Don't add fuel to the fire with chloroquine.

1/7. Normal innate **immune response produces reactive oxygen species (ROS) to damage** nucleic acids and proteins of viruses, protozoans, bacterias ... [1,2]

Thus, **this mechanism is common** against coronavirus and malaria.

2/7. Chloroquine **induces ROS production too** [3,4,5] that seems to be helpful against those two infections at the first glance ... [6,7]

3/7. **Glucose-6-phosphate dehydrogenase (G6PD)** is a main enzyme responsible for NADPH production involved in mechanisms of **antioxidant defense** [8,9] because **ROS damages the host also** [10].

4/7. G6PD deficient subjects are vulnerable to oxidative stress [11] that is why they are resistant to malaria [12].

G6pd deficiency is an evolutionary developed protective condition against malaria.

5/7. But! G6PD deficient subjects have an increased susceptibility to human coronaviruses [13] because **ROS-mediated ARDS complicates the course of the disease** [14].

That is why g6pd deficiency is live-threatening in COVID-19.

6/7. G6pd deficiency can be genetic [15,16] and **acquired (!)** condition [17] due to obesity [18], aging [19,20,21], diabetes [22,23 24], hypertension [25]. Such patients **have permanent background inflammatory "firestorm" caused by ROS already [26]**.

7/7. **Background ROS + COVID ROS + Chloroquine ROS $\Longrightarrow$ Inadequate SIRS**

References:

1. Similarly, we observed that intracellular **ROS generation increased 60 minutes after IAV infection.** Viral titers and mRNA levels of IAV were significantly higher in cases with scavenging ROS, in cases with an induced IFN-λ mRNA level, or where the secreted protein concentration of IFN-λ was attenuated after the suppression of ROS generation.
10.1165/rcmb.2013-0003OC

2. It is known that **malaria infection is accompanied by increased production of reactive oxygen species (ROS)** and that **malaria parasites are sensitive to oxidative damage.**
10.1081/dct-120017558

3. Inhibition of autophagy by **CQ pre-treatment** led to accumulation of acidic vacuoles (AVOs) which acquainted with unprocessed damage mitochondria that subsequently **promoted ROS generation,** and resulted releases of Cyt C in cytosol that caused caspase-3 dependent apoptosis cell death in ART-treated A549 cells.

10.1016/j.biochi.2014.10.001

4. Swiss albino mice were administered with different amounts of **CQ** ranging from human therapeutic equivalent of 360 mg/kg body wt. to as high as 2000 mg/kg body wt. We observed statistically significant **generation of reactive oxygen species**, **liver toxicity**, and **oxidative stress**.
10.1155/2013/141734

5. **Chloroquine treatment** mediated **oxidative stress** in the host and this effect was exacerbated in Plasmodium falciparum infected patients administered with the drug. Similarly the levels of vitamins A, C, and beta-carotene were decreased in the treatment groups while plasma ceruloplasmin was increased in the groups.
10.1081/dct-120017558

6. This finding shows that **CQ** remains highly efficacious for the treatment of uncomplicated ***P. falciparum* malaria** in Gracias a Dios, Honduras.
10.4269/ajtmh.12-0671

7. We report, however, that **chloroquine** has strong antiviral effects on **SARS-CoV infection** of primate cells.

10.1186/1743-422X-2-69

8. But there has been a growing understanding of the central importance of **G6PD** to cellular physiology as it is a major source of **NADPH** that is required by many essential cellular systems including the **antioxidant pathways,** nitric oxide synthase, NADPH oxidase, cytochrome p450 system, and others. Indeed G6PD is essential for cell survival.

10.1002/iub.1017

9. **Protection against oxidative damage** largely relies on the reductive power of NAPDH, whose levels are mostly determined by the enzyme **glucose-6-phosphate dehydrogenase (G6PD).**

We conclude that a modest **increase in G6PD activity** is beneficial for healthspan through increased NADPH levels and **protection from the deleterious effects of ROS.**

10.1038/ncomms10894

10. During a **malaria infection**, **both host** and **parasite** are **under oxidative stress**. Increased production levels of reactive oxygen species (ROS, e.g superoxide anion and the hydroxyl radical) are produced by activated neutrophils in the host and during degradation of haemoglobin in the parasite.
10.1007/bf00717727

11. **Glucose-6-phosphate dehydrogenase (G6PD) deficient** subjects are vulnerable to **oxidative stress**.
PMID: 24363724

12. **G6PD deficiency** can potentially **protect against uncomplicated malaria** in African countries, but not severe malaria.
10.1038/srep45963

13. Viral gene expression and viral particle production of **glucose-6-phosphate dehydrogenase (G6PD)–deficient** and G6PD-knockdown cells **were much higher** than their counterparts when **human coronavirus (HCoV) 229E** was applied at 0.1 multiplicity of infection.
10.1086/528377

14. The acute lung injury resulting from **adult respiratory distress syndrome (ARDS)** is thought to be largely mediated by activated neutrophils. Because activated neutrophils produce the **superoxide radical**, which is both bacterial and cytotoxic to host cells, this **oxygen-derived free radical is likely responsible for at least part of the neutrophil-mediated lung injury**. In a rat model of ARDS resulting from intratracheal instillation of interleukin-1, recombinant human manganous superoxide dismutase significantly decreased lung leak.
10.1289/ehp.94102s1057

15. In this study, we obtained an estimate of **4.9%** for the **global prevalence of G6PD deficiency.**
10.1016/j.bcmd.2008.12.005

16. In contrast, we now report that the **G6PD deficiency**, which has the highest known incidence in the world, and which affects about **70% of males**, is almost entirely attributable to a single widespread mutation, **G6PD Mediterranean**.

10.1007/bf00218277

17. **Oxidative stress** and impairment of synthesis or release of **nitric oxide (NO)** are being regarded as causative factors in the pathogenesis of **hypertension**, **diabetes mellitus** and **atherosclerosis**, among other conditions.
PMID: 11763298

18. The **activity and expression of G6PD** in the **obesity-prone group** rats **were lower** than those in the control and obesity-resistant group rats (P<0.05).
PMID: 23805524

19. We observe a significant age-dependent decrease in G6PD activity ($p < 0.0001$). Our findings on erythrocyte G6PD and their correlation with GSH and FRAP provide evidence of a higher oxidative stress in old age population.
10.3109/13813455.2015.1136648

20. Although tissue **glutathione content decreased with age**, the other markers of oxidative stress were little changed during aging.
10.1016/j.exger.2003.10.014

21. These data suggest that platelet **NO production** and responsiveness **decrease with age**, and this is reflected in increased circulating MPA.
10.1016/j.cardiores.2007.05.021

22. The **mRNA and protein expression levels of G6PD** in DRGs **were significantly decreased** in **diabetic** rats when compared with age-matched control rats.

10.1177/1744806919838659

23. The data indicate that **low G6PD activity** is another risk factor for **diabetes**.
10.1385/ENDO:19:2:191

24. Basal platelet **nitric oxide** production **was lower** in **diabetic** patients than in healthy subjects. Nitric oxide release was reduced by in vitro homocysteine incubation, being lower in platelets from diabetic patients than in platelets from control subjects.

10.1007/s001250100581

25. This study demonstrates that a **moderate decrease in G6PD activity is associated with PAH.**

10.1371/journal.pone.0203493

26. **G6PD deficiency causes problems primarily when the deficiency is complicated by the treatment of malaria.** Treatment can cause (severe) hemolysis in G6PD-deficient patients. Therefore, patients should be screened for G6PD deficiency before treatment with these potential hemolytic agents.

10.1369/jhc.2009.953828

Chloroquine and **hydroxychloroquine have few contraindications**. Either a previous hypersensitivity to any 4-aminoquinoline compounds or the underlying presence of retinopathy are the only absolute exclusions to these medications. **Patients also should be tested for a G6PD deficiency before starting chloroquine or hydroxychloroquine.** Patients with a G6PD deficiency are at increased risk for hemolysis when given these drugs. Both chloroquine and hydroxychloroquine are safe to use throughout pregnancy. https://www.ncbi.nlm.nih.gov/books/NBK470158/