

11

**WORKSHOP
NAZIONALE CISAI**

TORINO 2023

20 • 21 APRILE



Tollerabilità dei farmaci antinfettivi e co-morbilità associate all'infezione da HIV

Presidenti del Convegno

Paolo Bonfanti, Antonio Di Biagio, Giancarlo Orofino

FONDAZIONE | ASIA

CISAI

Paolo Maggi

Università della Campania, Luigi Vanvitelli
UOC Malattie Infettive e Tropicali AORN Caserta

HIV e SARS-COV-2: impatto clinico sulle persone HIV di due pandemie

Il sottoscritto **prof. Paolo Maggi**
in qualità di docente

ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Grant for publication, Advisory board fees, Conference hospitality:

Gilead Science

Advisory board fees:

ViiV Healthcare

Advisory board fees, Conference hospitality:



MSD

Advisory board fees, Conference hospitality:

Janssen

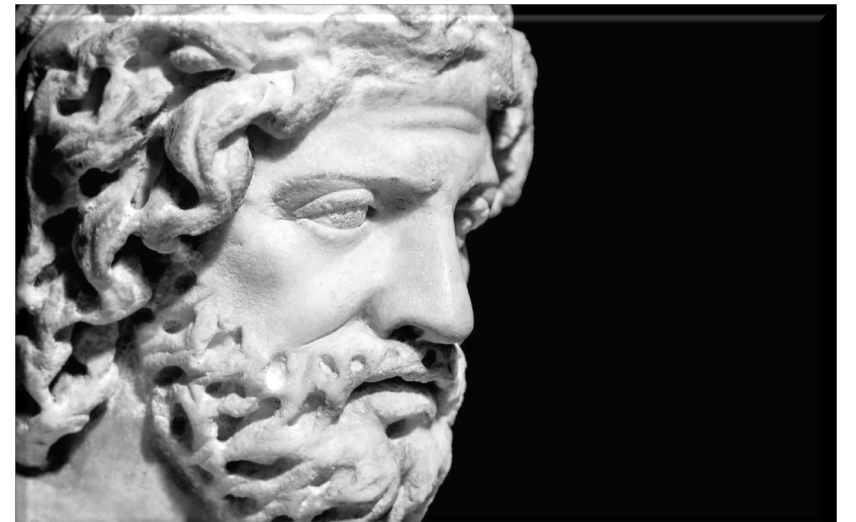
Review

HIV and COVID-19 Co-Infection: Epidemiology, Clinical Characteristics, and Treatment

Dimitris Basoulis ¹, Elpida Mastrogianni ², Pantazis-Michail Voutsinas ² and Mina Psychogiou ^{2,*}

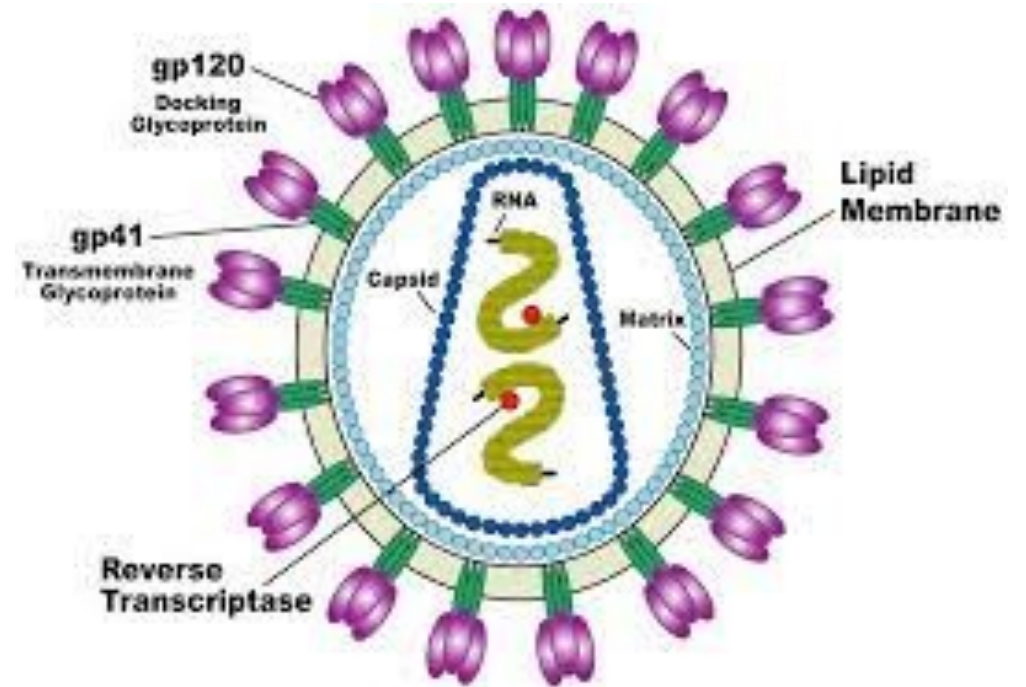
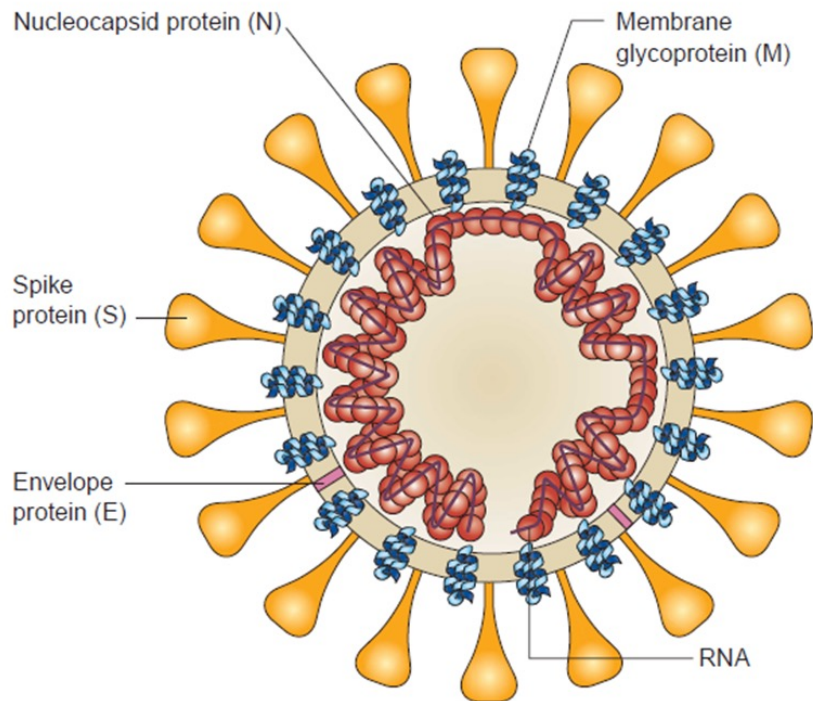
Viruses **2023**, *15*, 577. <https://doi.org/10.3390/v15020577>

«COVID-19 and HIV are reminiscent of Plutarch's Parallel Lives—
two different diseases associated with similar
media frenzy, fear of the unknown and stigma»



In persons living with HIV (PLWH), levels of **immune activation and inflammation** remain elevated even when viral suppression is maintained, and this may contribute to the insurgence of several comorbidities.

On the other hand, residual immune dysregulation can hamper the immune response to infections.



Immune activation and inflammation seem to play a pivotal role also in SARS-CoV-2, and some comorbidities are tied to a worse outcome in this disease,

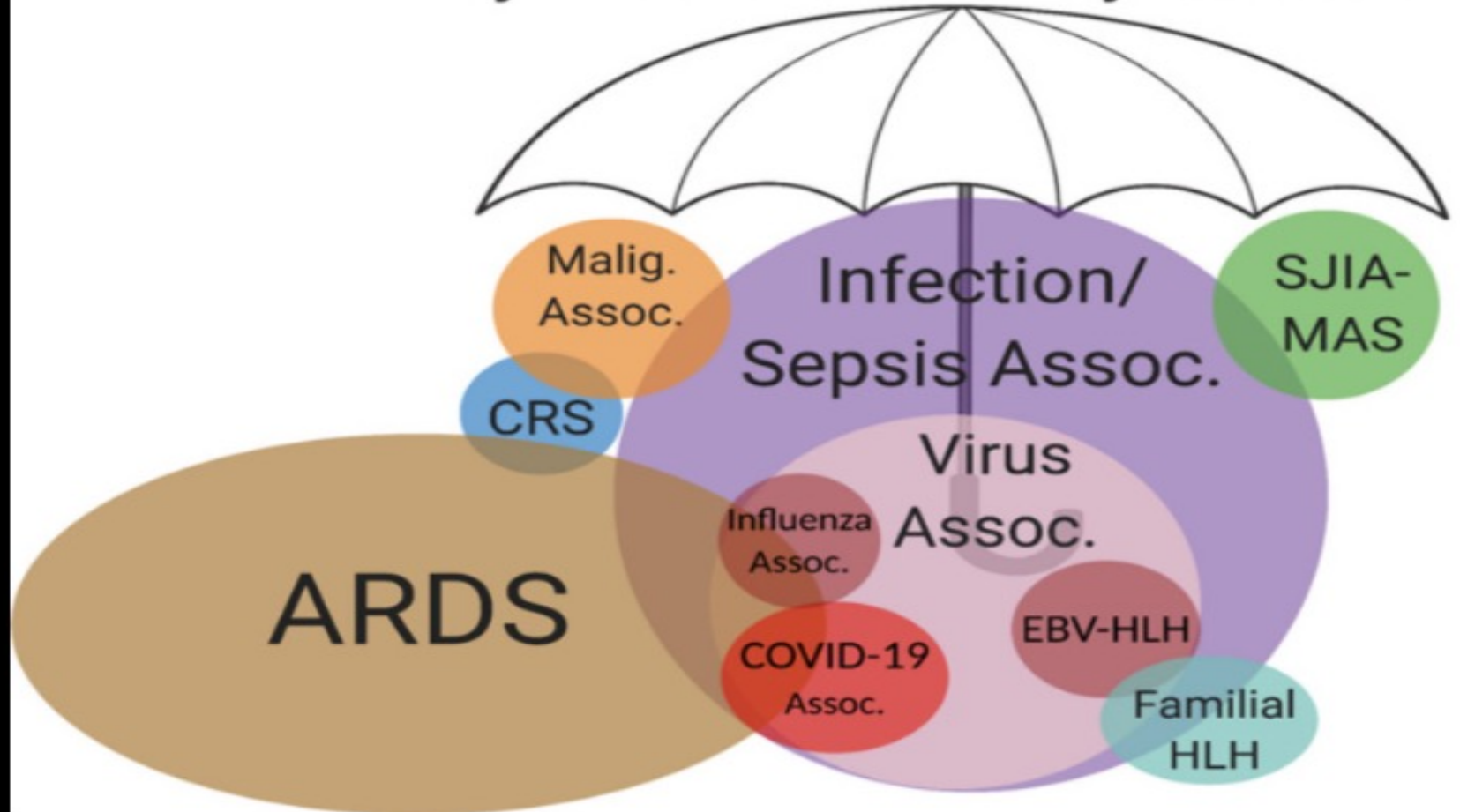
Although it is still unclear if PLWH experience a worse outcome in the case of COVID-19 [1,2].



Dangerous liaisons? The role of inflammation and comorbidities in HIV and SARS-CoV-2 infection

Paolo Maggi , Elena Ricci , Vincenzo Messina , Angela Salzillo , Filomena Simeone , Angelo Iodice & Giuseppe Vittorio Socio

Cytokine Storm Syndromes

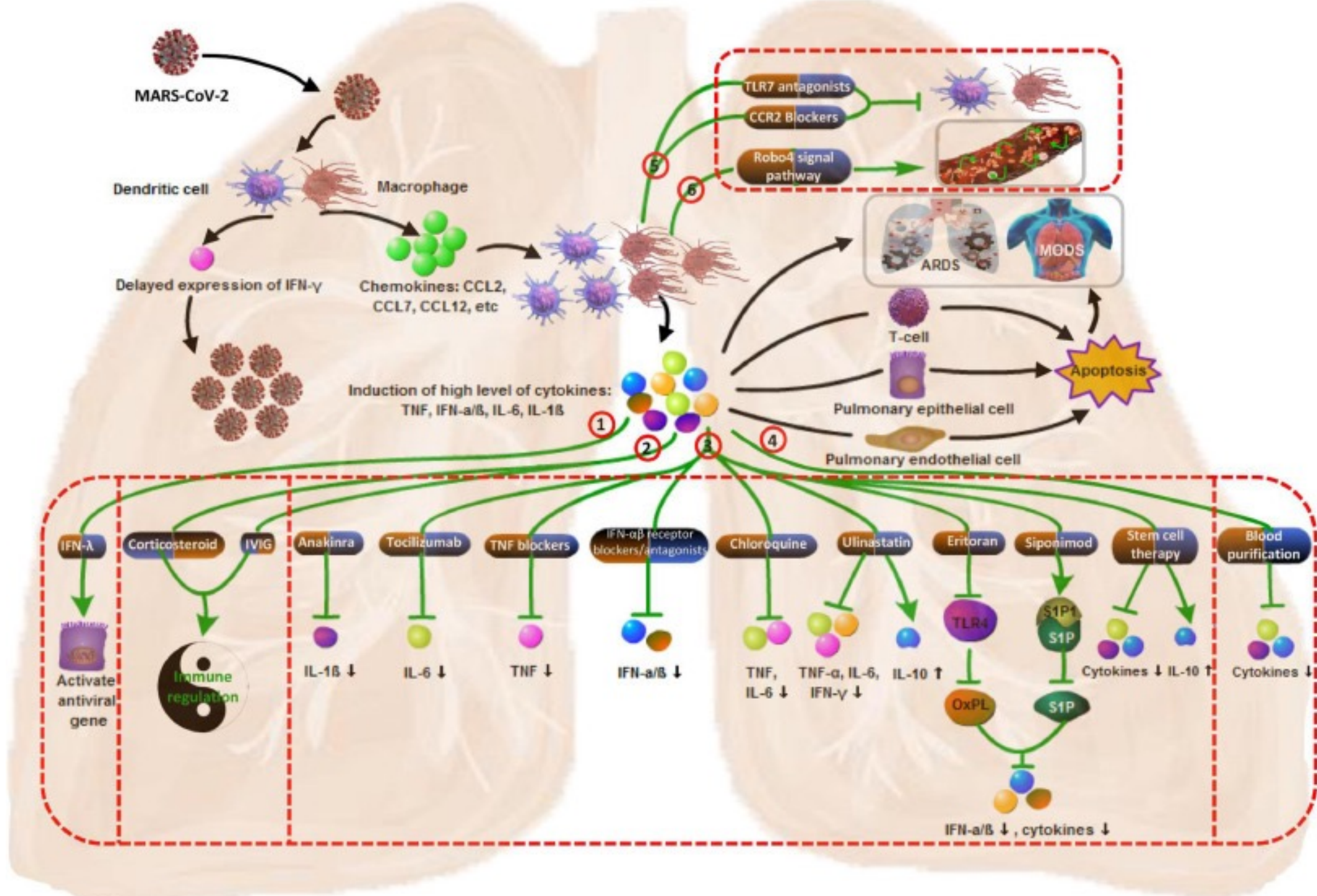


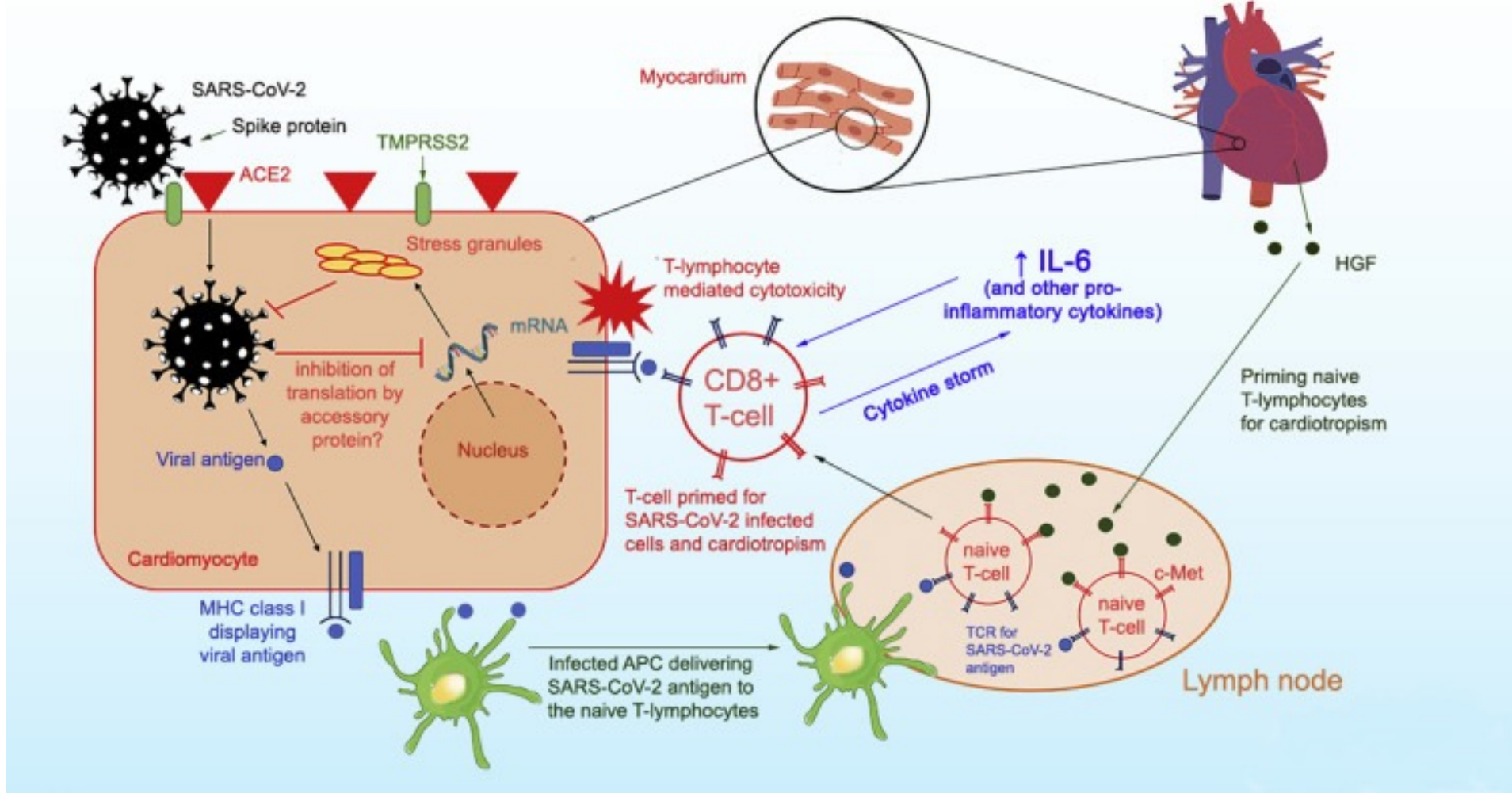
[See this image and copyright information in PMC](#)

Figure 1 The family of conditions characterized by cytokine storm. Malig. = malignancy; Assoc. = associations; SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CRS = cytokine release syndrome; ARDS = acute respiratory distress syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.



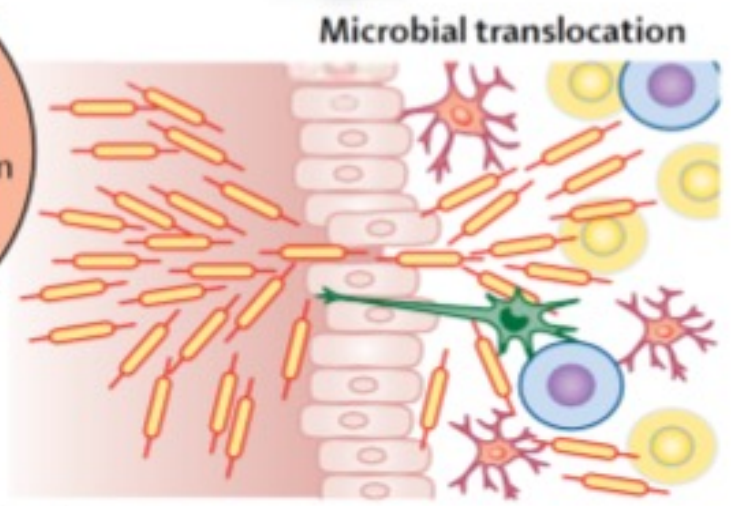
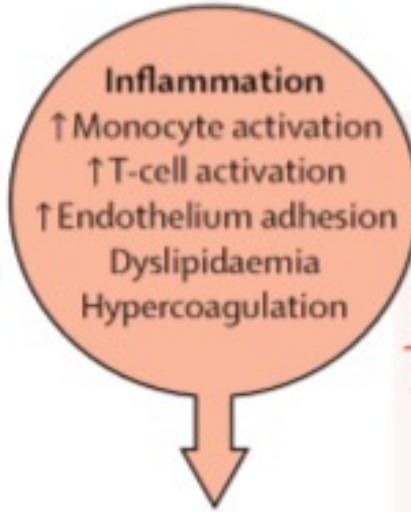
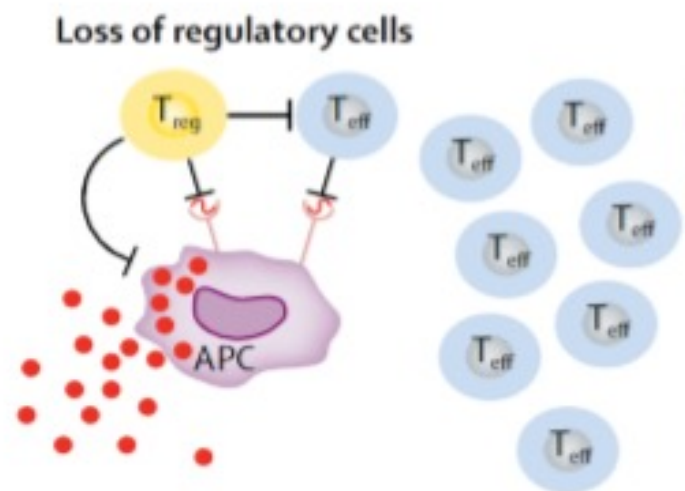
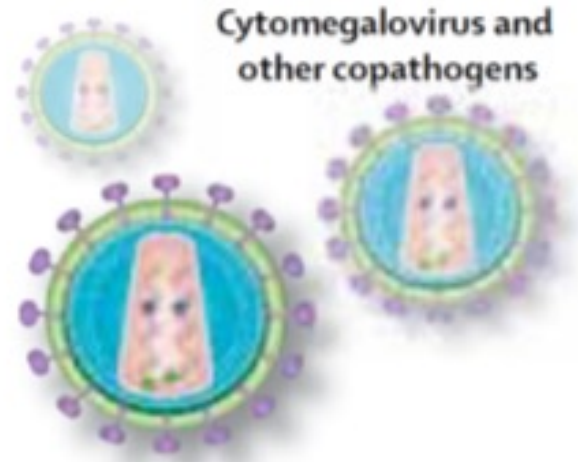
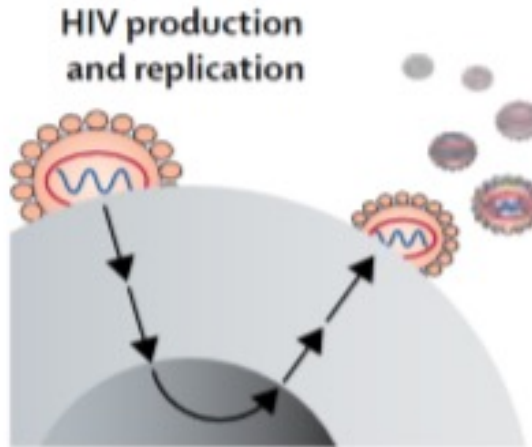
Too much of a good thing...





HIV: a cytokine breeze





Comorbidities

(cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis, neurocognitive disease)

A1
Pa:

Inflammation and comorbidity in HIV

- **DC signs.** (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin)
- **sCD14** (macrophages), **sCD163** (monocytes/macrophages)
- D-dimer
- Soluble TNF receptors 1 and 2
- IL-6

Summary table. Markers of inflammation and comorbidities in SARS-CoV-2 and HIV infection.

Marker	SARS-CoV-2	HIV
IL-2 r	Increased	Reduced
IL-6	Increased	Increased
TNF-a	Increased	Increased
IL-17	Increased	Reduced
D-dimer	Increased	Increased
DC SIGNS	Favors CRS	Favors HIV access
CD4+ cells	Decreased	Decreased
Th17	Increased	Decreased
Comorbidity		
Diabetes	Favors CRS	Favored by HIV
Cardiovascular disease	Favors CRS	Favored by HIV
Coagulation disturbances	Favors CRS	Favored by HIV
Metabolic syndrome	Favors CRS	Favored by HIV
Vitamin D deficiency	Favors CRS (?)	Favors disease progression

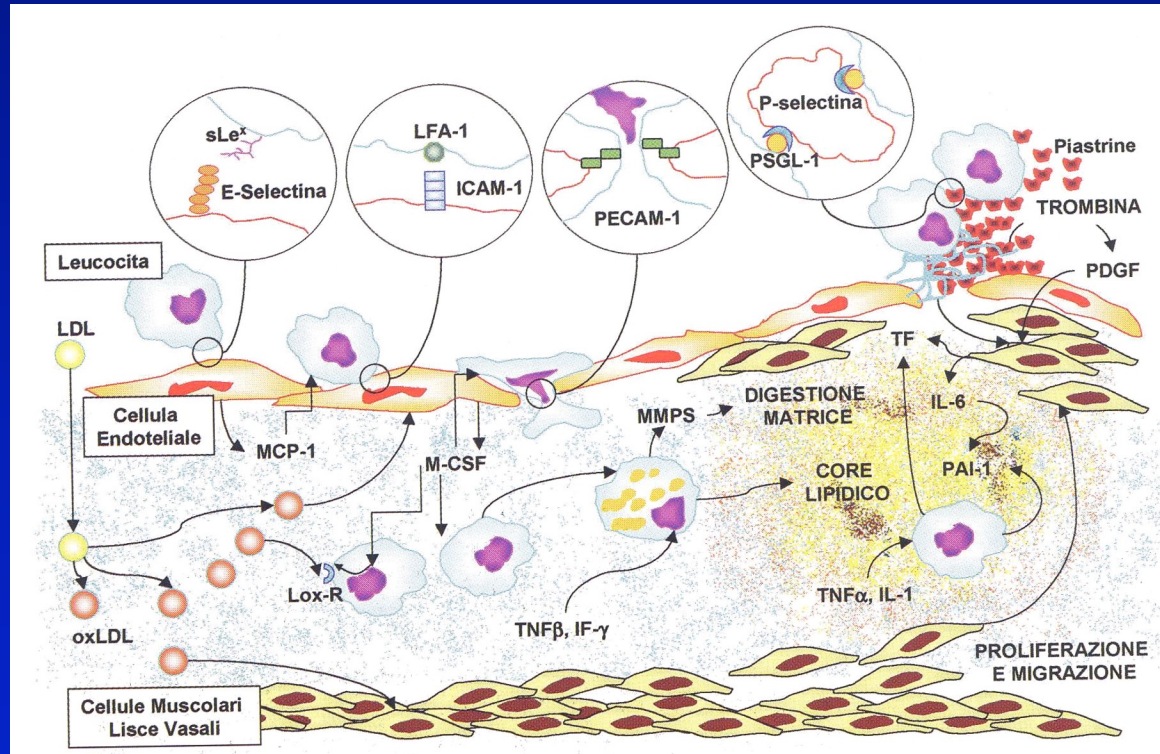
Effetti sull'Endotelio del Processo Infiammatorio

Ridotta biodisponibilità di NO

Aumentata sintesi di Endotelina-1

Effetto protrombotico attivazione del TF

Aumento di O_2^- e dei ROS



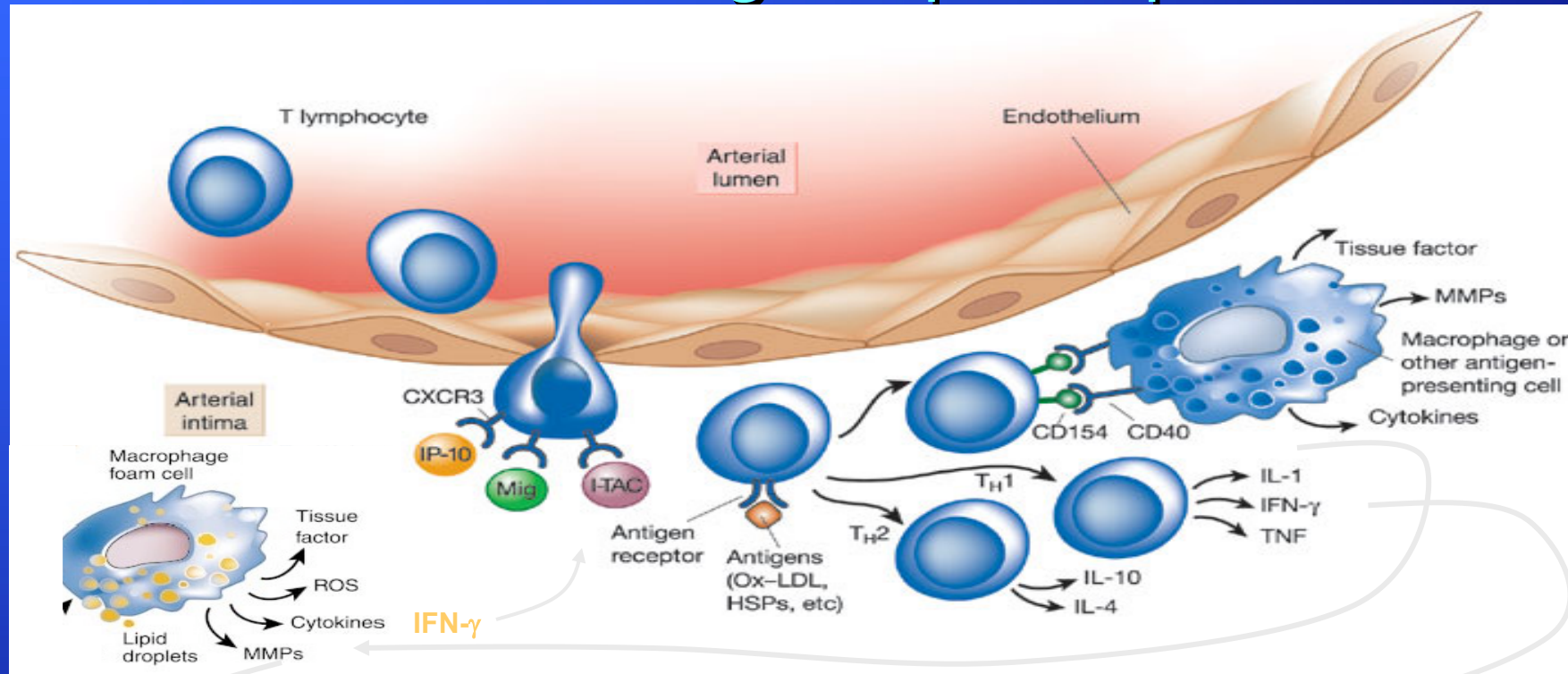
Aumentata migrazione e proliferazione delle CML. Attivazione del PDGF

Aumentata adesività tra Leucociti e Endotelio. Aumentata produzione di IL-6 e di CRP

Attivazione della Matrix Metalloproteinas e attivazione dei Macrofagi

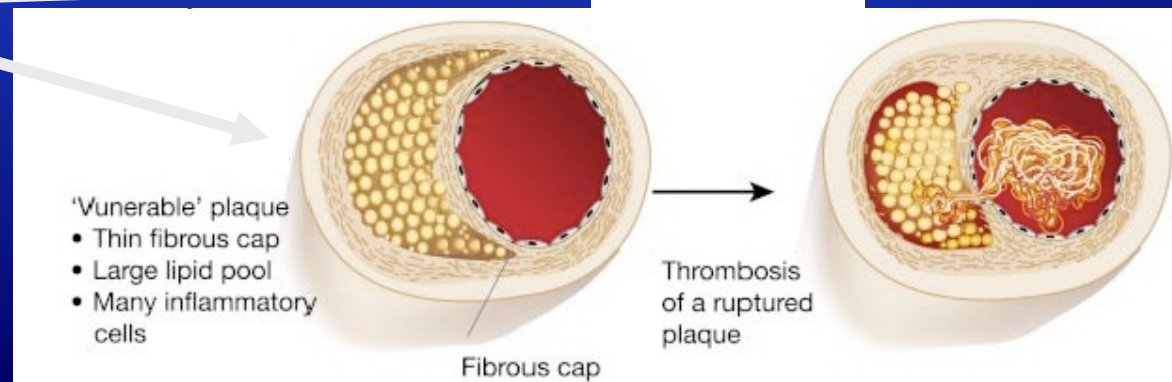


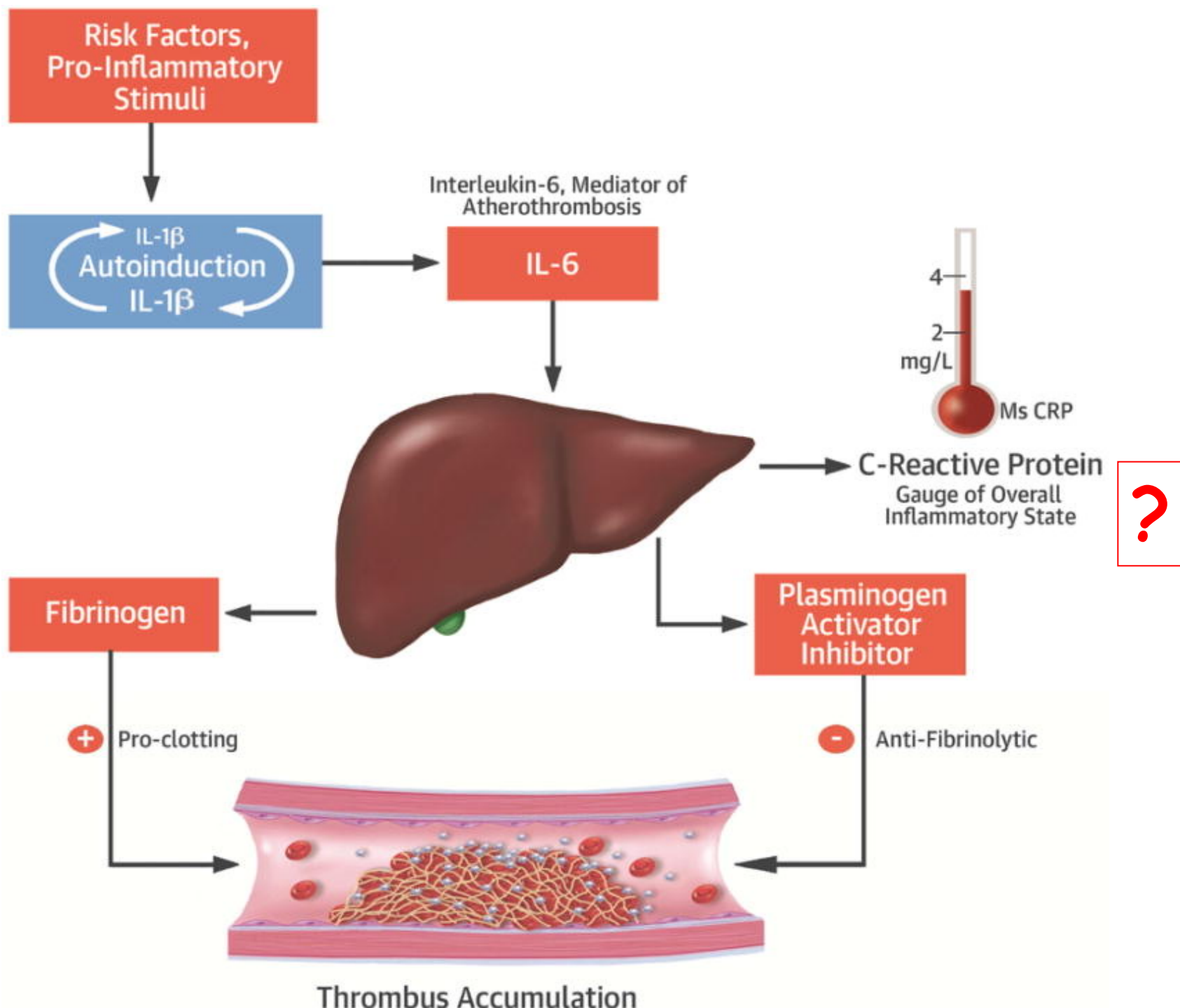
T-lymphocytes and Macrophages Interact In Promoting Plaque Rupture



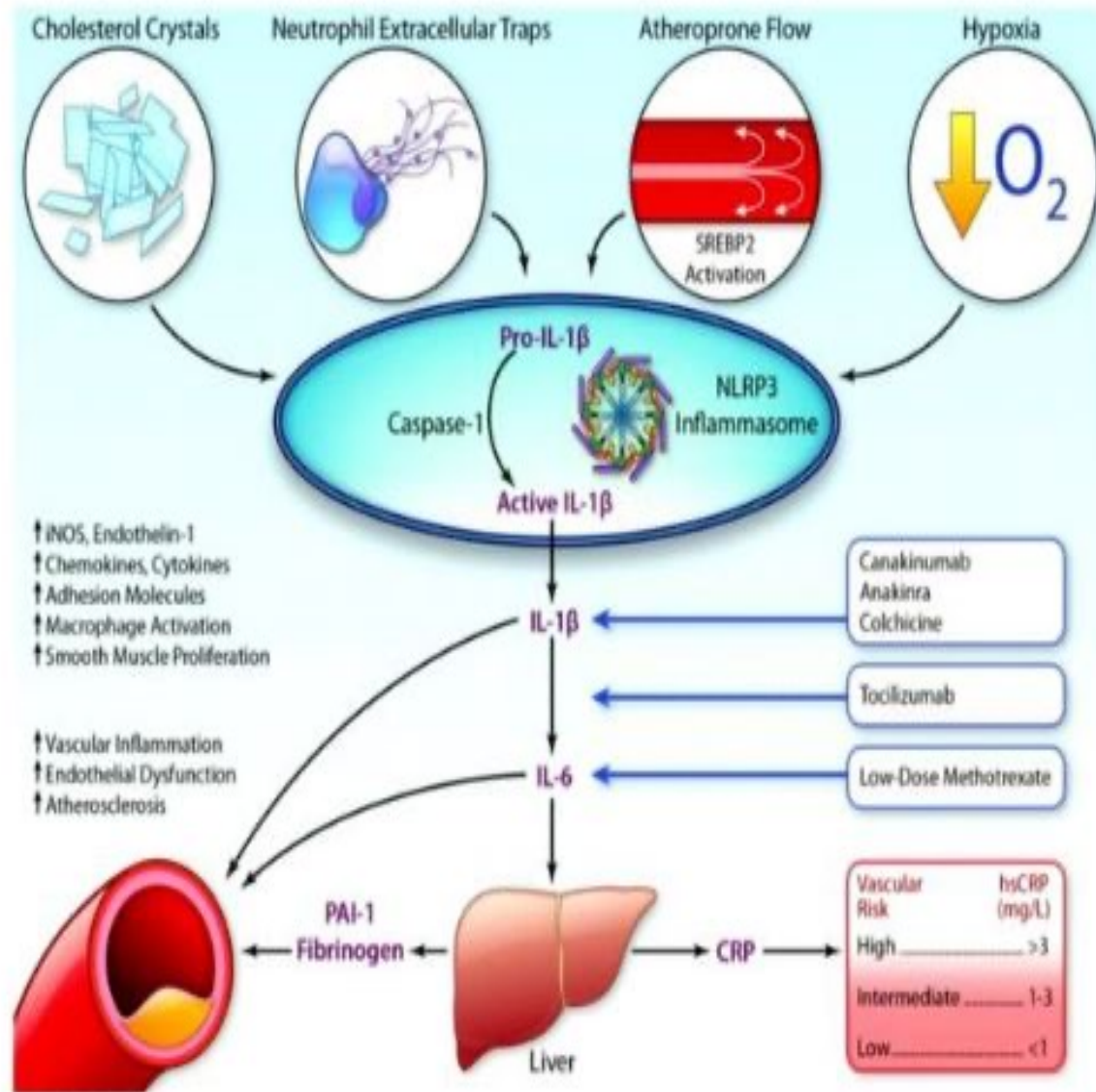
Collagen degrading enzymes \uparrow

Collagen formation \downarrow

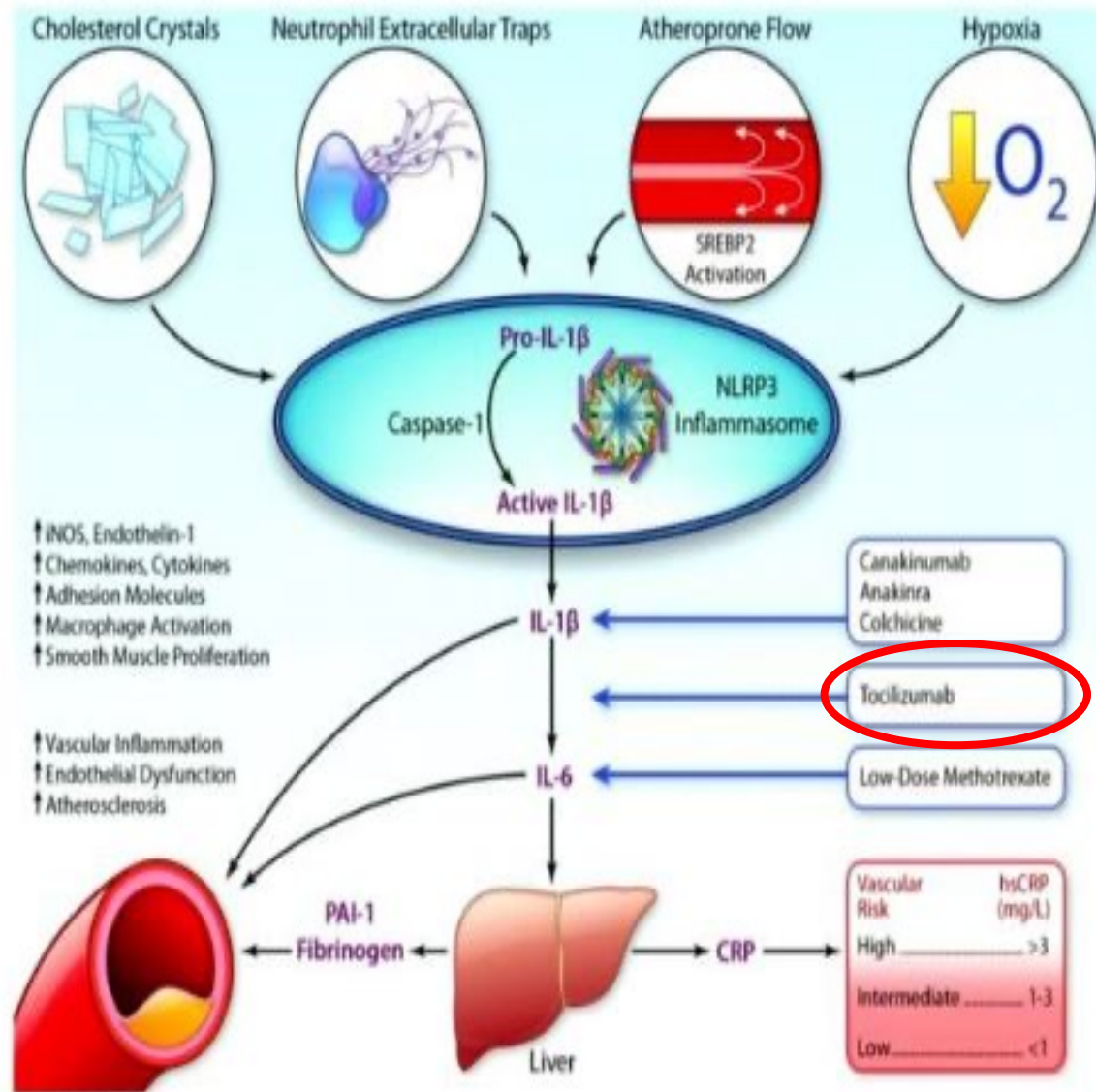




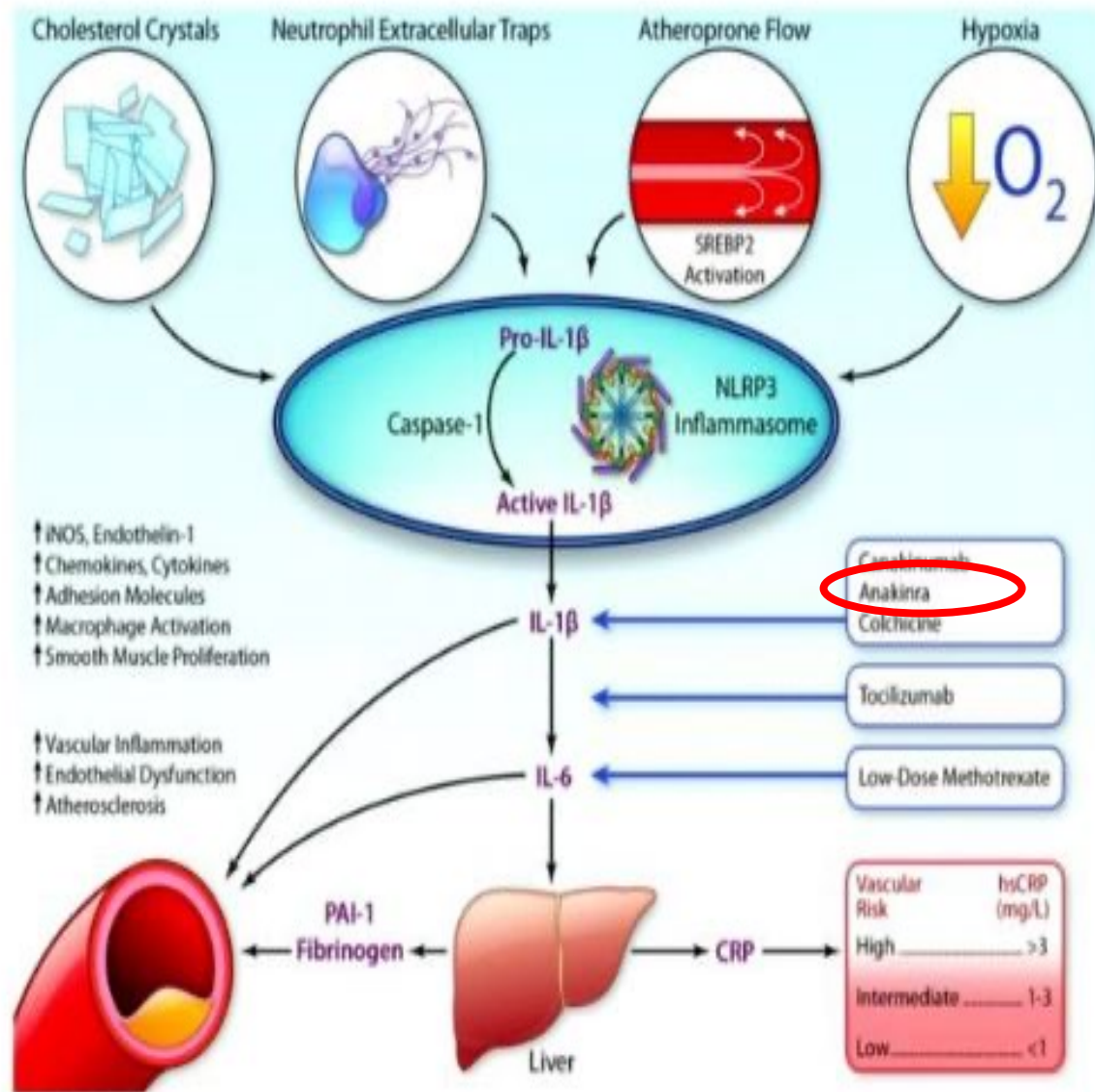
Targeting inflammation: Moving upstream



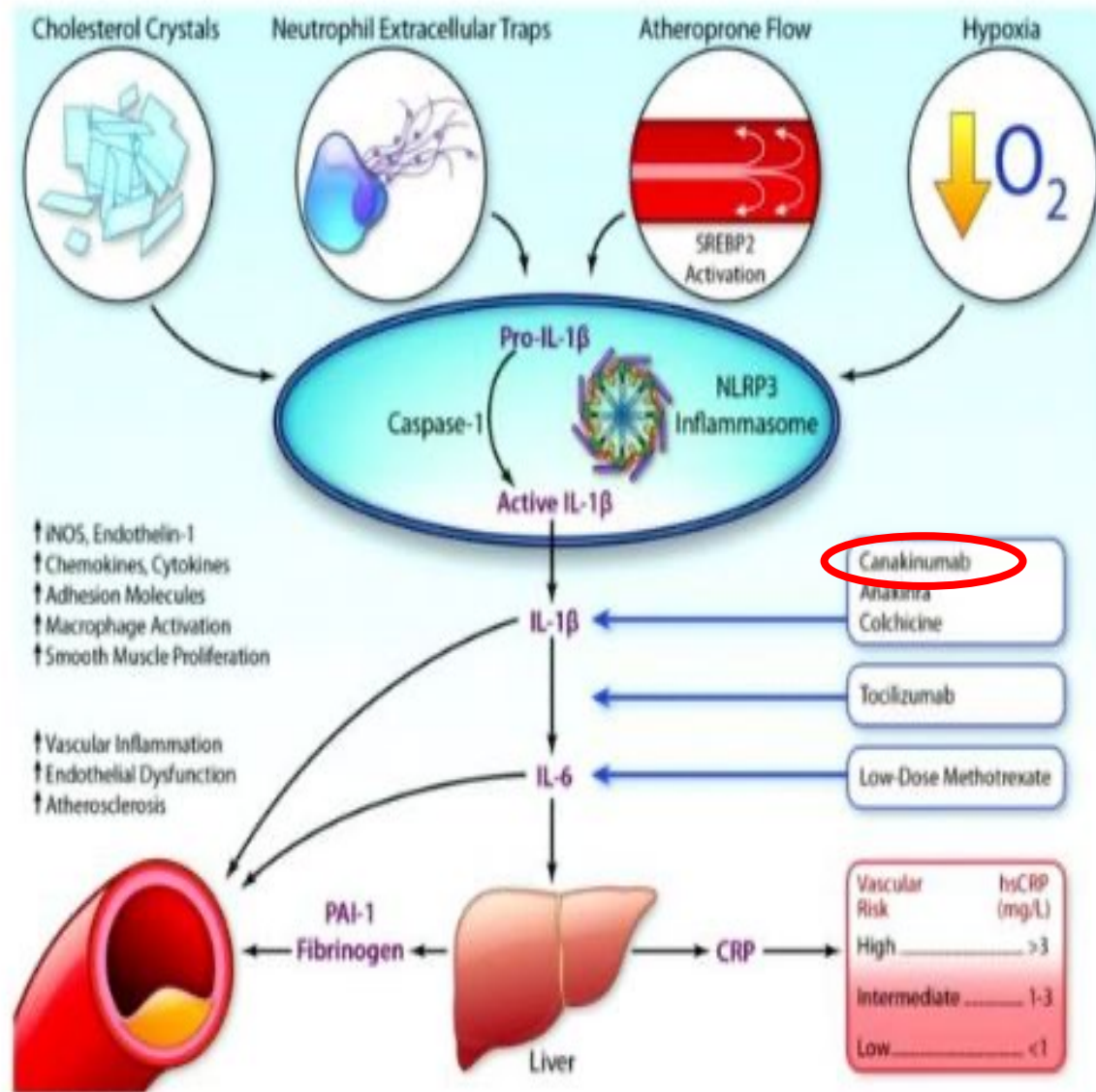
Targeting inflammation: Moving upstream



Targeting inflammation: Moving upstream



Targeting inflammation: Moving upstream








Journal of the American College of Cardiology

Volume 72, Issue 22, 4 December 2018, Pages 2809-2811



Letters

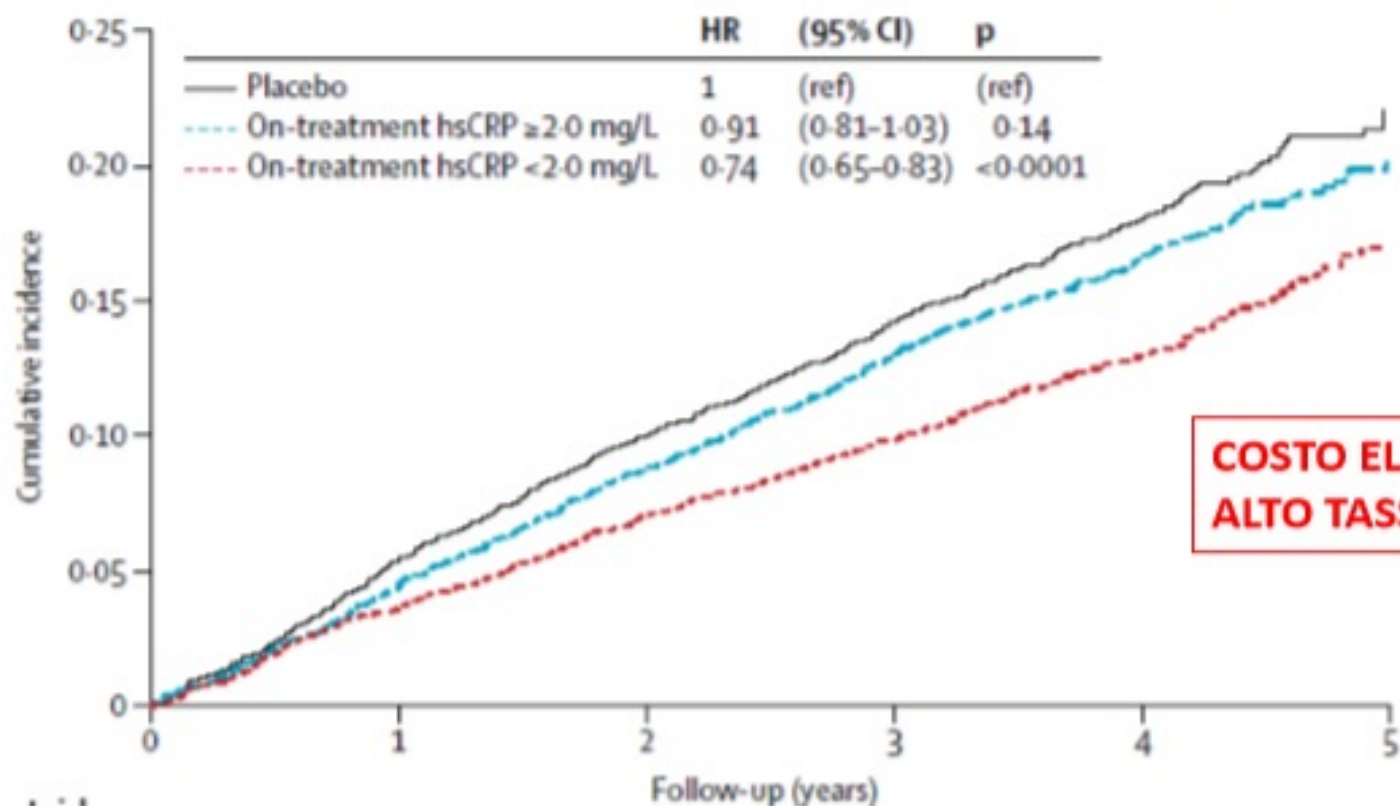
IL-1 β Inhibition Reduces Atherosclerotic Inflammation in HIV Infection

Priscilla Y. Hsue MD   , Danny Li BS, Yifei Ma MS, Amorina Ishai MD, Maura Manion MD, PhD, Matthias Nahrendorf MD, Peter Ganz MD, Paul M Ridker MD, Steven G. Deeks MD, Ahmed Tawakol MD

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS study

- 10,061 pts with previous MI AND hsCRP ≥ 2 mg/l
- Primary end point: non fatal MI, non fatal stroke, or CV death



**COSTO ELEVATO (\$200.000/anno)
ALTO TASSO DI INFEZIONI FATALI**

Ridker, Lancet 2018

Summary table. Markers of inflammation and comorbidities in SARS-CoV-2 and HIV infection.

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IL-6	Increased	Increased
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D-dimer	Increased	Increased
DC SIGNS	Favors CRS	Favors HIV access
CD4+ cells	Decreased	Decreased
Th17	Increased	Decreased

Comorbidity

Diabetes	Favors CRS	Favored by HIV
Cardiovascular disease	Favors CRS	Favored by HIV
Coagulation disturbances	Favors CRS	Favored by HIV
Metabolic syndrome	Favors CRS	Favored by HIV
Vitamin D deficiency	Favors CRS (?)	Favors disease progression

PLoS One
2020;15:e0238215
Ssentongo P, et al.

Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis.

the presence of:

- cancer
- CVD
- congestive heart failure
- hypertension
- diabetes
- and CKD

increased the mortality risk in COVID-19 patients.



Diabetes Metab.

2020 Oct;46(5):403-405. doi: 10.1016/j.diabet.2020.05.005.

Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients.

Marfella R, Paolisso P, Sardu C, Bergamaschi L, D'Angelo EC, Barbieri M, Rizzo MR, Messina V, **Maggi P**, Coppola N, Pizzi C, Biffi M, Viale P, Galié N, Paolisso G.

on 475 patients positive for COVID-19, it was observed that **hyperglycemic patients** (even if on-diabetic) vs. normoglycemic patients had **higher IL-6 levels**, persisting after TCZ administration. In hyperglycemic patients, **higher L-6 levels lessened the effects of TCZ** while the TCZ effect lost significance when IL-6 levels were added to the Cox regression model. In both diabetic and non-diabetic patients, evidence suggested that COVID-19 was not optimally managed during hyperglycemia.



Diabetes Care

2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723.

Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control?

Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, **Maggi P**, Coppola N, Paolisso G, Marfella R.



Diabetes Obes Metab

Marfella R, D'Onofrio N, Sardu C, Scisciola L, **Maggi P**, Coppola N, et al.
2021 Sep 8. doi: 10.1111/dom.14547.

**Does poor glycemic control affect the immunogenicity of COVID-19
vaccination in patients with Type 2 Diabetes: The CAVEAT study.**

Glycaemic control is associated with SARS-CoV-2 breakthrough infections in vaccinated patients with type 2 diabetes

[Raffaele Marfella](#)^{✉1,2}, [Celestino Sardu](#)¹, [Nunzia D'Onofrio](#)¹, [Francesco Prattichizzo](#)³, [Lucia Scisciola](#)¹

[Vincenzo Messina](#)⁴, [Rosalba La Grotta](#)³, [Maria Luisa Balestrieri](#)¹, [Paolo Maggi](#)¹, [Claudio Napoli](#)¹, [Antonio Ceriello](#)^{✉3} and

[Giuseppe Paolisso](#)^{1,2}

Abstract

[Go to:](#) ▶

Patients with type 2 diabetes (T2D) are characterized by blunted immune responses, which are affected by glycaemic control. Whether glycaemic control influences the response to COVID-19 vaccines and the incidence of SARS-CoV-2 breakthrough infections is unknown. Here we show that poor glycaemic control, assessed as mean HbA1c in the post-vaccination period, is associated with lower immune responses and an increased incidence of SARS-CoV-2 breakthrough infections in T2D patients vaccinated with mRNA-BNT162b2. We report data from a prospective observational study enrolling healthcare and educator workers with T2D receiving the mRNA-BNT162b2 vaccine in Campania (Italy) and followed for one year (5 visits, follow-up 346 ± 49 days) after one full vaccination cycle. Considering the 494 subjects completing the study, patients with good glycaemic control (HbA1c one-year mean < 7%) show a higher virus-neutralizing antibody capacity and a better CD4 + T/cytokine response, compared with those with poor control (HbA1c one-year mean ≥ 7%). The one-year mean of HbA1c is linearly associated with the incidence of breakthrough infections (Beta = 0.068; 95% confidence interval [CI], 0.032-0.103; $p < 0.001$). The comparison of patients with poor and good glycaemic control through Cox regression also show an increased risk for patients with poor control (adjusted hazard ratio [HR], 0.261; 95% CI, 0.097-0.700; $p = 0.008$). Among other factors, only smoking (HR = 0.290, CI 0.146-0.576 for non-smokers; $p < 0.001$) and sex (HR = 0.105, CI 0.035-0.317 for females; $p < 0.001$) are significantly associated with the incidence of breakthrough infections.



J Am Heart Assoc.

2020 Sep;9(17):e016948. doi: 10.1161/JAHA.120.016948

Sardu C, **Maggi P**, Messina V, Iuliano P, Sardu A, Iovinella V, Paolisso G, Marfella R.

Could Anti-Hypertensive Drug Therapy Affect the Clinical Prognosis of Hypertensive Patients With COVID-19 Infection? Data From Centers of Southern Italy

Anti-hypertensive drugs didn't affect the prognosis in patients with COVID-19. Lowest values of left ventricle ejection fraction predicted deaths, while **highest values of interleukin-6** predicted the admission to intensive care unit, mechanical ventilation, heart injuries, and deaths



BMC Cardiovasc Disord

2020;20:373. <https://doi.org/10.1186/s12872-020-01658-z>.

Sardu C, Marfella R, **Maggi P**, Messina V, Cirillo P, Codella V, et al.
Implications of ABO blood group in hypertensive patients with covid-19.

Overall, these data indicate that individuals with hypertension and COVID-19 had significantly **higher values of prothrombotic indexes**, as well as **higher rates of cardiac injury and deaths**, if they **were in the non-O blood group**, in comparison to the O group.

Tempo di bilanci

Conflictin
g
Discordant



Epidemiology

- According to meta-analysis data, the global pooled prevalence of PWH among COVID-19 cases is estimated to be 2%.
- Europe 0.5%
- North America 1.2%
- Africa 11%
- Asia 1%

The high rates in North America can be attributed to the fact that studies from the USA were represented mainly by studies from **the states of New York and Georgia**, which are known for higher HIV positivity rates in the population. The highest prevalence from Africa is also explained by the contribution of data from **eastern and southern Africa**, regions highly affected by the HIV pandemic.

- Other large clinical cohorts have shown that **although PWH are more likely to be tested for SARS-CoV-2, there is no evidence of higher positivity rates compared to PWoH.**

Park, L.S. SARS-CoV-2 Testing and Positivity Among Persons with and Without HIV in 6 US Cohorts. *Am. J. Ther.* **2022**, *90*, 249–255.

Rasmussen, L.D. Outcomes following severe acute respiratory syndrome coronavirus 2 infection among individuals with and without HIV in Denmark. *Aids* **2022**, *37*, 311–321.

- **Prolonged viral shedding** might be detected in the setting of prolonged HIV infection, low CD4 counts and unsuppressed viral load, which has previously been described in immunocompromised hosts .

Wang, W.; Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* **2020**, *323*, 1843–1844.

Aydillo, T. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. *N. Engl. J. Med.* **2020**, *383*, 2586–2588.

- PWH rates of **hospital admission range from 0.7% to 1.9%**



Miró, J.M. COVID-19 in patients with HIV—Authors' reply. *Lancet HIV* 2020, 7, e383–e384

- While findings from case series and larger studies did not suggest increased rates of hospital admission in this patient population

Shaley, N. Clinical Characteristics and Outcomes in People Living with Human Immunodeficiency Virus Hospitalized for Coronavirus Disease 2019. *Clin. Infect. Dis.* 2020, 71, 2294–2297.

Richardson, S. The Northwell COVID-19 Research Consortium. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA* 2020, 323, 2052–2059



- Another study in New York showed that HIV infection alone is associated with an increased risk for severe disease and hospitalization, while **the risk of hospitalization was higher among those with advanced HIV disease**

Tesoriero, J.M. COVID-19 Outcomes Among Persons Living with or Without Diagnosed HIV Infection in New York State. *JAMA Netw. Open* 2021, 4, e2037069.



- Results from a **meta-analysis of six studies** showed that PWH are indeed more likely to be hospitalized due to COVID-19 compared to PWhoH (**OR: 1.49**; 95% CI 1.01-2.21)



Danwang, C.; Outcomes of patients with HIV and COVID-19 co-infection: A systematic review and meta-analysis. *AIDS Res. Ther.* 2022, 19, 3

Clinical Outcomes

- Data regarding the clinical outcomes of COVID-19 in PWH have been conflicting, with discordant results between different regions and within specific geographical territories.
- Early in the course of the pandemic, single-center studies based on small cohorts of patients showed that **PWH had a similar or even lower (Gervasoni) risk of severe disease and mortality, compared with PWoH.**

Inciarte, A. Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: A single-center, prospective observational study. *Aids* **2020**, *34*, 1775–1780.

Vizcarra, P. Description of COVID-19 in HIV-infected individuals: A single-centre, prospective cohort. *Lancet HIV* **2020**, *7*, e554–e564.

Karmen-Tuohy, S. Outcomes Among HIV-Positive Patients Hospitalized With COVID-19. *JAIDS J. Acquir. Immune Defic. Syndr.* **2020**, *85*, 6–10.

Gervasoni, C. Clinical Features and Outcomes of Patients with Human Immunodeficiency Virus With COVID-19. *Clin. Infect. Dis.* **2020**, *71*, 2276–2278.



AIDS

2020; Oct 1;34(12):1775-178034:1775–80

Inciarte A, et al.

Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-center, prospective observational study.

PLWH diagnosed with COVID-19 **were not different from the rest of the Barcelona HIV cohort**. Clinical presentation, severity of the disease, and mortality did not depend on HIV-related or ART-related factors. **The standardized incidence rate of COVID-19 was lower in PLWH than in the Barcelona general population**, although no comparison of mortality rates was performed between the two groups.



JAIDS
2020 Sep 1;85(1):6-10.
Karmen-Tuohy S, et al.

Outcomes among HIV-positive patients hospitalized with COVID-19.

This finding was confirmed in a study comparing 42 HIV-negative and 21 HIV-positive COVID-19 patients. (NY City) **SARS-CoV-2-HIV coinfection did not have a significant impact on clinical features, course of hospitalization, or outcomes** as compared to SARS-CoV-2 infection alone.



Artists: [unreadable]
Artists: [unreadable]
Artists: [unreadable]

- Conversely, collective data from several centers in the UK showed that PWH had a **2.9 times higher risk of COVID-19 death** than PWoH after adjusting for age and gender.
- Interestingly, among PWH, the risk was significantly greater for people of **black ethnicity** compared to non-black ethnicity, with a hazard ratio (HR) of 4.31 versus 1.84.



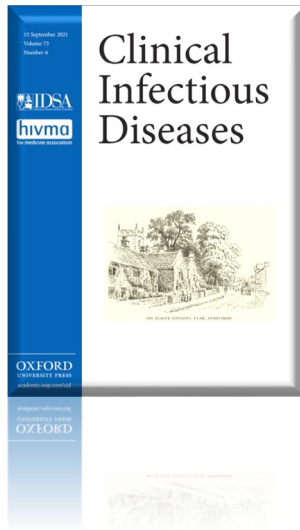
AIDS

2020; Nov 34:F3–8

Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR.

Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study.

In a study comparing COVID-19 outcome between PLWH and non-HIV subjects crude COVID-19 mortality (West Virginia) resulted higher in PLWH. However, as regards COVID-19 outcomes, propensity matched analyses revealed no difference in HIV infection status, suggesting that **higher mortality was likely driven by higher number of comorbidities.**



Clin Infect Dis. 2020
Geretti AM, et al.

Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO clinical characterization protocol (UK): a prospective observational study.

On the contrary, a comparison between HIV-negative and positive patients, admitted in 207 hospitals across the United Kingdom, showed a **higher day 28 mortality in PLWH**, after considering potential risk factors such as age, sex, comorbidities and need for oxygen at presentation. **In particular, in people aged less than 60 years the adjusted hazard ratio was 2.87 an increased risk due to HIV status**



AIDS.

2020 Nov 1;34(13):1983-1985

Di Biagio A, Ricci E, Calza L, Squillace N, Menzaghi B, Rusconi S, Orofino G, Bargiacchi O, Molteni C, Valsecchi L, Cenderello G, Ferrara S, Saracino A, **Maggi P**, Falasca K, Taramasso L, Bonfanti P; CISAI Study group.

Factors associated with hospital admission for COVID-19 in HIV patients.

Di Biagio et al. described the epidemiological, clinical features and the outcomes of 69 HIV patients with confirmed SARSCoV-2 in a network of Italian centers. Characteristics of patients and median days between symptoms and diagnosis were similar by hospital admission. **Admitted patients had lower current lymphocytes count and nadir CD4 cells, values that also correlated to the worse outcome of COVID-19. Antiretroviral drugs and disease severity did not seem to be associated.**

- **Meta-analyses** have had inconsistent findings, with some showing increased odds of mortality among PWH



Mellor, M.M. Risk of adverse coronavirus disease 2019 outcomes for people living with HIV. *Aids* **2021**, *35*, F1–F10.

Hariyanto, T.I. Human immunodeficiency virus and mortality from coronavirus disease 2019: A systematic review and meta-analysis. *South. Afr. J. HIV Med.* **2021**, *22*, 7.

Ssentongo, P.; Epidemiology and outcomes of COVID-19 in HIV-infected individuals: A systematic review and meta-analysis. *Sci. Rep.* **2021**, *11*, 6283.

Wang, Y. Systematic Review and Meta-Analyses of The Interaction Between HIV Infection And COVID-19: Two Years' Evidence Summary. *Front. Immunol.* **2022**, *13*, 864838.

- And others showing no differences in outcomes between HIV and non-HIV populations



Dzinamarira, T. Risk of mortality in HIV-infected COVID-19 patients: A systematic review and meta-analysis. *J. Infect. Public Health* **2022**, *15*, 654–661.

- The largest international multicenter study on hospitalized patients with COVID-19 to date, with data collected by the **WHO Global Clinical Platform for COVID-19**, came to the conclusion that **PWH were 15% more likely to develop severe or critical COVID-19 and were 38% more likely to die in hospital compared to PWoH**



Bertagnolio, S. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: Analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV* **2022**, *9*, e486–e495

- Data from the largest cohort of **US COVID-19** cases showed that PWH had a **higher prevalence of all comorbidities** compared to PWoH

Yang, X. Associations between HIV infection and clinical spectrum of COVID-19: A population level analysis based on US National COVID Cohort Collaborative (N3C) data. *Lancet HIV* **2021**, *8*, e690–e700.

- A multicenter study proved that **viremia** was significantly associated with COVID-19 disease severity and that **CD4 a T-cell count < 200 cells/mm³** is a factor that leads to increased mortality and increased probability of admission to hospital

Shapiro, A.E. Factors Associated with Severity of COVID-19 Disease in a Multicenter Cohort of People With HIV in the United States, March–December 2020. *Am. J. Ther.* **2022**, *90*, 369–376.

- Data from the US National COVID Cohort Collaborative showed that a **lower CD4 cell count** among PWH is associated with a higher risk of adverse COVID-19 outcomes, and **unsuppressed viral load** had an increased risk of hospitalization but not death .

Yang, X. Associations between HIV infection and clinical spectrum of COVID-19: A population level analysis based on US National COVID Cohort Collaborative (N3C) data. *Lancet HIV* **2021**, *8*, e690–e700.

- Other studies confirm the role of **unsuppressed viral load** in poor COVID-19 outcomes

Bertagnolio, S. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: Analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV* **2022**, *9*, e486–e495

Nomah, D.K. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: A retrospective cohort study. *Lancet HIV* **2021**, *8*, e701–e710.

The vaccination era



- Fully vaccinated PWH were not found to be at increased risk of severe illness compared to PWoH.
- Nevertheless, the risk of severe breakthrough illness was 59% higher in PWH with a CD4 cell count < 350 cells/ μ L compared to PWoH. Among PWH, previous COVID-19 seemed to be protective .

Lang, R. Analysis of Severe Illness After Postvaccination COVID-19 Breakthrough Among Adults with and Without HIV in the US. *JAMA Netw. Open* 2022, 5, e2236397.

Dandachi, D. Characteristics, Comorbidities, and Outcomes in a Multicenter Registry of Patients with Human Immunodeficiency Virus and Coronavirus Disease 2019. *Clin. Infect. Dis.* 2021, 73, e1964–e1972.

Kamis, K.F.M. Risk Factors for Hospitalization in People with HIV and COVID-19. *Am. J. Ther.* 2021, 88, e22.

- CD4 counts < 250 cells/mL have been associated with decreased immunogenicity, and it appears that humoral immunity conferred through vaccination wanes faster in PWH, making booster vaccination doses more important.

Yin, J. Immunogenicity and efficacy of COVID-19 vaccines in people living with HIV: A systematic review and meta-analysis. *Int. J. Infect. Dis.* 2022, 124, 212–223.

- Recent studies show that **PWH are able to mount a strong humoral response to COVID-19 vaccines**, especially if they are on ART with suppressed viral loads, higher CD4 cell counts, and higher CD4/CD8 ratios.

Chun, H.M. A Systematic Review of COVID-19 Vaccine Antibody Responses in People With HIV. *Open Forum Infect. Dis.* **2022**, *9*, ofac579.

- **Even under the condition of low CD4 counts**, despite low humoral responses, the CD4 cellular immune response to vaccination seems to be preserved.

Bessen, C. Impact of SARS-CoV-2 vaccination on systemic immune responses in people living with HIV. *Front. Immunol.* **2022**, *13*, 1049070.

- **All guidelines recommend that PWH be vaccinated fully and with booster doses against SARS-CoV-2.**
- **Several studies have shown that the immunogenicity of available vaccines, both in the main vaccination and the booster vaccination, is similar in healthy controls and PWH, especially when CD4 counts are well preserved.**

Merchant, E.A Co-infection with coronavirus disease 2019, previously undiagnosed human immunodeficiency virus, *Pneumocystis jirovecii* pneumonia and cytomegalovirus pneumonitis, with possible immune reconstitution inflammatory syndrome. *Idcases* **2021**, *24*, e01153.

Bertolini, M. COVID-19 associated with AIDS-related disseminated histoplasmosis: A case report. *Int. J. STD AIDS* **2020**, *31*, 1222–1224.

Kingery, J.R. Health Status, Persistent Symptoms, and Effort Intolerance One Year After Acute COVID-19 Infection. *J. Gen. Intern. Med.* **2022**, *37*, 1218–1225.

Peluso, M.J Goldberg, S.A.; Arreguin, M.I.; et al. Postacute sequelae and adaptive immune responses in people with HIV recovering from SARS-CoV-2 infection. *Aids* **2022**, *36*, F7–F16.

Nault, L. COVID-19 vaccine immunogenicity in people living with HIV-1. *Vaccine* **2022**, *40*, 3633–3637.

Vergori, A.;. Immunogenicity to COVID-19 mRNA vaccine third dose in people living with HIV. *Nat. Commun.* **2022**, *13*, 4922.

- **The response to different types of vaccines was reported in a meta-analysis to be similar in PWH.**

Yin, J. Immunogenicity and efficacy of COVID-19 vaccines in people living with HIV: A systematic review and meta-analysis. *Int. J. Infect. Dis.* **2022**, *124*, 212–223.



The impact of ART

- PWH under ART had a less severe clinical presentation of COVID-19 than the general population regarding better prognosis and faster resolution of symptoms

Bertagnolio, S. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: Analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV* 2022, 9, e486–e495

- Data from a multicenter cohort from Madrid HIV clinics with more than 75,000 participants showed that the risk for COVID-19 hospitalization differed based on **backbone regimens**, with the risk per 10,000 persons at **10.5 for TDF/FTC, 20.3 for TAF/FTC, 23.4 for ABC/3TC, and 20.0 for other regimens.**
- del Amo, J.; Polo, R.; Moreno, S.; Díaz, A.; Martínez, E.; Arribas, J.R.; Jarrín, I.; Hernán, M.A. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy. *Ann. Intern. Med.* 2020, 173, 536–541.



- Other cohorts did not show that ART provided protection against COVID-19 severity

Inciarte, A. Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: A single-center, prospective observational study. *Aids* **2020**, *34*, 1775–1780.

Cabello, A. COVID-19 in people living with HIV: A multicenter case-series study. *Int. J. Infect. Dis.* **2021**, *102*, 310–315.

- Socioeconomic factors play a role in COVID-19 outcomes among PWH. **Racial disparities** in prevalence and outcomes for HIV disease are well described, and a similar pattern of incidence and outcome appears to follow the COVID-19 disease

Williamson, E.J. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **2020**, *584*, 430–436.

- Data indicating **poor outcomes among Black PWH and those living in high-poverty neighborhoods** come from **USA, UK and Paris** .

Meyerowitz, E.A. Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV. *Aids* **2020**, *34*, 1781–1787.

Bhaskaran, K. HIV infection and COVID-19 death: A population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV* **2020**, *8*, e24–e32.

Etienne, N. HIV infection and COVID-19: Risk factors for severe disease. *AIDS* **2020**, *34*, 1771–1774.

In the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study (MACS/WIHS) Combined Cohort Study (MWCCS), where the median age of the population was 57 years, 74% had undetectable HIV viral loads, and the median CD4+ T lymphocyte cell count was 682 cells/mm³, symptom profiles were similar in PWH and HIV seronegative participants:

- headache (23% vs. 24%)
- myalgias (19% vs. 18%)
- shortness of breath (14% vs. 13%)
- chills (12% vs. 10%)
- fever (6% vs. 6%)
- loss of taste or smell (6% vs. 7%)

Rhinorrhea, sore throat and cough, for which prevalence was slightly but significantly lower in PWH.

D'Souza, G. COVID-19 symptoms and SARS-CoV-2 infection among people living with HIV in the US: The MACS/WIHS combined cohort study. *HIV Res. Clin. Trials* **2020**, *21*, 130–139.

- There are cases with poorly controlled HIV or AIDS and OI at the same time.
- Of special interest is co-infection in PWH with **COVID-19 and PJP** since the two infections may present with similar features of exercise desaturation, dry cough and relatively normal chest auscultation on clinical examination.

Coleman, H. Coronavirus disease 2019 and *Pneumocystis jirovecii* pneumonia: A diagnostic dilemma in HIV. *Aids* **2020**, *34*, 1258–1260.

Mang, S. *Pneumocystis jirovecii* Pneumonia and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection in a Patient with Newly Diagnosed HIV-1 Infection. *Clin. Infect. Dis.* **2021**, *72*, 1487–1489.

- Another interesting case involved a patient with **COVID-19 and AIDS-related disseminated histoplasmosis**.

Bertolini, M. COVID-19 associated with AIDS-related disseminated histoplasmosis: A case report. *Int. J. STD AIDS* **2020**, *31*, 1222–1224.

- Also, there has been a case of a person with previously undiagnosed HIV infection who presented with **COVID-19, PJP and CMV pneumonitis simultaneously**. His course was further complicated with immune reconstitution inflammatory syndrome (**IRIS**).

Merchant, E.A. Co-infection with coronavirus disease 2019, previously undiagnosed human immunodeficiency virus, *Pneumocystis jirovecii* pneumonia and cytomegalovirus pneumonitis, with possible immune reconstitution inflammatory syndrome. *Idcases* **2021**, *24*, e01153.

Data available on risk factors for **post-acute COVID-19 syndrome** among PWH are limited

- A retrospective observational cohort study from the US showed that PWH, when adjusting for demographics, comorbidities, and severity of illness, were significantly more likely to report persistent symptoms at least nine months out from diagnosis.

Kingery, J.R. Health Status, Persistent Symptoms, and Effort Intolerance One Year After Acute COVID-19 Infection. *J. Gen. Intern. Med.* **2022**, *37*, 1218–1225.



- A case-control study in the pre-vaccine era found that PWH had **4.01-fold higher odds of post-acute COVID-19 syndrome** when adjusting for age, hospitalization and time since infection .

Peluso, M.J.. Postacute sequelae and adaptive immune responses in people with HIV recovering from SARS-CoV-2 infection. *Aids* **2022**, *36*, F7–F16.

There exists a consensus amongst HIV societies with regards to the treatment of PWH and COVID-19 co-infection

BHIVA, IDSA, EACS, NIH, IAS and DHHS guidelines recommend a standard treatment for COVID-19 in HIV infected individuals:

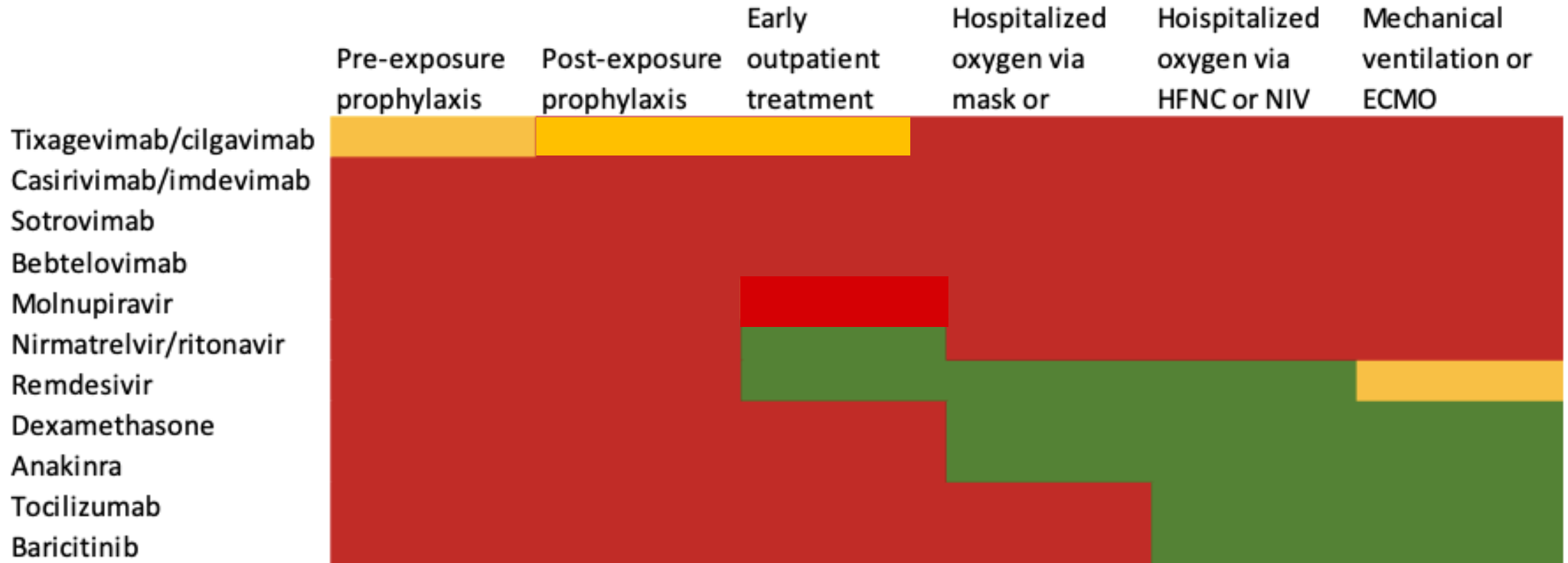


Figure 1. Current guidelines for the treatment of COVID-19. Red: this treatment is no longer recommended. Orange: this treatment is recommended lacking other options or in specific regions and populations. Green: this treatment is recommended for all patients.

Pre-Exposure Prophylaxis

Tixagevimab and cilgavimab (Evusheld) :

- In the PROVENT trial, only a very small fraction of HIV patients participated in the trial, with the authors listing only 15 (0.4%) and 9 (0.5%) participants with "immunosuppressive disease" (without further clarification if any of those were PWH at all) in the AZD7442 and placebo arms, respectively.
- The monoclonal combination has been approved for use in PWH to prevent COVID-19 infection. Tixagevimab/cilgavimab at a dose of 150/150 mg is recommended for individuals with advanced or untreated HIV infection, defined as having CD4 counts < 200 cells/mm³ or a history of an AIDS-defining condition without immune reconstitution or clinical manifestations of symptomatic HIV.

Early Outpatient Treatment Small Molecules

Molnupiravir

- MOVE-OUT registrative trial: 1433 non-hospitalized SARS-CoV-2-PCR-positive participants. **No individuals with HIV infection participated in the trial**, and patients with advanced disease were excluded, in accordance with protocol

Nirmatrelvir/ritonavir (Paxlovid)

- EPIC-HR trial: 2246 participants were randomized **Only one HIV-positive individual participated in the trial.**

Remdesivir

- (ACTT1 trial): 1062 participants were randomized, **only a few immunocompromised patients participated in the trial, and investigators did not disclose if any PWH participated.**

Monoclonal Antibodies

- **Tocilizumab:** in the RECOVERY **fifteen PWH** (seven and eight in each arm) were included.
- **Baricitinib:** JAK 1 and 2 inhibitor. ACTT-2 trial: The authors reported **30 participants with immune deficiency, yet there is no mention if any were PWH.**

Dexamethasone

- In the RECOVERY trial, **12 PWH** took part in the dexamethasone arm and 20 in the control group.

Real-world data

- In the British observational cohort **OpenSAFELY** study, the investigators attempted to compare effectiveness between **sotrovimab and molnupiravir** during a period covering both the Delta and Omicron variants.
- In their primary analysis cohort, they included 6020 patients (3331 in the sotrovimab arm and 2689 in the molnupiravir, with **73 and 118 PWH in each arm**).
- Only a small percentage of patients met the primary endpoint of **hospitalization or death**; 2.05% in the molnupiravir group and 0.96% in the sotrovimab group, comparing the two, showed that sotrovimab was associated with a substantially lower risk compared to treatment with molnupiravir (HR 0.54, 95% CI 0.33 to 0.88, $p = 0.01$)
- **Sotrovimab as an adjunctive to remdesivir** therapy in severely immunocompromised AIDS patients. **Two case reports** suggested that their use of showed a dramatic improvement in symptoms and rapid viral clearance.

Remdesivir

- Recent publication examined **the effect of cobicistat on remdesivir treatment** and found that cobicistat not only has a **moderate antiviral effect** on its own, but it can also synergize and **enhance remdesivir in an animal model** of COVID-19 infection

Shytaz et al. The FDA-Approved Drug Cobicistat Synergizes with Remdesivir to Inhibit SARS-CoV-2 Replication In Vitro and Decreases Viral Titers and Disease Progression in Syrian Hamsters. *Mbio* 2022, 13, e0370521

Nirmatrelvir/ritonavir

- gastrointestinal discomfort
- contraindicated in patients with eGFR < 30 mL/min.
- ART regimens containing ritonavir or cobicistat-boosted medications will exhibit potentially significant interactions that warrant closer monitoring
- significant pill burden

It is however recommended that ART regimens be continued without modifications .

Dexamethasone



- added risk for opportunistic infections, mainly PJP and tuberculosis.
- corticosteroid levels are increased after exposure to ritonavir or
- **Rilpivirine co-administration should be avoided**
- Efavirenz needs, a doubling of the recommended dose of dexamethasone

Anakinra and Tocilizumab

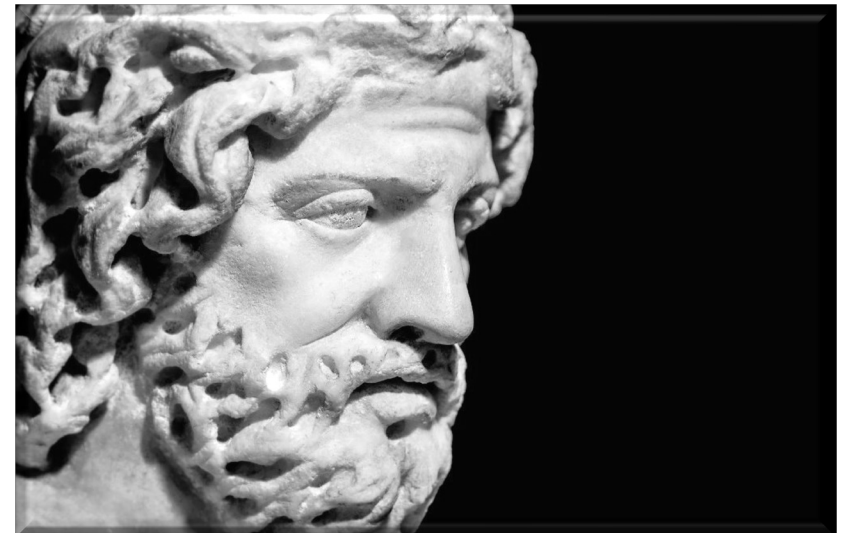
- opportunistic infections.
- hematological toxicity when combined with zidovudine.

Review

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Dimitris Basoulis ¹, Elpida Mastrogianni ², Pantazis-Michail Voutsinas ² and Mina Psychogiou ^{2,*}

«COVID-19 and HIV are reminiscent of Plutarch's Parallel Lives—two different diseases associated with similar media frenzy, fear of the unknown and stigma»



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«COVID-19 and HIV are reminiscent of Plutarch's Parallel Lives—two different diseases associated with similar media frenzy, fear of the unknown and stigma»

«Our hope remains that both pandemics will, in the future, only be part of literature—similar to that of Plutarch—and be extinct from every-day life».

