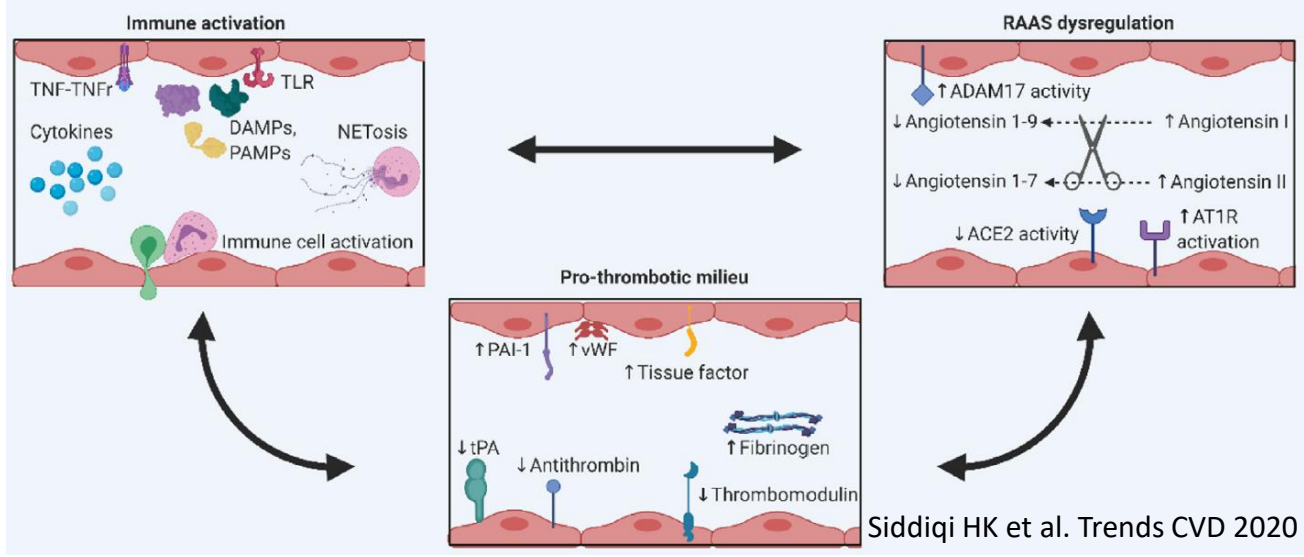


Gandhi RT et al. NEJM nov 2020

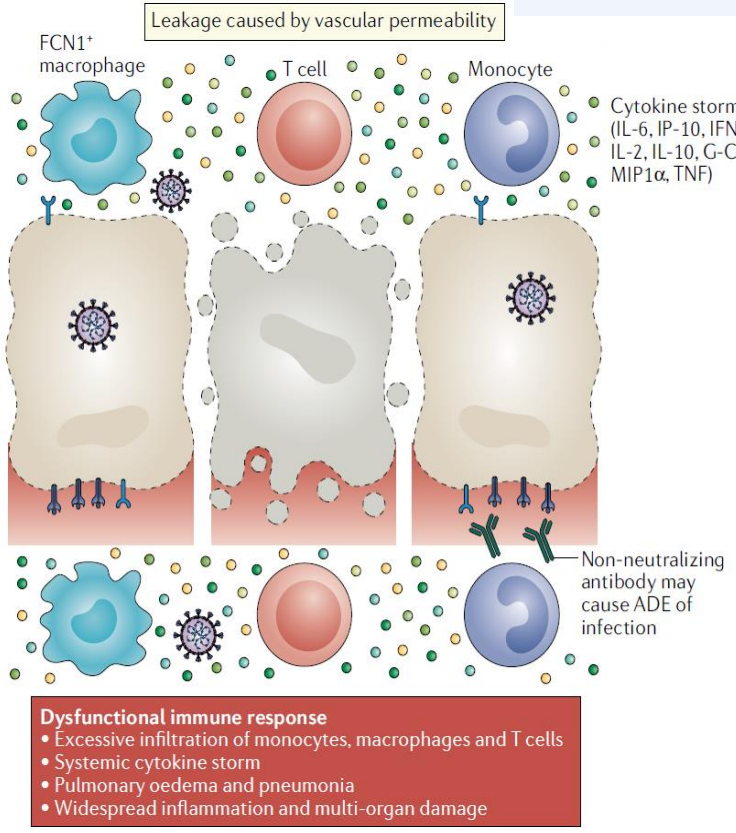
« L'orage cytokinique »



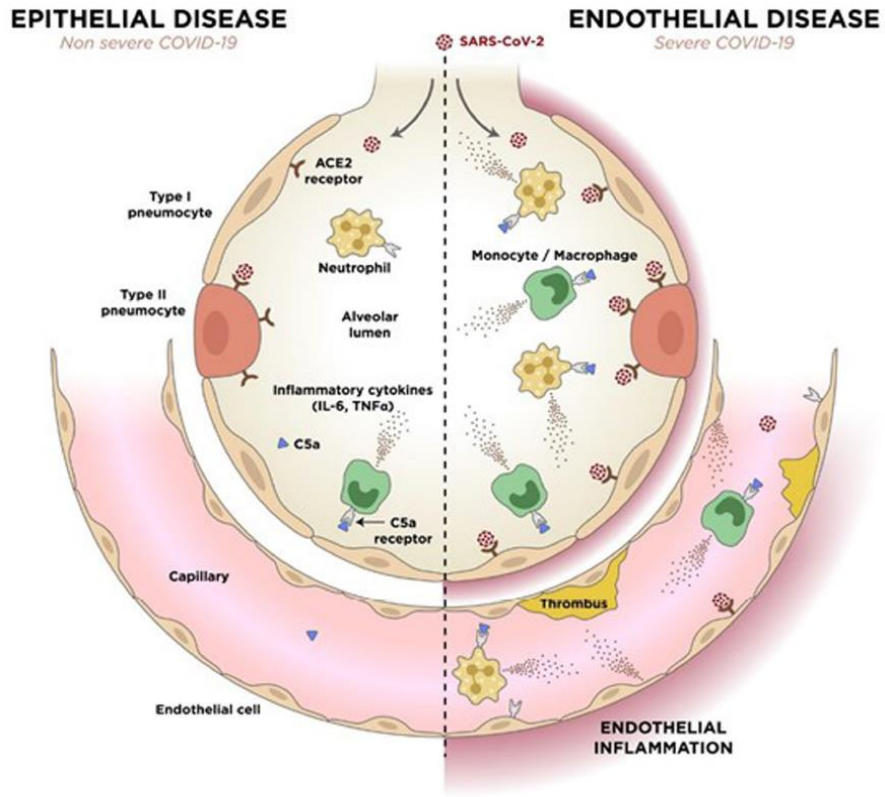




Siddiqi HK et al. Trends CVD 2020



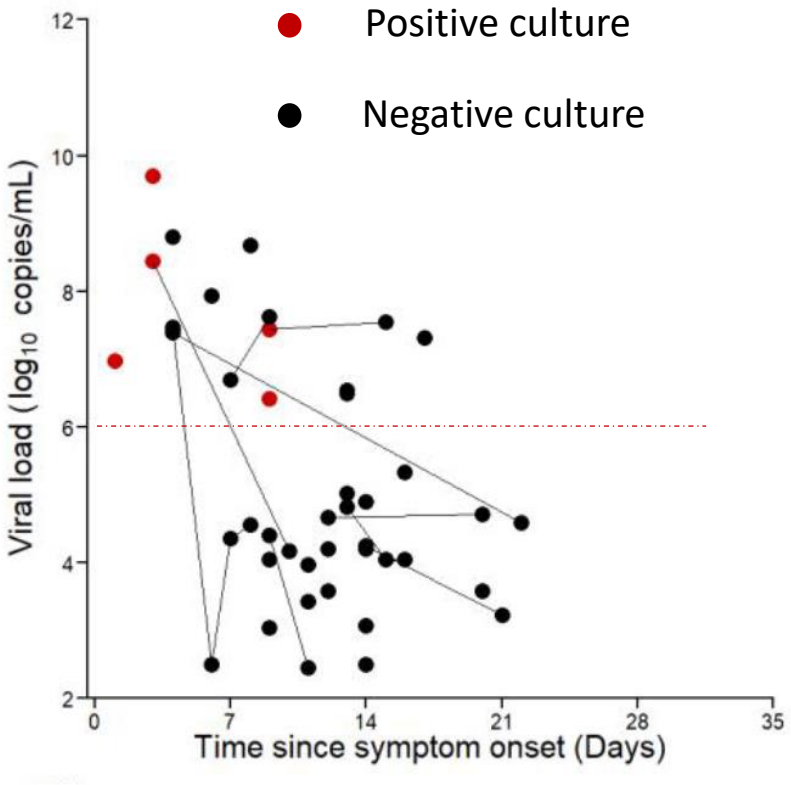
Tay et al. Nat Review Immunol 2020



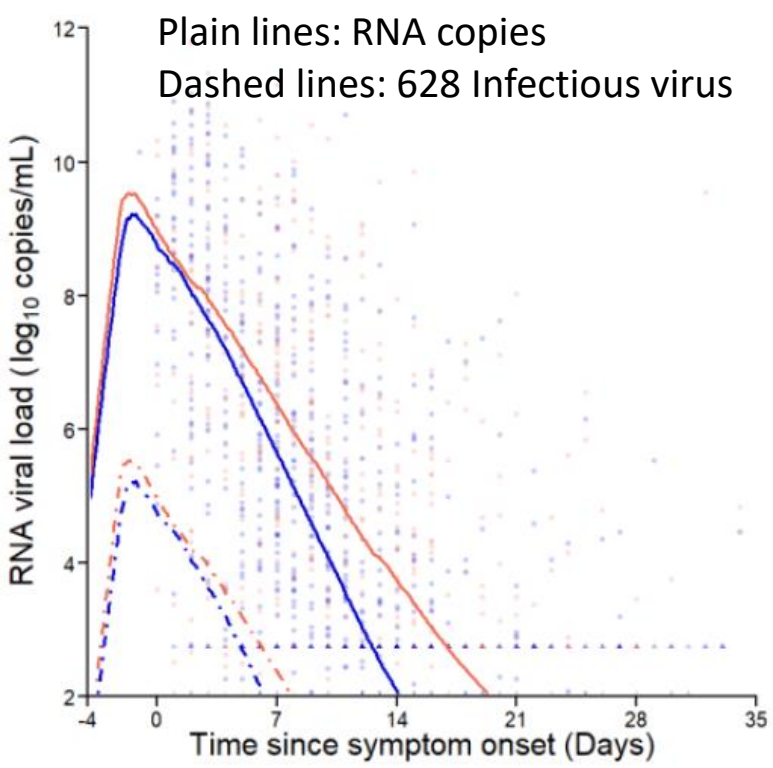
Carvelli J et al. Nature 2020

SARS - CoV 2 et cinétique virale, modélisation

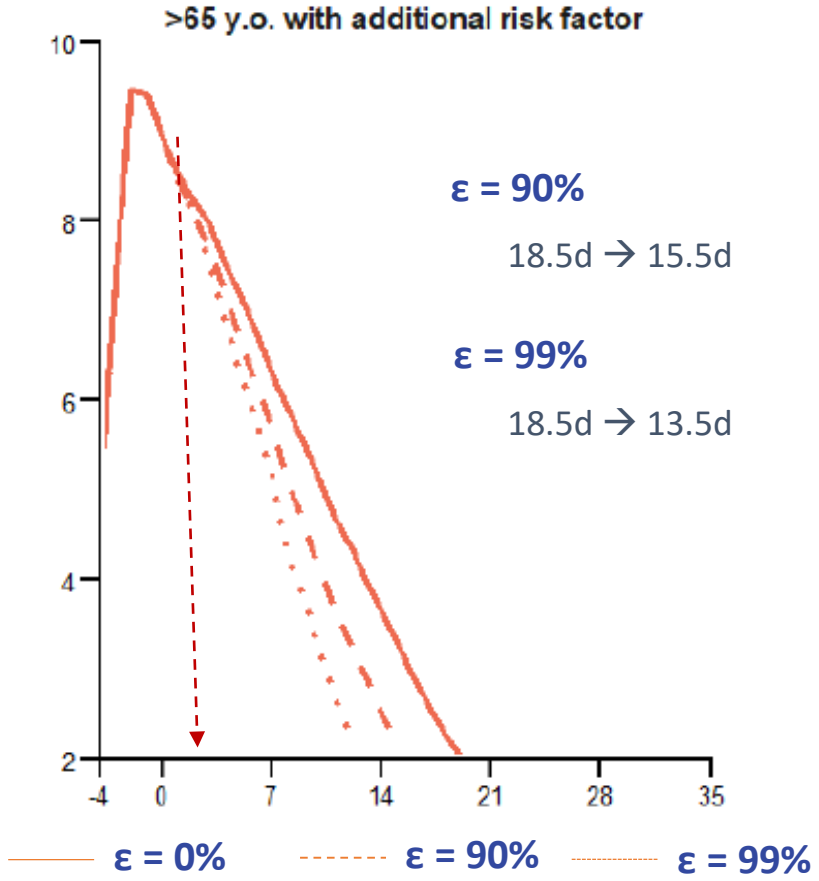
Réplication virale active vs excrétion virale (culture vs PCR)



Viral load data in 607 samples where virus culture was done.



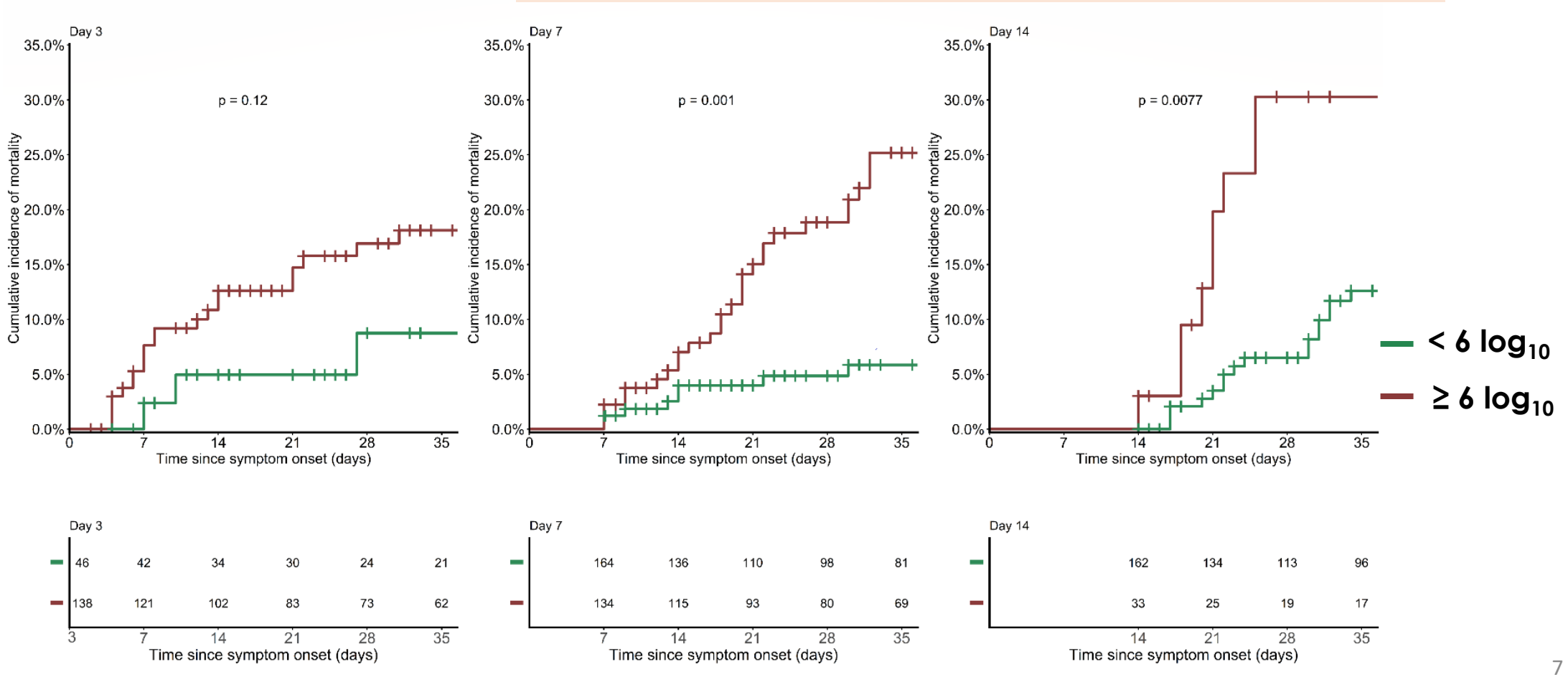
Blue: patients <65 yo
Orange: patients ≥ 65 yo



Nadège Néant, Jérémie Guedj et al. for French Cohort study group

Cinétique virale // mortalité

Corrélation significative à partir de J7

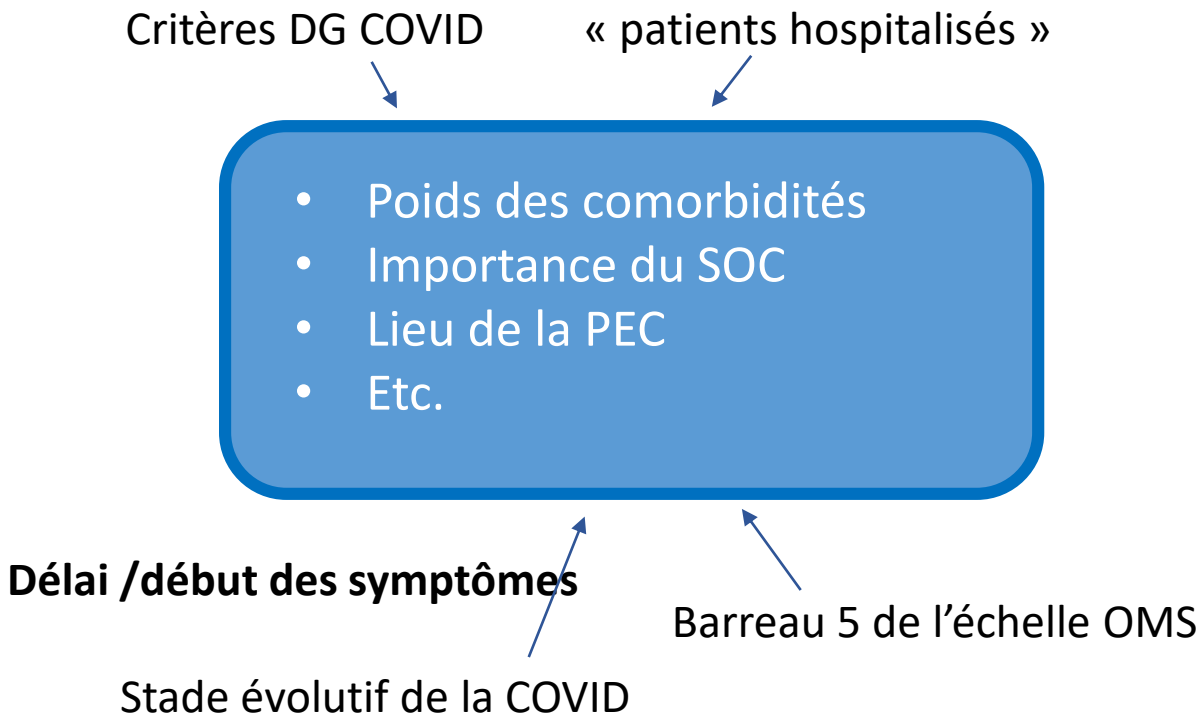


Jérémie Guedj et al. for French Cohort study group, ECCMID 2020

Considérations méthodologiques **simples**

• Population cible

Un contours de l'échantillon adapté à la fenêtre virale ou au phénotype des patients

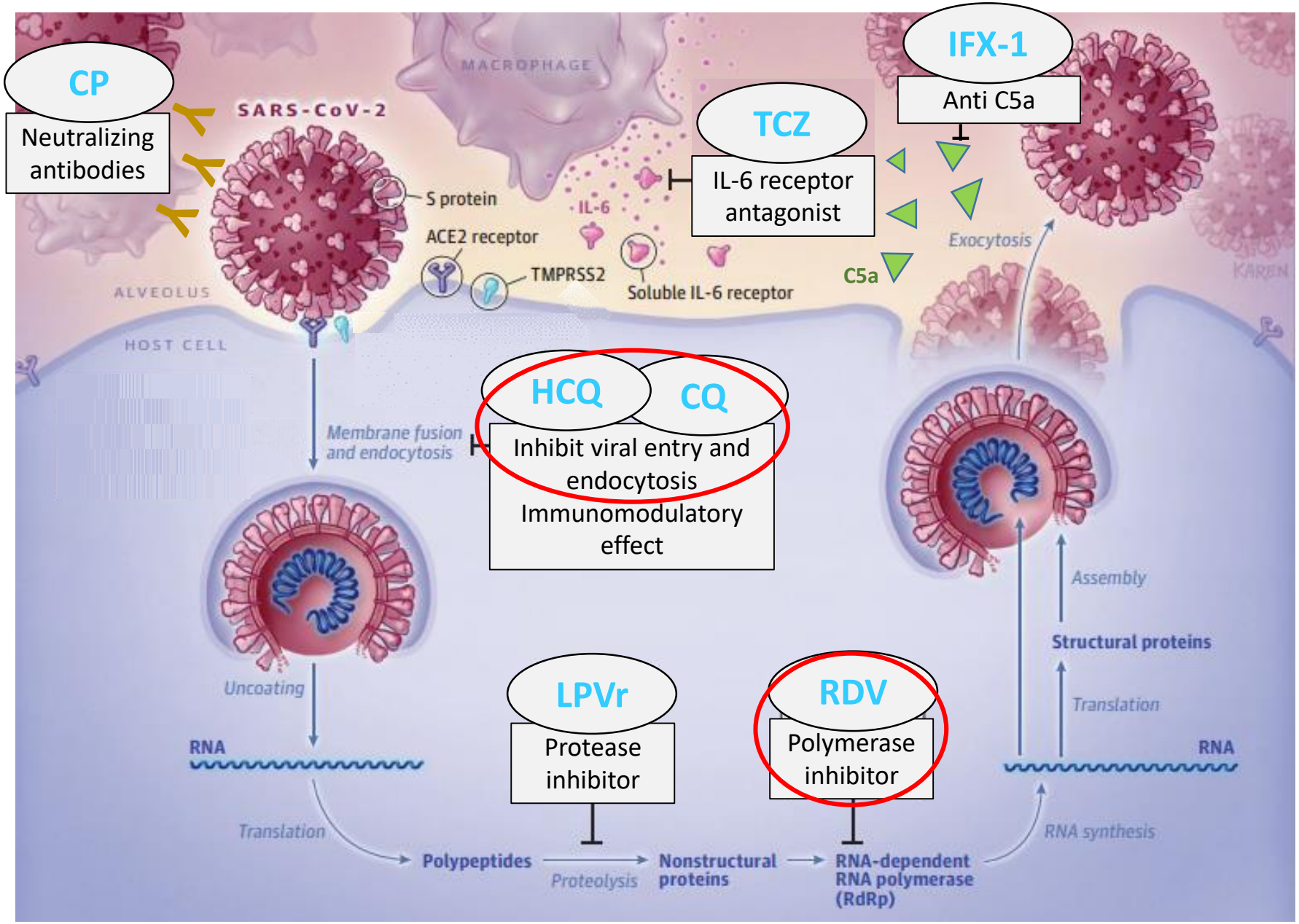


• Critères de jugements

Un CJP pas trop éloignée de l'intervention évaluée

- Données virologiques ❑
- Données inflammatoires ❑
- Evolution de la maladie ❑
- Durée de la maladie ❑
- Mortalité J14* ❑
- J28 *
- J60

*SF1 → ICU : 10j. ICU → décès : 3 sem.

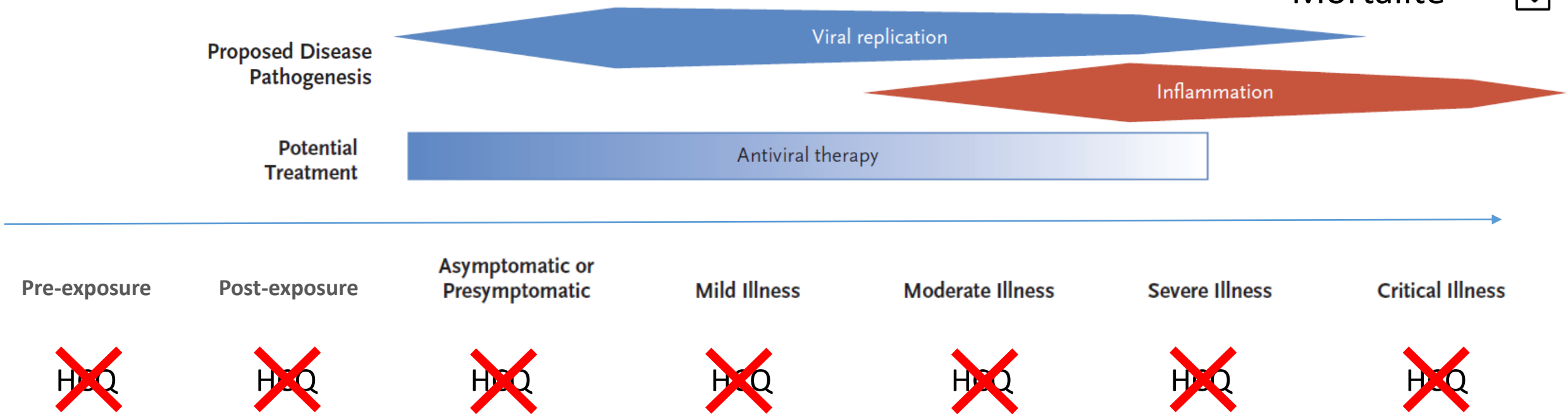


CT: corticosteroids
CP: convalescent plasma
CQ: chloroquine
HCQ: hydroxychloroquine
IFX-1: vilobelimab
LPVr: lopinavir/ritonavir
RDV: remdesivir
TCZ: tocilizumab

Sanders JM *et al. JAMA.* May 2020

Hydroxychloroquine; « fin de partie »

Charge virale ☑
Maladie ☑
Mortalité ☑



Abella BS *et al. JAMA Int Med.* Sep 2020

Boulware DR *et al*. *NEJM.* May 2020

Mitja *et al CID jul 2020,*
Skipper *et al. Ann Intern Med Oct 2020*

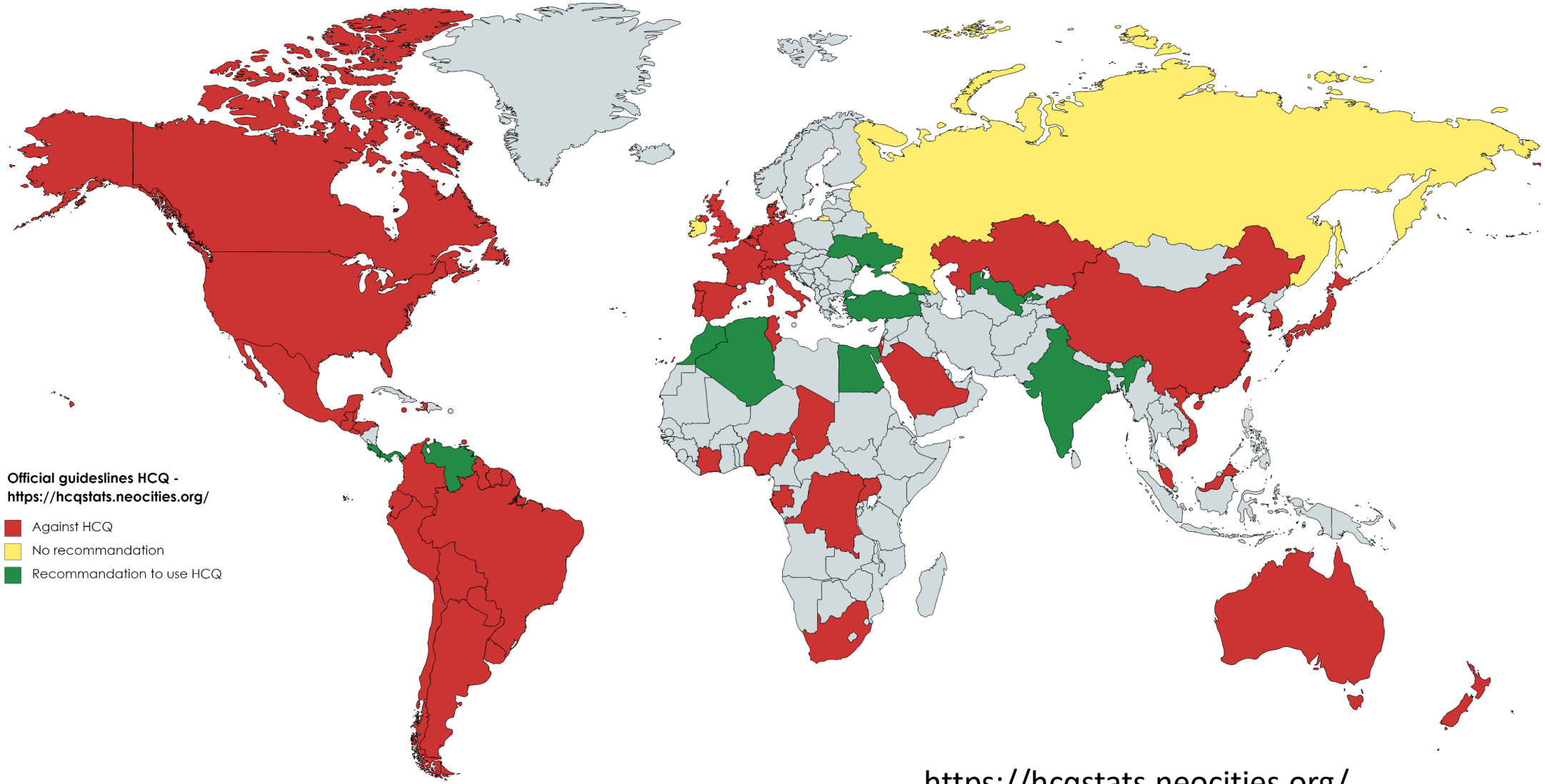
Self *et al*. *JAMA.* Nov 2020

RECOVERY Horby P et al. *NEJM.* Oct 2020

Cavalcanti *et al*. *NEJM.* Jul 2020
Tang W *et al. BMJ*. May 2020

Septembre 2020

Hydroxychloroquine; « fin de partie »



https://hcqstats.neocities.org/

R

Novembre 2020

Population

This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

World Health Organization

	Disease severity: Non-severe	Severe	Critical
	Absence of signs of severe or critical disease	SpO_2<90% on room air Respiratory rate >30 in adults Raised respiratory rate in children Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock
Remdesivir	✖ Recommendation against (weak)		
Corticosteroids	✖ Recommendation against (weak)	✔ Recommendation in favour (strong)	

Rochwerg B *et al*. BMJ. Nov 2020

Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity Octobre 2020

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS (recommendations are listed in order of preference in each category below; however, all options are considered acceptable)
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulotary therapy recommended The panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, NonInvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or NonInvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Therapeutic Management of Patients with COVID-19, NIH Guidelines, octobre 2020

Recommandations en France

Haut Conseil de la Santé Publique

Juillet 2020

Compte tenu des données actuelles disponibles issues de la littérature n'apportant pas la preuve d'un bénéfice sur l'évolution du Covid-19 des traitements à effet antiviral supposé,

le HCSP ne recommande pas leur usage en dehors des essais cliniques.

- Pour les patients atteints de Covid-19 pris en charge en ambulatoire :
  - L'abstention de prescription d'un traitement spécifique, sauf dans le cadre d'un essai thérapeutique tel que défini ci-dessus.
- Pour les patients atteints de Covid-19 hospitalisés en médecine (avec pneumonie oxygéno-requérante) ou en réanimation :
  - La prescription de tout médicament spécifique, est laissée à l'appréciation du prescripteur, après l'évaluation du rapport bénéfice/risque et sur décision collégiale.

AMM en Europe et en France

Spécialité pharmaceutique	**REMDESIVIR 100 mg solution à diluer pour perfusion** **REMDESIVIR 100 mg poudre pour solution à diluer pour perfusion**
Substance active	Remdesivir
Titulaire	Gilead Sciences SAS
Statut	ATU cohorte du 02/07/2020 Arrêt le 24/10/2020
AMM	03/07/2020 (VEKLURY)
Indications	Le remdesivir est indiqué pour le traitement de la maladie COVID-19 chez les adultes et les adolescents (âgés de 12 ans et plus et pesant au moins 40 kg) ayant une pneumonie nécessitant une oxygénothérapie (voir rubrique 5.1). **Au vu des limites de la démonstration clinique en termes d'efficacité et de sécurité, toute initiation de traitement doit faire l'objet au préalable d'un avis collégial.**

ansm
Agence nationale de sécurité du médicament et des produits de santé

Veklury is an antiviral medicine used to treat coronavirus disease 2019 (COVID-19). It is used in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) with pneumonia requiring supplemental oxygen.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Remdesivir, le « match »

ACTT 1 – Gilead

- Randomized, double-blind, placebo-controlled, multicenter (73 centers), academic study, USA
- **Inclusion criteria**: SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, SpO_2 < 94% (room air) or requiring supplemental oxygen, mechanical ventilation, or ECMO
- **Primary outcome**: time to recovery
    - 541 **RDV** group, 521 **placebo** group (1:1)
    - Age med. : 59y, 69% male
    - 31% diabetes – 51% HTA – 45% obese
    - SF med. : 9 days [6-12]
    - 13% H+ O2- / 41% H+ O2+ / 35% VNI – IOT – ECMO
    - Mortality D28: 11.4% - 15.2%

Beigel JH *et al*. *NEJM.* Nov 2020

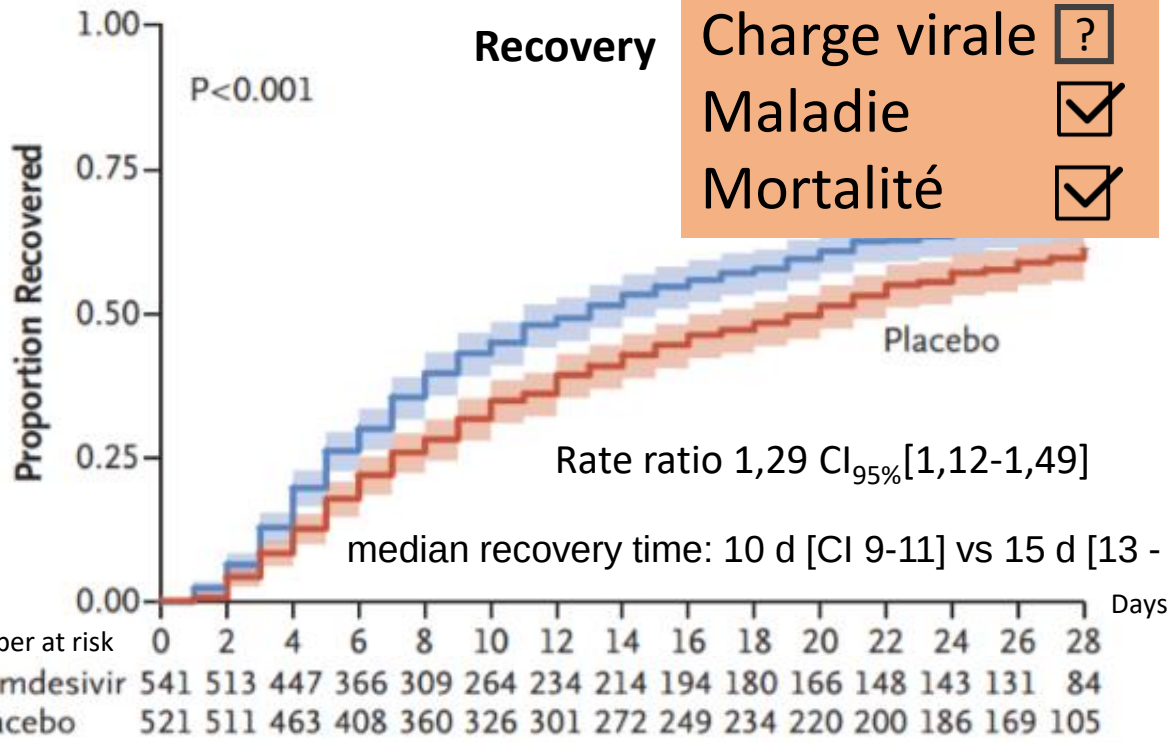
SOLIDARITY - WHO

- Open label pragmatic randomized, multicenter (405 hospitals in 30 countries in all 6 WHO regions), academic study, WHO
- **Inclusion criteria**: ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug
- **Primary outcome**: In-hospital mortality
    - 2708 **RDV** group, 2743 **SOC** group (1:1)
    - 19% age >70y, 62% male
    - 25% diabetes - 21% CV disease, - ?% obese
    - SF med. : ?
    - 24% H+ O2- / 9% IOT
    - Mortality D28: 11.8%

Hongchao P *et al*. MedRxiv Oct 2020

ACTT 1 – Gilead

Charge virale ?
Maladie ☑
Mortalité ☑

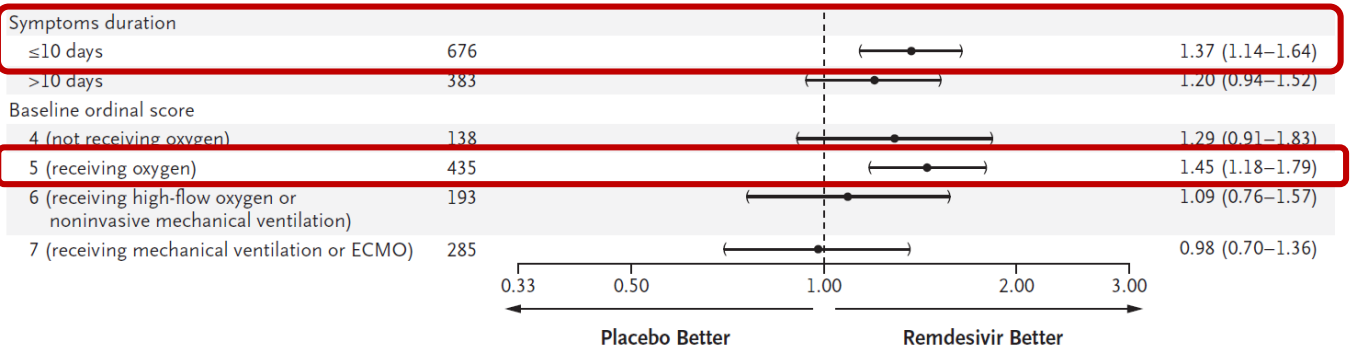


Rate ratio 1,29 $CI_{95\%}$[1,12-1,49]

median recovery time: 10 d [CI 9-11] vs 15 d [13 - 18)

D29 mortality: RDV 11,4% *vs.* placebo 15,2%; HR 0,73 [0,52-1,03]

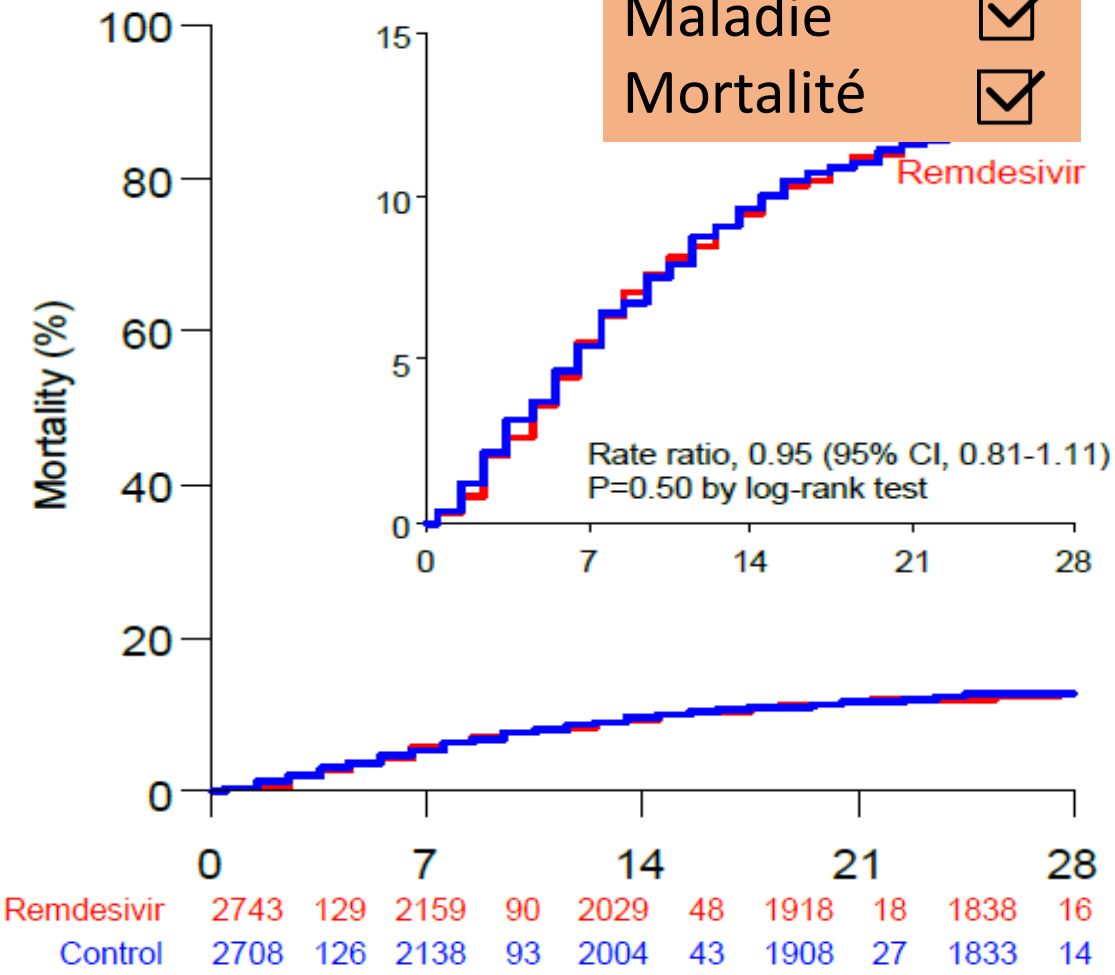
D15 mortality: RDV 6.7% *vs.* placebo 11.9%; HR 0.55 [0.36-0.83]



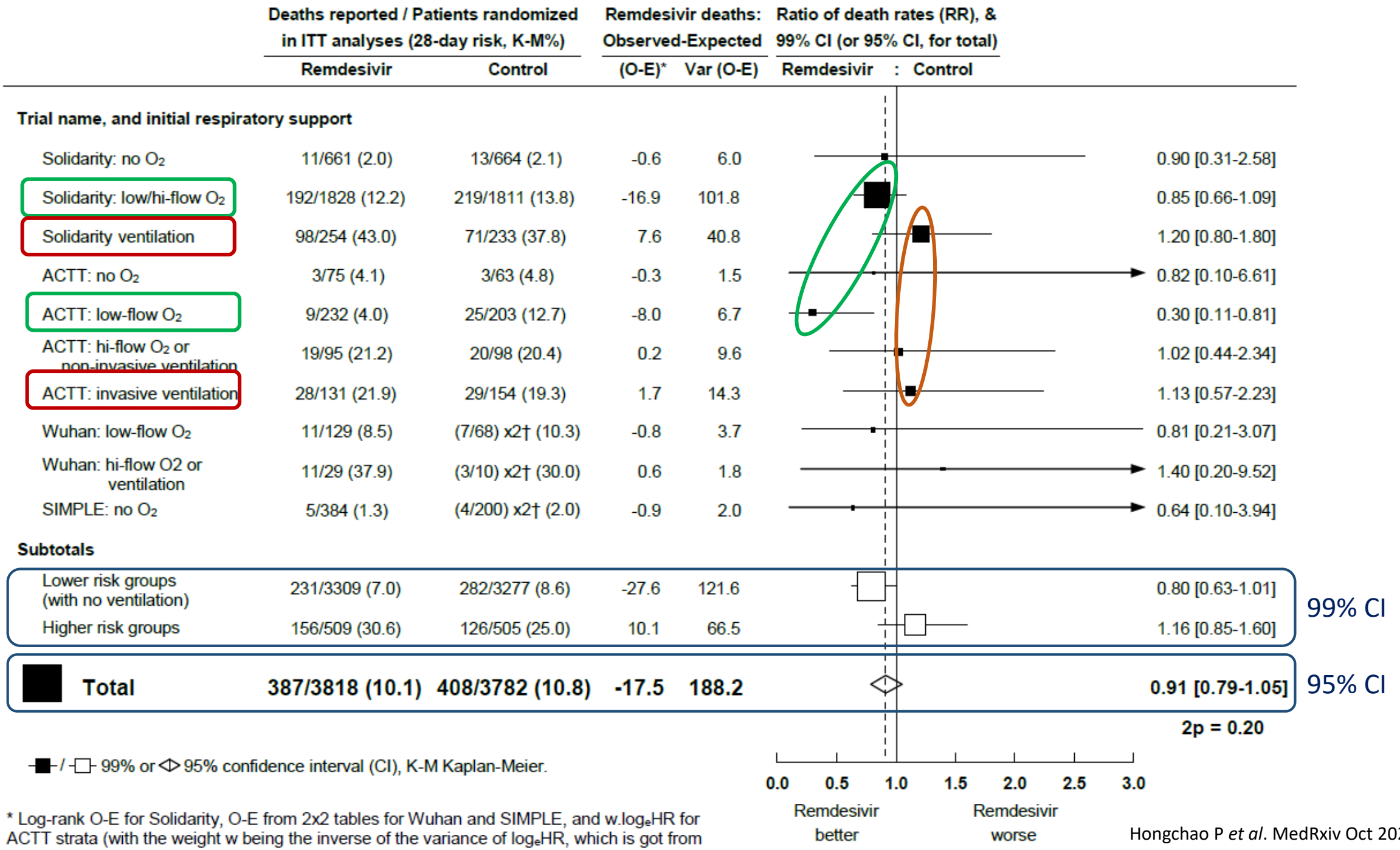
Beigel JH *et al*. *NEJM.* Nov 2020

SOLIDARITY - WHO

Charge virale ☐
Maladie ☑
Mortalité ☑



Hongchao P *et al*. MedRxiv Oct 2020

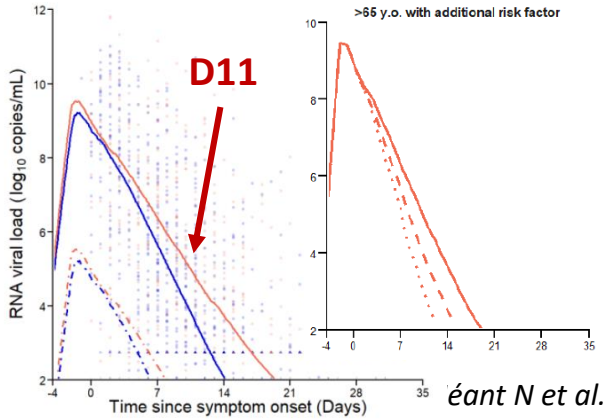


Hongchao P *et al*. MedRxiv Oct 2020

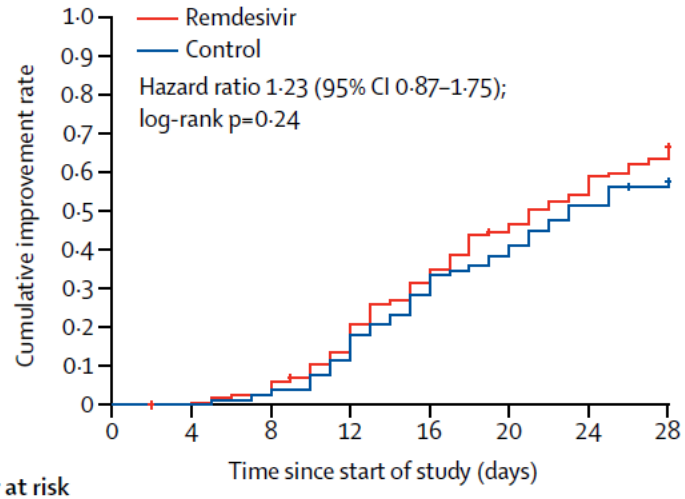
Remdesivir, le « match » - come-back in China

- Randomized, double-blind, placebo-controlled, multicenter, academic study, China
- **Inclusion criteria:** age ≥ 18yo, positive SARS-CoV-2 RT PCR, pneumonia confirmed by chest Imaging, SpO_2 < 94% (room air) or PaO_2/FiO_2 ≤ 300 mmHg, within 12 days of symptom onset
- **Primary outcome**: time to clinical improvement within 28 days after randomization
- **Secondary outcome** : D28 mortality, **SARS-CoV-2 viral load**

- 158 **RDV** vs 79 **placebo** (2:1)
- Age med. : 65y, 60% male
- 23% diabetes – 40% HTA
- SF med. : **11 days [9-12]**
- 13 - 18% critical (VNI – IOT – ECMO)
- Mortality D28: 14% - 13%



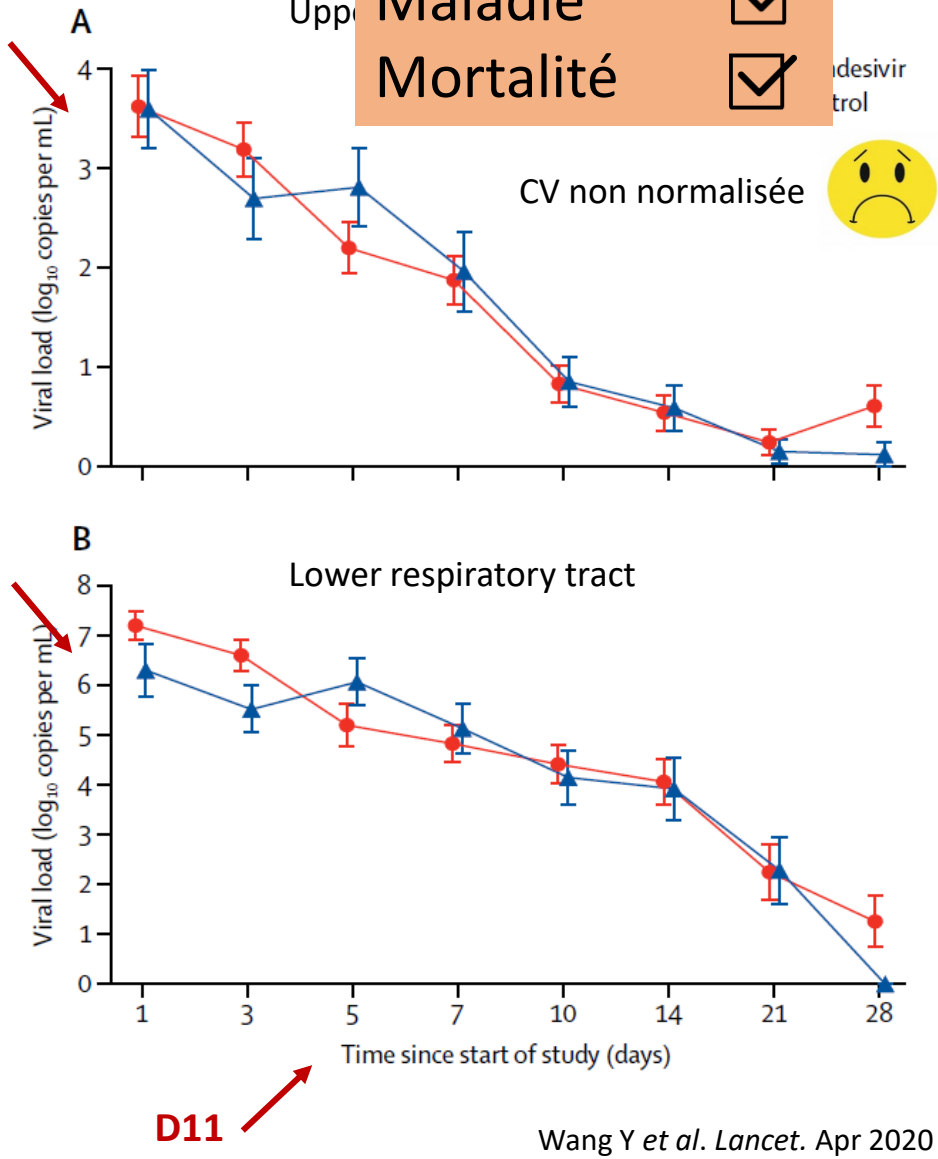
Time to clinical improvement in the intention-to-treat population



Number at risk (number censored)								
Remdesivir	158 (0)	155 (2)	147 (0)	123 (1)	101 (0)	82 (1)	63 (0)	25 (26*)
Control	78 (0)	78 (0)	75 (0)	64 (0)	52 (0)	46 (0)	38 (0)	17 (16*)

éant N et al. for French Cohort study group

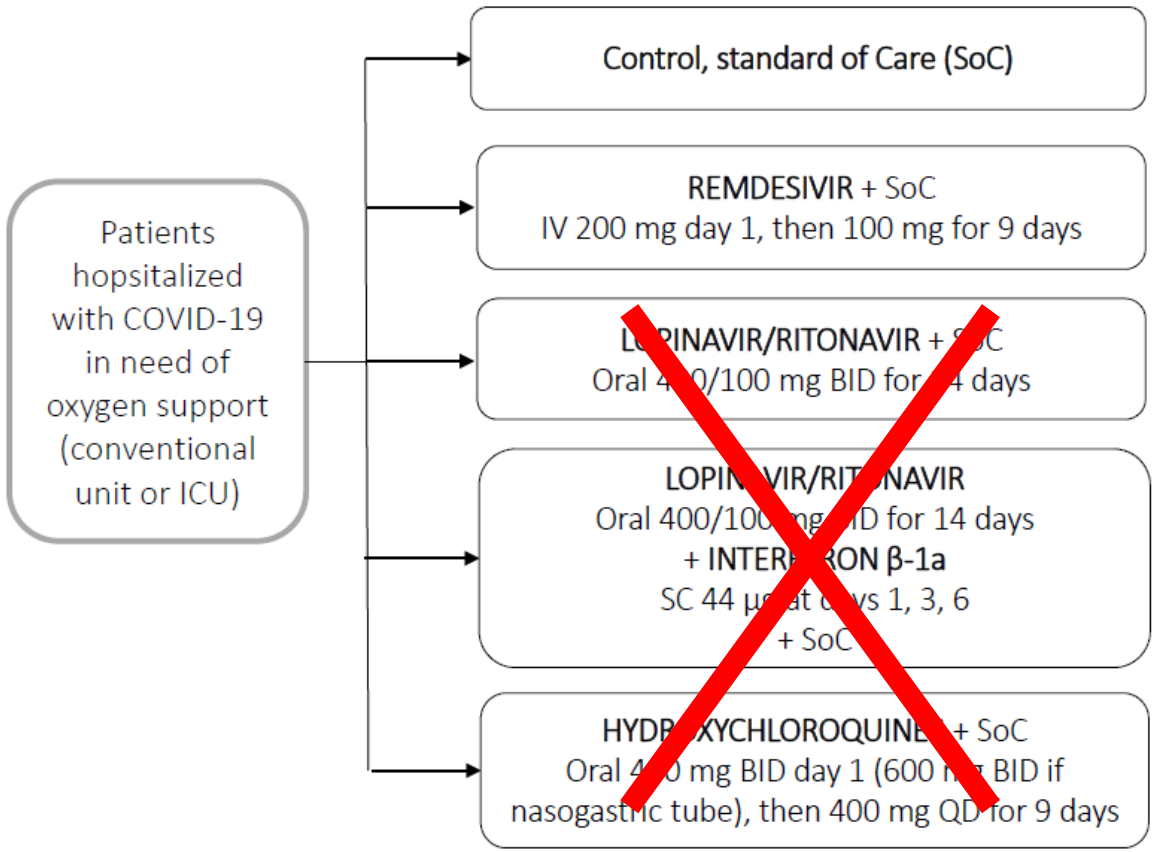
Charge virale ☑
Maladie ☑
Mortalité ☑



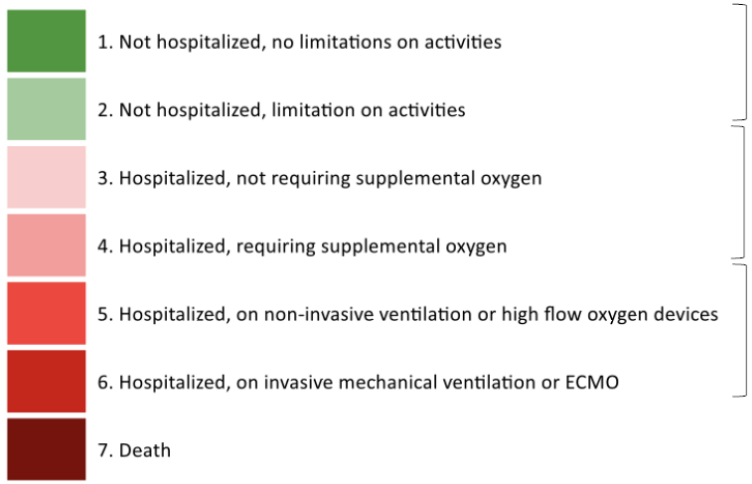
Wang Y *et al. Lancet.* Apr 2020

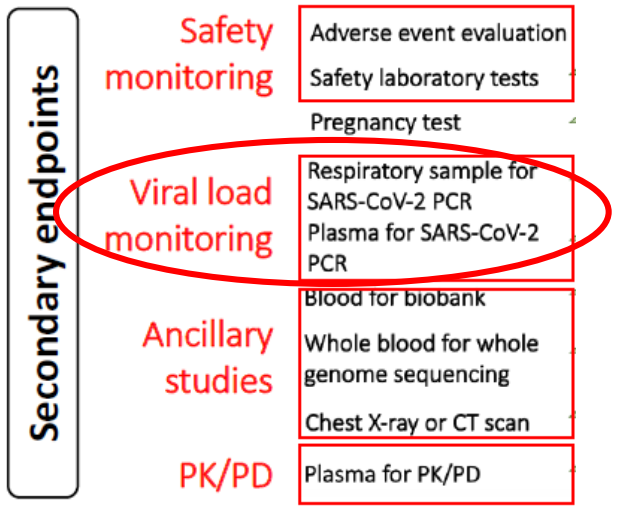
Remdesivir, l'arbitre?

DISCOVERY



Primary end-point : WHO 7-point ordinal scale at day 15





CV normalisée

* SF med. : **9 days [7-12]**

Ader F *et al*. DISCOVERY RCT

Remdesivir, l'argument massue?

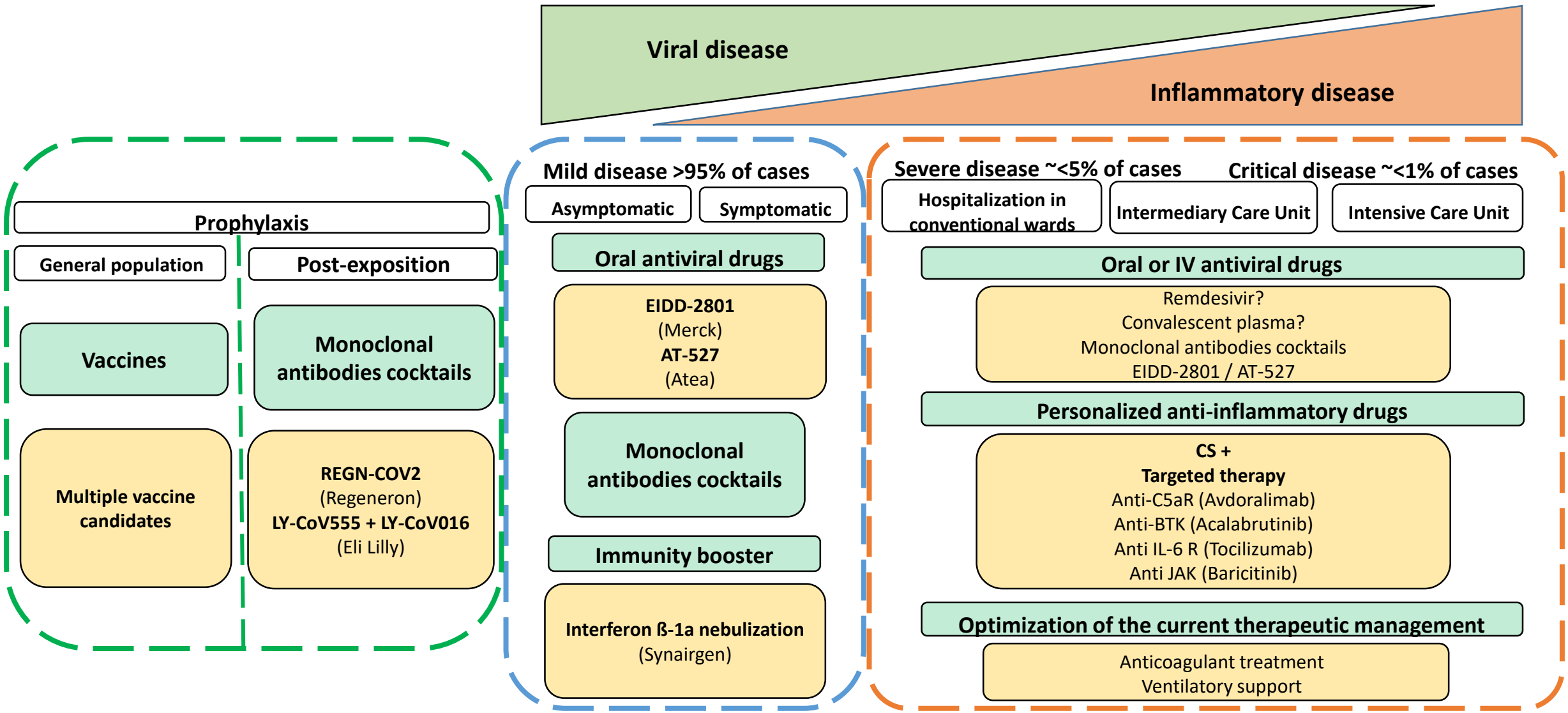
A five day course of treatment for one patient costs around **$2340 (£1773; €1976)** for government programmes and $3120 for private insurers, although Gilead has reached agreements to make cheaper generic versions of the drug available in low and middle income countries.

For comparison, **Tamiflu costs less than $75 per course** of treatment to shorten symptom duration for patients with influenza (generic versions of the drug can cost even less).

The European Medicines Agency had already granted conditional approval similar to the FDA's EUA for remdesivir back in July. On 8 October, the European Commission followed up by signing a joint procurement framework contract with Gilead for a six month supply of up to **500 000 treatment courses** of remdesivir worth **$1.2bn**.
But what the European Commission didn't know was that **Gilead had already received a draft manuscript of the Solidarity findings in September**. The **commission** only learnt about remdesivir's lacklustre performance in Solidarity **the day after it signed the contract with Gilead**.

Hsu J. BMJ Nov 2020

Covid-19, traitement antiviral – la suite



Slide: Nathan Peiffer Smadja

The end

- To see the good target from the good window

  Reshape the design of the next RCT
- Is the virus only the trigger?

  Not for everybody; predictive VL at D7? Mab in primary care?
- To be or not to be in the SOC?

  Medical and cost-effectiveness strategy at planetary scale
- From reporposing to innovating approach

  We are going through a transition period

COREB
mission nationale
Coordination Opérationnelle
Risque Epidémique et Biologique

https://www.coreb.infectiologie.com/

REACTing
research & action
targeting emerging infectious diseases

https://reacting.inserm.fr/

Scientific update on COVID-19

Updated on November 19th 2020