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Review Article

The Dark Side of the COVID-19 Treatments on *Mycobacterium tuberculosis* Infection

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Abstract. Since the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) at the end of 2019, a number of medications have been used to treat the infection and the related Coronavirus disease – 19 (COVID-19).
Some of the administered drugs were tested or used in practice only on the basis of biological plausibility; a promising strategy was to target the host immune response, with host directed therapies (HDTs), to reduce systemic hyperinflammation and hypercytokinemia responsible for additional tissue damage.
We summarize the treatments against SARS-CoV-2 and underline their possible effects on *Mycobacterium tuberculosis* (*Mtb*) infection. Both SARS-CoV-2 and *Mtb* respiratory infections impair the host's immune response. Furthermore, little research has been conducted on the impact of medicaments used to counteract COVID-19 disease in patients with Latent Tuberculosis Infection (LTBI). A number of these drugs may modulate host immune response by modifying LTBI dynamic equilibrium, favoring either the host or the bacteria.

Keywords: SARS-CoV-2, Mycobacterium tuberculosis, COVID-19, Tuberculosis, Host directed therapies.

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Introduction. COVID-19 pandemic has shown a significant disruptive impact on Tuberculosis (TB) services, with negative effects on prompt diagnosis, treatment and immunization.[1,2] Pressure on laboratories and pharmaceutical industries led to the readaptation of many TB labs to detect SARS-CoV-2 as well as Bacillus Calmette-Guérin (BCG) shortages and consequent decrease of newborn vaccinations.[3] Estimates indicate a 25% drop in the global BCG coverage and an increase in pediatric deaths ranging from 0.5% to 17%.[4]

In several countries, reports suggest a decline in case notification in the last few months due to massive cancellation of routine health services in many settings.[5–7] Although it has been noted that many of the preventive measures implemented to reduce SARS-CoV-2 incidence also have a clear benefit on reducing *Mycobacterium tuberculosis* (*Mtb*) transmission, 2020 saw the first year-over-year increase in TB deaths from 2005, regardless of physical distancing and PPE (personal protective equipment) wearing measures.[2,8]

In Canada, the pandemic significantly affected latent TB infection (LTBI) and active TB treatment, leading to ineffective measures for TB elimination.[9] In Spain, newly diagnosed TB patients had more extended pulmonary disease, moreover there was a rise in household transmission probably due to anti-COVID-19

measures.[10] Also, in England, it has been observed a fall in rates of TB treatment initiation during the period of government-imposed lockdown (March 23–May 10, 2020), and an increase of cases of disseminated TB during the COVID-19 pandemic.[11] All this makes it important to evaluate the measures against COVID-19 globally and not only considering the pathologies related to SARS-CoV-2,

The COVID-19 emergence prompted the scientific community to focus on determining the mechanisms of transmission, the identification of virulence factors of SARS-CoV-2 and the development of suitable therapies.[12] Therapeutical management of COVID-19 is in constant change, and treatment guidelines are readily updated based on scientific evidence and experts' opinion (National Institutes of Health, n.d.) as we entered in an era of "hype-based medicine",[13] the long forgotten eminence-based medicine regained importance as the number of trials on possible therapies multiplied, some of them causing overnight changes in the management of COVID-19 patients.[14] The lack of antiviral therapies and the rapid spread of the infection convinced investigators and pharmaceutical companies to focus on the development of vaccines,[15] able to induce neutralizing antibodies against SARS-CoV-2 Spike protein in naive subjects. The developed vaccines do not only trigger a humoral response against the protein, but they impact all the components of the immune response.

As most of the therapies used against COVID-19 disease therapies do not target SARS-CoV-2, but aim to regulate the host immune response[16,17] it is reasonable to consider the long-term effects of these therapies on subjects with latent TB infection (LTBI).

In this commentary, we aim to summarize treatments against SARS-CoV-2 and underline their possible effects on *Mtb* infection highlighting likely "side" effects that could help to contain virus-mediated damage and, conversely, prompt mycobacterial replication in both early infection or during *Mtb* latency.

Therapies Against SARS-CoV-2 Infection. SARS-CoV-2 represents the biggest therapeutic challenge of our century. At present, approximately 2900 clinical trials have been registered,[14] designing new molecules and repurposing existing drugs based on the virus biology and pathogenesis.

Therapeutical approaches range from convalescent plasma of people who have recovered from COVID-19, to medications which are commonly used to treat autoimmune or inflammatory diseases as well as drugs used to treat other infections.[18,19]

Pharmaceuticals used for COVID-19 target different pathogenetic mechanisms, with the aim of a) blocking viral replication, summarized in points 1-3 of the **Figure 1,** and b) reducing tissue damage, modulating the immune responses, and preventing over-inflammation (**Figure 1**, points 4-6).

The first class includes antivirals to prevent spike-protein-mediated cell fusion, thus blocking viral entry (**Figure 1**, point 1), inhibit gene transcription (**Figure 1**, point 2) or prevent proteolytic processing and block viral docking (**Figure 1**, point 3), as explained in **Table 1**.[20-23] Interestingly, several agents show no effects on SARS-CoV-2 even though they were described to have activity against other infections.[24]

SARS-CoV-2 infection causes an overproduction of type I interferons triggering the transcription of several genes and the recruitment of CD4+ T helper lymphocytes, responsible for the Th1/Th2 response.[25] For this reason, immunomodulators (corticosteroids, interferons, monoclonal antibodies against inflammatory cytokines) have been suggested, and largely used, to reduce the over-inflammation that is responsible for several systemic disease manifestations.

However, the NHS Panel failed to evaluate the real role of some of these therapies due to insufficient evidence to recommend either for or against their use.[26]

Examples of drugs in this category are IL-1 inhibitors, colchicine, the antiparasitic agent ivermectin,[12] and thalidomide.[27] Some others are currently recommended as IL-6 inhibitors and Janus Kinase inhibitors (refer to Table 1 and **Figure 1**, point 4 to 6).

Although, the use of immunomodulatory treatments had an immediate impact on the care of patients infected with SARS-CoV-2, their long-term effects are unknown.

Impact of the Therapies Against SARS-CoV-2 on *Mycobacterium tuberculosis.* *Mtb* infection represents a classical model of persistent infection, a situation in which a microorganism can persist indefinitely within the host,[28,29] establishing an equilibrium between the pathogen and the host immune response whose modification could increase the risk of relapse and disease. Indeed, host immune response can limit *Mtb* spread, after macrophages killing evasion, creating a multicellular structure known as granuloma,[30] which entraps mycobacteria that persist in a heterogeneous range of states.[31] In the last decades, to deal with the emergence of *Mtb* strains resistant anti-TB drugs (*MDR/RR-Mtb* and *XDR-Mtb*), a novel approach has been proposed targeting the host and so named host directed therapies (HDTs).[32–35] HDTs can support antimycobacterial host response at different stages: a) perturbating granuloma integrity to enhance drug penetration; b) modifying autophagy or phagosome maturation to increase intracellular killing; c) promoting cell-mediated response; d) inducing antimicrobial peptides and controlling inflammation response by avoiding tissue damage.[36] While the use of HDTs seem to support anti-TB treatment in symptomatic individuals,[37] no data nor anecdotal knowledge support the use of such therapies in people with asymptomatic or

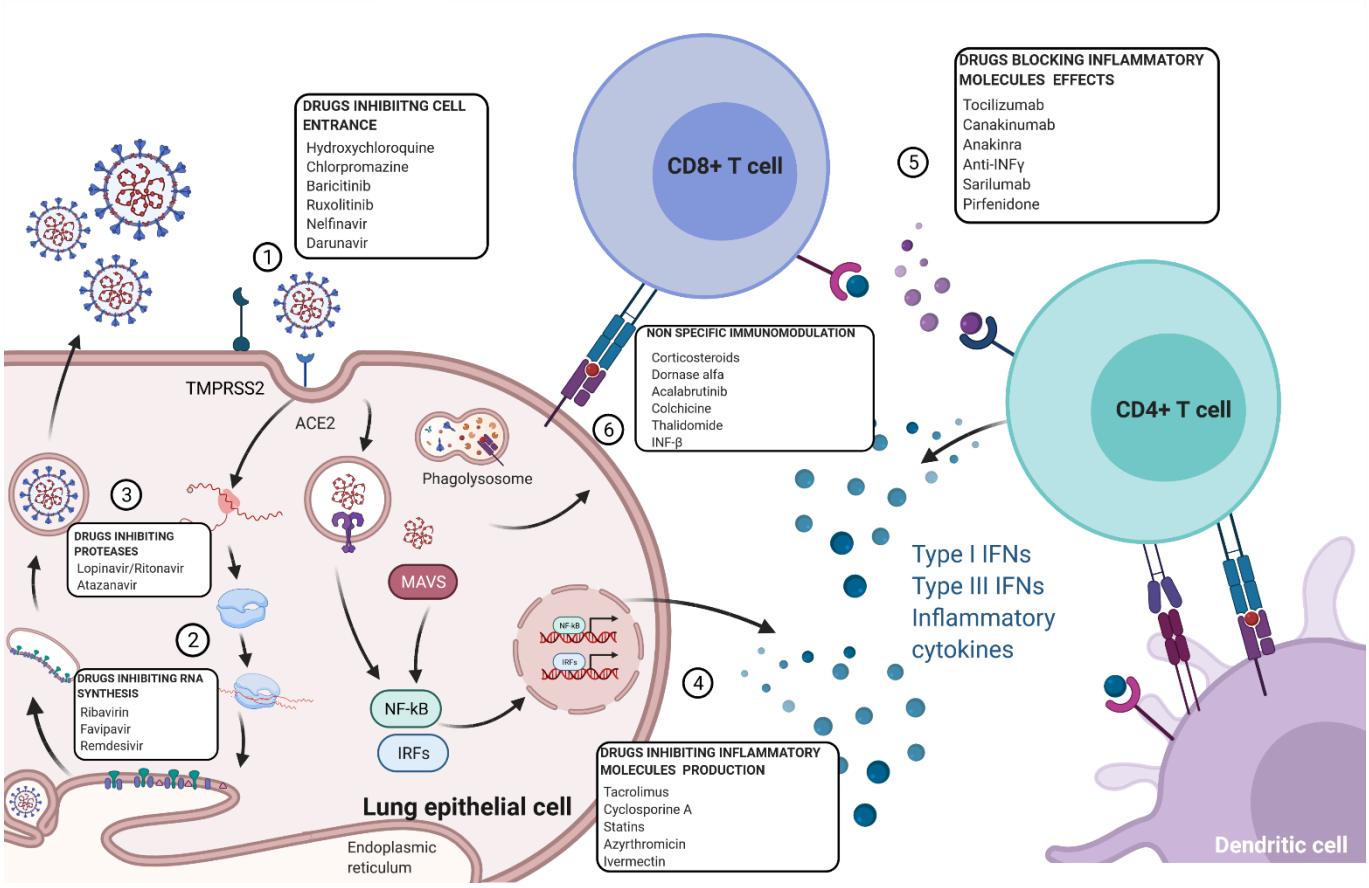

Figure 1. Schematic representation of the pharmaceuticals used against SARS-CoV-2 infection. The first class of molecules includes antivirals to prevent viral entry (point 1); the second class includes compounds that inhibit gene transcription (point 2) and the third class accounts molecules that prevent proteolytic processing and block viral docking (point 3). The points 4-6 described medications that reduce tissue damage, modulating the immune responses or preventing over-inflammation.

subclinical infection.[38]

In other words, it is undeniable that some immunomodulatory treatments may alter the host-*Mtb* equilibrium, favoring either the host or the bacteria. In this scenario, we cannot exclude that those immunomodulatory therapies used against COVID-19 may have a negative effect on infected individuals causing symptomatic TB.

A recent paper highlighted the relationship between SARS-CoV-2 and *Mtb* infection, showing that asymptomatic SARS-CoV-2 seropositive individuals with a positive IGRA exhibited heightened levels of humoral, cytokine production, and systemic inflammation compared to individuals negative for *Mtb* infection.[39] *Mtb* is apparently able to modulate the host immune response in SARS-CoV-2-infected individuals. Furthermore, various clinical cases describe TB reactivation following SARS-CoV-2 infection confirming the concerns that COVID-19 associated CD4+ T-cell depletion or altered T-cell function can have similar implications as HIV for TB disease progression, promoting the development of active TB.[25,40] Moreover, some studies highlighted a higher probability to develop severe disease in patients with SARS-CoV-2 / *Mtb* co-infection compared to COVID-19 patients.[41,42] Unfortunately, we have little information on TB occurrence after COVID-19 treatments.[43] On the other hand, there was a delay in the onset of the pandemics in many countries endemic for TB. Moreover, those countries showed lower COVID-19's severe cases and SARS-CoV-2 related-mortality.[44] Intriguingly, one of the variables that was mathematically linked to COVID-19 low spread was BCG vaccination,[45] which is known to stimulate non-specific heterologous immune responses inducing cross-protective effects toward non-tuberculosis-related diseases, included SARS-CoV-2.[15,46,47] Indeed, numerous clinical trials are currently registered to update on the benefits of BCG vaccinations against SARS-CoV-2 exposure.[15,47]

We can classify therapies used against COVID-19 based on their activity on *Mtb* infection in four main drug classes: a) drugs acting directly on *Mtb* (**Figure 2**, point 1); b) drugs that modify phagosome acidification (**Figure 2**, point 2); c) drugs with adjuvant function that can indirectly modulate the infection (**Figure 2**, point 3) and d) drugs with immunomodulatory activity (**Figure 2**, point 4). Although many anti-COVID-19 pharmaceutics appeared to impair mycobacterial growth in *in vitro* experiments, (**Figure 2**, point 1),[48–51] we focus our attention on their immunomodulatory effects (**Table 1**).

	DRUG CLASS	DRUG	Mechanism of action against SARS-CoV-2	REFEERENCE	Mechanism of action against *M. tuberculosis*	REFERENCE
	Anti-gout	Colchicine	Down regulates multiple inflammatory pathways and modulates innate immunity.	Schlesinger N. et al, 2020	Not useful in TB pericarditis	Liebenberg J.J. et al, 2016
Immunomodulatory drugs	Statins	Statins	Inhibit pro-inflammatory cytokine production (TNF-α, IL-10, IL-6 and IL-8) in mononuclear, synovial and endothelial cells. Inhibit T-cell proliferation affecting MHC-II mediated T-cell activation	Satoh M. et al, 2015	Promotes phagosome maturation and autophagy resulting in a decreased *Mtb* load	Parihar S.P. et al. 2014
	Corticosteroids	Dexamethasone Budesonide Hydrocortisone	Theoretically suppress systemic and lung inflammation related to SARS-CoV-2 infection	Martinez M.A. et al, 2019	Reduce ARDS in TB patients	Hagan G. et al, 2013
	Anti-fibrotic /anti-inflammatory	Pirfenidone	Inhibits the effects mediated by IL-1 and IL-4	Vitiello A. et al, 2020	Has a detrimental effect on *Mtb* containment in granulomas and results in an accelerated cavitation and reduced bacterial clearance	Ahidjo, Bintou A et al, 2016
	Recombinant human DNase 1	Dornase alfa	Improves oxygenation and ventilation by reducing Neutrophilic Extracellular Trap (NET)	Weber A.G. et al, 2020	-	-
	Bruton's tyrosine kinase inhibitor	Acalabrutinib	Regulates macrophage signaling and activation, targeting excessive host inflammation	Roschewski, Mark et al, 2020	NA	-
	Immunomodulatory	Thalidomide	Attenuates exaggerated inflammation and cytokine storms	Khalil A. et al, 2020	Inhibits TNF-alpha secretion promoting mycobacterial replication	Wang L. et al, 2017, Tramontana J.M. et al. 1995, Verbon, A et al., 2000
	IL-6 antagonist	Tocilizumab Sarilumab	Counteracts cytokine storm indirectly blocking mIL-6R and sIL-6R transduction signals	Le RQ. Et al, 2018 Benucci M. et al, 2020	Potential reactivation of LTBI	Lim C.H. et al, 2017
	IL-1 blocker	Anakinra	Dumpers inflammatory responses	Shakoory B. et al, 2016	Increases the risk of opportunistic infections	Salliot C. et al, 2009
	Anti-IL-1β antibody	Canakinumab		Magro G., 2020		
	Anti-IFNγ	Emapalumab	Proposed to reduce inflammatory response	Magro G., 2020	IFNγ neutralization could potentially facilitate the development of infections caused by several pathogens including mycobacteria	Merli P. et al 2020
	Calcineurin inhibitors	Cyclosporine A Tacrolimus	Halts the production of the pro-inflammatory molecules (TNF-α and IL-2)	Pfefferle S. et al, 2011	NA NA	- -
	Immunomodulatory	IFN-β	Stimulates the immune system to blunt viral replication and eradicate offending pathogens	Bakadia B.M. et al, 2021	IFN-β plays may be a useful therapeutic strategy to control Mtb infection	Sabir N. et al, 2017
	Anticoagulant	Low molecular weight heparin	Reduces clot pathway hyperactivity related to pro-inflammatory state	Heng M. et al, 2020	Prevent concomitant pulmonary embolism	Osorio N. et al, 2020

	DRUG CLASS	DRUG	Mechanism of action against SARS-CoV-2	REFEERENCE	Mechanism of action against *M. tuberculosis*	REFERENCE
Antibiotics	Macrolide	Azythromicin	Reduces production of pro-inflammatory cytokines such as IL-8, IL-6, TNF alpha, reduce oxidative stress, and modulate T-helper functions	Pani A. et al, 2020	Long-term azithromycin use may predispose CF patients to NTM infection In the acute phase, azithromycin reduces the production of pro-inflammatory cytokines (IL-8, IL-6, TNF alpha, and MMPs). In the resolution phase, it increases neutrophil apoptosis and the oxidative stress inflammation-related	Renna M. et al. 2011 Amsden GW. 2005, Lin S.J. Et al. 2016
	Tetracycline	Doxyclicine	Exhibits anti-inflammatory effects along with *in vitro* antiviral activity against several RNA viruses	Castro J.Z. et al, 2010	Blocks mycobacterial growth in infected macrophages suppressing MMP-1 and MMP-3 secretion Reduces pro-inflammatory cytokines, including IL-6 and tumor necrosis factor (TNF)-α and suppresses TNF-α secretion by macrophages	Walker N.F. et al. 2012 Fredeking T. et al, 2015, Walker N.F. et al, 2012
Antivirals and antiviral-like drugs	Antiviral	Remdevisir	Inhibits viral RNA polymerase decreasing viral replication	Barlow A. et al, 2020	Reduces levels of IL-1β, TNF-α, IL-6 and IL-18	Li Y.-N. et al, 2020
		Favipavir		Javorac D. et al, 2020	Decreases levels of TNF-α	Tanaka T. et al, 2017
		Ribavarin	Inhibits viral RNA synthesis	Barlow A. et al, 2019	Reactivation during therapy against HCV Decreases levels of IL-1β, TNF-α, IL-6 and IFN-γ	Abutidze A. et al, 2016 Liao S.et al,2017
	Protease inhibitors	Lopinavir/ ritonavir	Inhibits 3-chymotrypsin-like protease resulting in decreased viral replication	Fagone P. et al, 2015	Lopinavir reduces levels of IL-6 and TNF-α; Ritonavir reduces levels of IFN-γ and IL-10	Fagone P. et al., 2015
		Nelfinavir	Inhibits cell fusion caused by the SARSCoV-2 spike (S) glycoprotein	Musarrat F. et al, 2020	Nelfinavir diester derivatives shows antimycobacterial activity	Sriram D et al. 2008, Brüning A. et al. 2010, Shen YUN. Et al. 2001
		Atazanavir	Blocks the major protease of SARS-CoV-2	Fintelman-Rodrigues N. et al, 2020	Reduces levels of IL-6 and TNF- α	Fintelman-Rodrigues N. et al., 2020
		Darunavir/ cobicistat	Inhibits viral entry	Kalil AC. Et al, 2020	NA	-
	Antipsychotics	Chlorpromazine	Decreases virus entry inhibiting clathrin-mediated endocytosis	Plaze M. et al, 2020	Enhance macrophagic mediated killing by promoting vacuolar acidification (M. bovis BCG)	Machado D. et al, 2016
	Antiparasitic	Hydroxychloroquine	Potentially inhibits cell entry impairing affinity between Spike protein and ACE 2 receptor	Infante M. et al, 2020	Impairs Mtb growth inactivating D+ NAD+ dependent DNA ligase A Modulates phagolysosomal pH inhbiting intracellular bacterial growth	Singh V. et al, 2010 Rolain J.M. et al, 2007
		Ivermectin	Modulates immune response through IFN-γ production	Soboslay P.T. et al, 1994	Shows bactericidal activity against mycobacterial species	Lim L. E. et al, 2013,
		Nitazoxanide	Potential antiviral properties (clinical trials in influenza and other virus infections)	Kelleni MT et al, 2020	Inhibits the growth of diverse strains of Mtb	Ranjbar S. et al, 2019; Cavanaugh J.S. et al, 2017
	Janus kinase (JAK) inhibitor	Baricitinib Ruxolitinib	Prevent viral entry and intracellular assembly of viral particles	Lu R. et al, 2020	Affects immune cell functions with negligible risk of active TB in low endemic areas	Cantini F. et al, 2020

Table 1. Summary reporting experimental evidence of the impact of drugs used against SARS-CoV-2 infection on *Mycobacterium tuberculosis* infection.

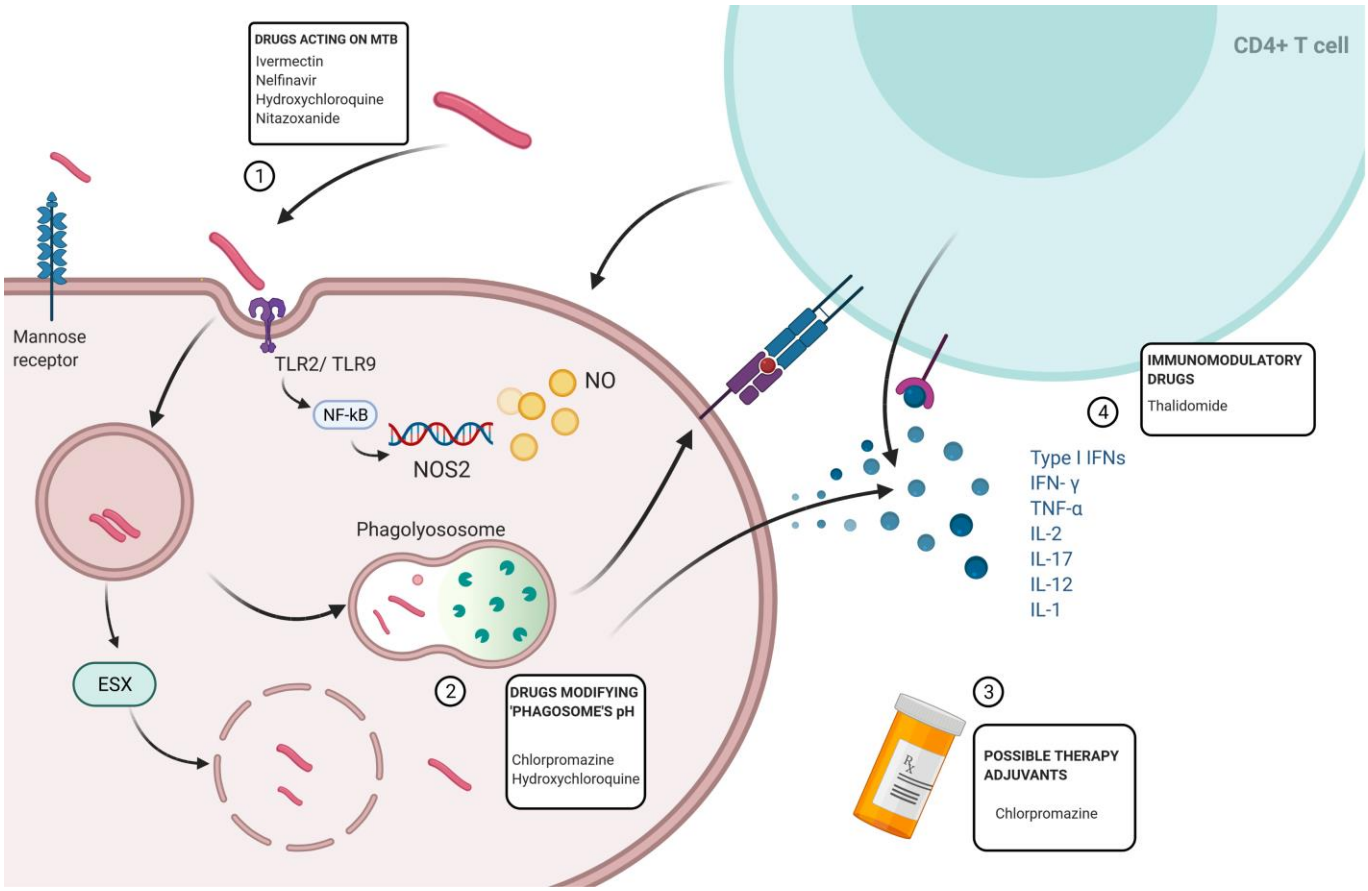

Figure 2. Schematic representation of the medications used against SARS-CoV-2 with effects on *Mycobacterium tuberculosis* infection. Therapies used against COVID-19 are classified based on their activity on *Mtb* infection in four main classes: drugs acting directly on mycobacteria (point 1) or indirectly showing ability to modify phagosome acidification (point 2), to modulate the infection with adjuvant functions (point 3) and to regulate hose immune response (point 4).

Hydroxychloroquine inactivates mycobacterial NAD+ dependent DNA ligase A[52] and modulates phagolysosome, reducing intracellular mycobacterial growth.[48] Similarly, chlorpromazine, an antipsychotic drug, has been observed to have antimycobacterial activity and to promote macrophagic killing by increasing phagosome acidification.[53] Acidification may though differently affect phagosomes at different stages of maturation.[54] Moreover, *Mtb* itself can influence phagosome maturation potentially counteracting these drugs.[55]

Nitazoxanide, which has been also suggested to modulate immune response inducing interferon-γ,[50,56] inhibits intracellular Mtb growth while amplifying *Mtb*-induced gene expression.

Thalidomide represents a compound that has been tested against *Mtb* infection showing a detrimental effect on infection control due to TNF-α inhibition with consequent increase in mycobacterial replication[57,58] (**Figure 2** and **Table 1**).

Interestingly, several drugs that have been proposed against SARS-CoV-2 have not been tested *in vitro* against *Mtb* infection (**Table 1**). This is true for several molecules that act on the host immune system to prevent over inflammation (which has been observed as a critical point for the progression of SARS-CoV-2 infection). These compounds, that dampen pro-inflammatory cytokines, could impair the fine equilibrium between *Mtb* replication and the host immune system response, thus promoting active disease. Among them, monoclonal antibodies such as IL-6 antagonists and antivirals have been observed to significantly modulate host cytokine response and potentially alter host immune response versus *Mtb* replication.[59] Interestingly, *Mtb* regulates IL-6 secretion to inhibit type I interferon signaling and causes disease progression which appears to be associated to *sigH* gene expression.[60] For this reason, IL-6 antagonist could have important implications during *Mtb* infection.

Another example are corticosteroids that are beneficial in hospitalized COVID-19 patients,[61,62] but, conversely, could increase the risk of LTBI reactivation or progression of sub-clinical TB.

Conclusions. Given the specific effect of COVID-19 on T-cells and for anti-COVID-19 treatments on LTBI, clinicians should consider monitoring patients with both previous COVID-19 infection and LTBI to rapidly

identify active disease and prevent *Mtb* transmission.

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