COVID-19: Implications for People with Chagas Disease
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Implications for People with Chagas Disease

The Chagas Disease and COVID-19 Writing Group

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Abstract

As the global COVID-19 pandemic advances, it increasingly impacts the vulnerable populations who already bear a heavy burden of neglected tropical diseases. Chagas disease (CD), a neglected parasitic infection, is of particular concern because of its potential to cause cardiac, gastrointestinal, and other complications which could increase susceptibility to COVID-19. The over one million people worldwide with chronic Chagas cardiomyopathy require special consideration because of COVID-19’s potential impact on the heart, yet the pandemic also affects treatment provision to people with acute or chronic indeterminate CD. In this document, a follow-up to the WHF-IASC Roadmap on CD, we assess the implications of coinfection with SARS-CoV-2 and Trypanosoma cruzi, the etiological agent of CD. Based on the limited evidence available, we provide preliminary guidance for testing, treatment, and management of patients affected by both diseases, while highlighting emerging healthcare access challenges and future research needs.
COVID-19: Implications for People with Chagas Disease

Introduction

In 2020, the SARS CoV-2 virus, which causes, COVID-19, took the world by storm. The biological and social implications of this global pandemic may not be fully understood for years. However, what is increasingly clear is that like other diseases, COVID-19 disproportionately affects those living at the social margins, while also being particularly severe in older individuals and those with certain underlying health conditions. These are both key considerations as COVID-19 increasingly intersects with the world’s neglected diseases, including Chagas disease (CD), a multi-systemic disorder caused by Trypanosoma cruzi (T. cruzi) that can affect the cardiovascular, digestive and central nervous systems (1). CD is endemic in much of Latin America, which is increasingly bearing the brunt of the pandemic. The first reported Latin American case was on February 26th, 2020 in Brazil; by June 30th, there were nearly 2.5 million confirmed infections and over 110,000 deaths in the region (2), with numbers still increasingly rapidly at the time of writing this paper. Several aspects of CD are concerning in light of what we know about COVID-19: many people living with CD are socioeconomically vulnerable, and with limited access to healthcare; the vast majority are undiagnosed; most are aging, and over a million have already progressed to a cardiac form of the disease (3, 4). In this paper we focus on the potential interactions between CD and COVID-19 in coinfected individuals, which become increasingly important as the pandemic spreads rapidly through the Latin American countries where CD is endemic.

In early 2020 the Inter-American Society of Cardiology and World Heart Federation published a roadmap that provides a comprehensive overview of CD, with steps for improving healthcare access (5) In April, the Drugs for Neglected Diseases initiative’s Chagas Research Platform reconvened some members of the roadmap writing group and other experts to write a follow-up paper exploring how COVID-19 might impact people living with CD, and to provide preliminary guidance based on the limited amount of evidence available on the topic. The group consisted of several CD experts, some of whom have been on the front lines during the current crisis treating patients with COVID-19 or performing research on new treatments. The following document summarizes the consensus opinion of these experts on SARS CoV-2/T. cruzi coinfection.
Pathophysiology of COVID-19 infection in relation to that of CD

CD is mainly transmitted through various species of hematophagous insects, although it can also be transmitted transplacentally, through infected blood transfusions or organ donations, laboratory accidents, needle sharing among intravenous drug users (IVDU), and orally through food and drink contaminated with triatomines, their feces, or secretions from some host reservoir species. After infection and an incubation period that ranges from 15 to 40 days, the acute phase of the disease generally lasts for one to two months and is followed by an indeterminate phase, when no clinical manifestations are observed. After decades of this silent state, roughly one-third of patients may develop a chronic form of the disease characterized by organ damage, mainly cardiovascular and gastrointestinal. The most serious sequelae of CD are stroke, sudden death from brady- or tachyarrhythmias, and congestive heart failure (1, 6).

COVID-19 interacts with the cardiovascular system on multiple levels. SARS-CoV-2 binds to the human angiotensin-converting enzyme 2 (ACE2) receptor mainly expressed in the lungs, heart, and vascular endothelium. Although analysis of the precise consequences is in its infancy, this may trigger an inflammatory response that in turn may lead to increasing myocardial injury and dysfunction (7, 8). There is uncertainty whether COVID-19 disease, as an altered immune state, can act as a potential trigger for CD progression, also influenced by both certain parasitic factors (type of strains, load of parasites) as well as host factors (genetic susceptibility and immune state, specifically IFN-Ɣ axis).

While parasitemia is low-level and evanescent in chronic CD, pharmacologic and disease-induced immunosuppression cause a risk for reactivation of parasitemia (9, 10), therefore there is a potential concern that COVID-19 disease could trigger reactivation of CD, either due to an acquired hemophagocytic lymphohistiocytosis-like disease (cytokine storm), the virus itself, or even the use of some COVID-19 treatments such as steroids, hydroxychloroquine (5) and other immune-modulating drugs (i.e. tocilizumab or other interleukin inhibitors), as interleukins are related to the progression of CD (11, 12). This may be influenced by certain parasitic factors (parasite load and/or T. cruzi strain) as well as host factors (genetic susceptibility and immune state, specifically IFN-Ɣ axis).
Implications for chronic Chagas cardiomyopathy

The pathogenesis of Chronic Chagas cardiomyopathy (CCC) involves a complex interaction of different processes, related to tissue damage due to parasite persistence, inflammation, autoimmunity, fibrosis, dysautonomia, and microvascular changes (13). Chronic, persistent infection of the myocardium elicits an inflammatory response which, although necessary for the control of parasite proliferation, results in tissue damage leading to myocardial fibrosis and cardiac remodeling (14). The pro-inflammatory response includes, but is not limited to, secretion of Th1 cytokines and chemokines, eicosanoids, and endothelin-1 (14).

Similar to *T. cruzi* infection, direct cytotoxicity of cardiac tissue also is possible with SARS-CoV-2, which binds to the ACE2 receptor to enter type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes. This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability, and myocardial infarction (MI) (15). Initial immune and inflammatory responses induce a severe cytokine storm (16), including cytokines and chemokines frequently related to the inflammatory response implicated in the pathogenesis of CCC, such as interleukin (IL)-6, TNF-alpha and CXCL10 (17, 18). Indeed, COVID-19-related myocarditis cases have been reported and are thought to be a combination of direct viral injury and cardiac damage due to the host’s immune response (19).

Further depression of the ventricular function by COVID-19 could be caused by additional mechanisms, such as myocardial infarction and microvascular dysfunction, also found in *T. cruzi* infection (15). Furthermore, arrhythmia is recognized as one of the possible clinical manifestations of COVID-19 patients, and could plausibly precipitate arrhythmias in patients with an arrhythmogenic substrate, such as CCC (19).

Finally, COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis (20). There are reports of upregulated procoagulative activity in plasma of chronic CD patients (21) and thromboembolic manifestations are also more frequent in CCC patients (22), although it is not clear if this interaction has clinical relevance.
Implications for chronic indeterminate CD

While patients living with the indeterminate form of CD are usually outpatients without manifest symptoms, these patients still require ongoing surveillance and care which has become increasingly difficult due to the pandemic. For instance, patients with chronic indeterminate CD need yearly follow up for cardiac tests, as annually 2-5% progress to chronic symptomatic disease, and ultimately 30-40% develop cardiac or gastrointestinal complications (1). They may also benefit from antiparasitic treatment, which in the case of women of childbearing age, can interrupt congenital transmission (23, 24). However, the 2-month course of treatment requires ongoing monitoring and laboratory testing due to the potential for side effects. This necessary care for patients with chronic indeterminate CD is likely to be hampered by the pandemic, both because of the potential risk of SARS-CoV-2 infection from attending healthcare facilities for routine appointments, (or the need to use public transportation to travel to and from appointments), and postponements or delays in routine care as healthcare personnel and resources are focused on COVID-19 cases.

Furthermore, if assessed with more sensitive technology, including echocardiography, Holter, and magnetic resonance with late gadolinium enhancement, a small number of indeterminate-phase patients may be reclassified as having CCC due to the presence of areas of fibrosis with wall motion abnormalities (25-30). Therefore, an unknown proportion of individuals classified as indeterminate form patients may indeed develop arrhythmias or other cardiovascular complications if challenged with a cytokine storm such as that triggered by COVID-19.

Implications for gastrointestinal and neurological forms of CD

Atypical chest pain, abdominal pain, and nausea are nonspecific symptoms related to upper digestive CD involvement, and both have been related to COVID-19 pulmonary and extrapulmonary clinical presentation (31, 32). However, constipation as the main symptom of lower digestive tract involvement due to T. cruzi infection is the opposite to diarrhea, the main gastrointestinal (GI) symptom observed in extrapulmonary forms of COVID-19. The presence of GI symptoms, widely described in COVID-19 series and present in 3-11.6% of patients with COVID-19 (31), has been associated with high ACE2 expression in the GI tract, that could indicate the potential of virus mutation towards increased transmissibility, decreased virulence and multiorgan infection (31). When GI symptoms that occur in both diseases are noted in an individual in an area of high SARS-CoV-2 transmission, etiological consideration must be
given to either CD progression or COVID-19, considering its implications in terms of mutation and transmissibility.

There is increasing evidence that coronaviruses are associated with neurological disorders (33). Studies on severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) suggest that coronaviruses are neurotropic. A systematic review of the literature until April 2020 associates multiple neurological disorders with COVID-19, including encephalitis, demyelination, and neuropathy (34). It could potentially induce the development of the chagasic neuropathy which is sometimes observed in chronic CD.

**Congenital cases**

Maternal fetal transmission of *T. cruzi* occurs in an average of 5% of the pregnancies of mothers with chronic CD (35). Parasite load is a key determinant of congenital transmission (36). The immunological response to COVID-19 is extensive, and its impact on *T. cruzi* parasitic load is unknown. Should it be found that COVID-19 increased parasitemia in pregnant women with CD, it could increase the likelihood of maternal-fetal transmission. Screening of infants born to *T. cruzi*-infected mothers remains crucial and could potentially be disrupted by the negative impact of COVID-19 on access to care (37, 38).

**Immunosuppressed patients**

Immunosuppressed patients are at increased risk of severe COVID-19, especially those with aggressive underlying disease, immunosuppressive active treatment, or lymphopenia. The overproduction of cytokines during COVID-19 infection leads to significant tissular damage, particularly in the lungs. This intense inflammatory process in immunosuppressed patients infected by COVID-19 and CD could influence the evolution of CCC and potentially trigger CD reactivation due either to viral infection interference, such as in HIV infection (39), or possible immunosuppressive therapy for COVID-19 (9,10) associated with the severity of underlying diseases. Conversely, any approach to improve the immune response at this level is desirable, either by using antiviral or cytokine blocking agents (IL-6, IL-1β, TNF-a) (40). On the other hand, we may consider the risk of inducing clinical activation of autoimmune disease in individuals with asymptomatic COVID-19 and, consequently, a potential reactivation of CD (41).
Epidemiological Considerations

The spread of the COVID-19 pandemic in countries affected by CD raises concerns for several reasons. The population with *T. cruzi* infection, which numbers over six million people worldwide (3, 42), is aging, at risk of CCC, has a significant burden of comorbidities, and is socioeconomically vulnerable. All of these factors could potentially increase the impact of COVID-19 in this population, especially within a scenario of weakened and overloaded health systems.

First, although the incidence of new CD infections is around 30,000 annually (3), this number has declined in recent decades, meaning a high proportion of people living with CD are older or aging (43). While >80% of COVID-19 cases are mild or asymptomatic, severe cases are more common among older adults. In a retrospective study the risk of mortality increased by 0.03-1.17 with every year of increased age in patients from Wuhan (44). Another study using data from various countries estimated a case fatality ratio of 4.5% in individuals older than 60, compared to 1.4% in those younger than 60, with the highest rates in patients over 80 (45). In the United States, 78.6% of deaths have occurred in people 65 or older (46).

Over one million people in the Americas suffer from CCC (3), and underlying cardiovascular disease is a major risk factor for hospitalization and death from COVID-19. The incidence of acute cardiac injury from COVID-19 has been reported as 8% in hospitalized patients (47), and in one Chinese study was much more prevalent in deaths (59%) than recovering patients (1%) (48). Cardiovascular disease was also identified in 30% of COVID-19 related deaths in Italy (49), while age>60 and Charlson Comorbidity Index >3 were associated with greater mortality in a U.S. cohort of 1305 hospitalized patients (50).

Finally, several studies have noted high levels of comorbidities among both patients with CD and those with severe forms of COVID-19. One Brazilian study identified a mean of 2.7 chronic comorbidities in CD patients (51). In 168 CD patients in São Paulo, 51.2% had hypertension and 23.8% diabetes mellitus (52). Another study in a younger sample of 137 patients in Switzerland found 2.9% had diabetes and 17% hypertension (53). Both hypertension and diabetes were associated with high mortality rates from COVID-19 in China (7.3 and 6.0% respectively) (54), and were 2-3 times more prevalent in severe vs. non-severe hospitalizations (47). Diabetes was also prevalent in a third of deaths in an analysis of Italian data (55). It is important to note that these comorbidities also reflect the older age of the populations which are especially impacted by both CD and COVID-19.
Social Context and Access to Healthcare

As the pandemic progresses from Europe and the United States into the Global South, it is increasingly impacting vulnerable populations. In the U.S., COVID-19 has thus far had a greater impact on Blacks and Latinos. According to the CDC, these groups have a higher prevalence of infection and higher weighted distribution of deaths than their share of the general population (56). A higher rate of deaths among people in Brazil who self-identify as black has also been reported (57, 58). These racial disparities are in turn framed by historically rooted socioeconomic considerations which often determine who is able to self-isolate and avoid exposure.

Moreover, social vulnerability has long been documented in people with CD (59), and groups with high burdens of CD, including indigenous people, the rural poor, and migrants may face particular challenges in accessing healthcare. People living at or near the poverty level are also especially vulnerable to the economic impact of the pandemic, as experts have warned that years of gains in reducing poverty are now in jeopardy. The UN predicts that as the global GDP shrinks by 3.2% in 2020, 34 million more people will be pushed into extreme poverty (60). The worsening economic situation threatens to make access to healthcare even more precarious for people living with CD, who are often forced to make difficult decisions between spending time and money on healthcare or other pressing priorities. Many work in the informal sector or in positions that do not offer paid time off or health insurance.

Also, people with CD may feel more reluctant to seek care in a clinic for fear of exposure to COVID-19, and may, therefore, put off addressing complications related to CD. Indeed, there have been reports of low utilization of services and delayed presentation for chronic conditions since the onset of the pandemic (61, 62). Finally, CD can create a significant emotional burden for affected people who worry about the progression of the disease, and the pandemic may make it harder to access both mental health services and traditional support networks of families and friends. Patients with CD who acquire COVID-19 may experience particular concern and anxiety. As COVID-19 becomes more a part of daily reality, creative responses will be needed from patient groups, social workers, mental health practitioners, and others to continue providing support to people with CD.
Recommendations for Healthcare Providers

Screening/testing of Chagas disease during the pandemic

While the indications for screening and diagnosing CD are unchanged during the COVID-19 pandemic, the timing of testing depends on the degree to which the diagnosis of Chagas disease will affect short term management of the individual being tested. Urgent testing remains appropriate for pregnant women, infants born to seropositive mothers, and any individual who will imminently receive immunosuppression. Screening of blood donations also remains critical. Patients presenting with clinical syndromes suggestive of CD should also receive urgent testing to guide evaluation and therapy. Women from CD-endemic countries who are pregnant should also be screened to evaluate for the possibility of maternal-fetal transmission. At present, widespread screening of individuals without symptoms from endemic countries could be postponed, depending on the state of SARS-CoV-2 circulation in the community and local guidelines, until it can be performed safely, with the understanding that while antiparasitic therapy may be indicated it can generally be delayed until the patient can report for lab testing and follow-up visits without significant risk of exposure.

Management of patients coinfectcd with Chagas disease and COVID-19

Below preliminary recommendations are provided for patients with CD who acquire COVID-19. The recommendations are divided depending on the patient’s form of CD.

Acute forms of CD

Acute cases of CD following congenital, vector, or oral transmission or via transfusion, laboratory accidents, and other routes generally warrant antiparasitic treatment as early as possible, even in the context of the COVID-19 pandemic. If the patient is coinfected and has both the acute form of CD and COVID-19, timely antiparasitic treatment of CD is also needed, but clinicians should be mindful of the severity of COVID-19 symptoms.

Congenital CD: Cases of congenital transmission are acute cases of CD, and treatment is effective with few side effects. COVID-19 is generally not severe in infants and children (63). If the child does not
have COVID-19 symptoms, antiparasitic treatment should be given as soon as the diagnosis of *T. cruzi* infection is established (37).

**Reactivation:** Patients must be admitted to the hospital and receive antiparasitic treatment with benznidazole (BZN) for 60 days. However, if a full 60 days of treatment is not possible because of adverse events, treatment should still be continued for as close to 60 days as possible using anti-histaminic and/or anti-inflammatory drugs. Reactivation involving myocarditis/meningoencephalitis is of particular concern, due to the occurrence of vascular/ nervous system/ myocardium involvement by COVID-19 and should be carefully monitored in the intensive care unit.

**Immunosuppression without reactivation:** In this case, antiparasitic treatment could be delayed until the patient can safely attend clinic, depending on self-isolation guidelines and risk of exposure to COVID-19. However, CD reactivation with signs in target organs should be closely monitored by clinical follow-up, direct microscopy (concentration methods) on peripheral blood and/or secretions (39), and, if possible, quantitative PCR during COVID-19 infection according to local protocols.

**Indeterminate chronic CD**

From an individual health management point of view, people with asymptomatic infection (in the indeterminate clinical form of CD) are those in whom there is evidence of *T. cruzi* infection, but no evidence of organ damage (mainly cardiovascular or digestive), assessed by (1) non-specific symptoms and (2) low sensitivity tests to detect early organ damage, such as electrocardiogram, chest X-ray, and barium swallow and enema (64). With or without antiparasitic treatment, regular monitoring is recommended to evaluate the clinical condition during follow-up and to quickly detect treatment failure and/or clinical progression.

As a general recommendation, and given the current epidemiological situation, it is important to assess the risk-benefit of referring a patient to a healthcare center. It is essential to preserve patient safety in terms of preventing new cases of COVID-19. However, it is also important from a public health perspective to optimize existing resources for health care. Outpatient visits as well as regular cardiovascular and gastrointestinal tests could be delayed if CD patients are stable. The use of telehealth tools for virtual consultation is highly recommended, including incorporating advice to patients about the need to contact healthcare facilities in case of the onset of symptoms, either from CD or possible COVID-19 infection.
**Etiological treatment of Chagas disease**

Etiological (antiparasitic) treatment in patients with CD without evidence of organ involvement, is recommended for acute cases and most chronic cases in the indeterminate form or with only mild cardiomyopathy (5, 65). In the current context of the pandemic, however, two main aspects should be taken into account: 1) drug characteristics and potential interactions with current treatment of COVID-19, and 2) the urgency of the indication for anti-*T. cruzi* drugs.

**Drug characteristics**

Benznidazole (BZN) and Nifurtimox (NFX) are the two drugs accepted by regulatory agencies for antiparasitic treatment of CD. Benznidazole (N-benzyl-2-nitro-1-imidazole acetamide, BZN) is a nitroimidazole that inhibits DNA, RNA, and protein synthesis of *T. cruzi*. Nifurtimox (5-nitrofuran 3-methyl-4-(5′- nitrofur furylideneamine) tetrahydro-4H-1,4-tiazine-1,1- dioxide, NFX) is a nitrofuran derivative whose mechanism of action involves various reduction and oxidation reactions of its nitro constituent, leading to the production by parasite enzymes of a variety of reactive oxygen species that react with cellular macromolecules and are lethal to the parasite. NFX also leads to the inactivation of a critical trypanosomal enzyme, trypanothione reductase (66).

In both cases, the mechanism of action is not completely described, and exploration of the potential interactions between BZN and NFX with most common drugs used in COVID-19 management should be taken into consideration and further explored. Due to the hepatic metabolism of BZN (95%) and NFX (>99%), hepatotoxicity in combination with anti-COVID-19 drugs must be monitored.

**Treatment indications and follow-up of patients under treatment**

Etiological treatment of *T. cruzi* infection is an emergency only under very specific circumstances (67). Even if adverse drug reactions (ADRs) related to BZN and NFX are non-severe in most cases (68), close follow-up of patients who start a BZN or NFX regime is recommended to identify side effects promptly and to monitor hepatic and hematologic function (53, 69, 70). To avoid unnecessary risks, during the COVID-19 pandemic, delaying
initiation of etiological treatment regimens for chronic *T. cruzi* infection without organ involvement is a valid course of action to avoid unnecessary exposure to COVID-19 in the healthcare setting, and because of limitations in follow-up due to decreased in-person care. Nevertheless, patients diagnosed with COVID-19 may receive immunosuppressive therapy, and close monitoring to diagnose CD reactivation early in its course is recommended. In the case of clinical and/or parasitological evidence of reactivation, starting treatment with BZN or NFX is an emergency (67).

If a patient is already receiving BZN or NFX, treatment should be continued, and self-quarantine measures to avoid COVID-19 should be taken. Telehealth tools for treatment follow-up are recommended as well as minimization of contact with healthcare facilities, which would primarily only be indicated to perform laboratory tests usually recommended during treatment to monitor hepatotoxicity and hemogram alterations due to BZN or NFX, or in the event of concerning ADRs. If a patient under treatment with BZN or NFX develops symptomatic COVID-19 infection, providers could consider on a case-by-case basis whether to interrupt treatment, depending on the severity of symptoms and the type of treatment required. There is no evidence of drug-drug interaction among antiparasitics for CD and drugs required to treat COVID-19, and treatment of CD in the indeterminate form is non-urgent.

Table 1 summarizes guidance for providing etiological treatment of CD during the pandemic, taking into account both the patient’s form of CD and their COVID-19 status.
Table 1. Etiological treatment recommendations for Chagas disease in the context of COVID-19 coinfection

| Chagas Disease Status                                      | COVID-19 Status                      | Guidance for Etiological Treatment with Benznidazole or Nifurtimox                                                                 |
|------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Chronic, indeterminate                                    | Negative                             | Consider delaying treatment to minimize risk of COVID-19 exposure to patients, based on local epidemiological context and current physical distancing regulations |
| Chronic, indeterminate                                    | Positive, with or without symptoms   | Consider delaying treatment until COVID-19 is completely resolved, and based on local epidemiological context and current physical distancing regulations |
| Acute cases                                                | Negative or positive, with or without symptoms | Initiate treatment.                                                                                                                                 |
| Clinical and/or parasitological evidence of reactivation    | Negative or positive, with or without symptoms | Initiate treatment.                                                                                                                                 |
| Chronic, indeterminate, currently undergoing etiological treatment | Positive, symptomatic               | Postpone treatment and closely monitor for reactivation of *T. cruzi* infection by direct microscopy on peripheral blood or fluids and/or quantitative PCR (if available) if immunosuppressive drugs are prescribed in the context of COVID-19 management. If reactivation is evident, re-start benznidazole/nifurtimox treatment. |
| Chronic, indeterminate, currently undergoing etiological treatment | Positive, asymptomatic              | Continue treatment.                                                                                                                                 |

*Note: T. cruzi is the etiological agent of Chagas disease*
In all cases, etiological treatment of Chagas disease should be accompanied by appropriate close follow-up including liver enzymes and blood count parameters. See Echeverria et al 2020 (67).

**Management of patients with Chagas cardiomyopathy and COVID-19**

COVID-19 has been associated with multiple cardiac manifestations that include cardiac arrhythmias, Type 2 and 1 myocardial infarction, heart failure exacerbations and acute fulminant myocarditis (71, 72). Potential implications between COVID-19 and CCC may be expected primarily due to the common immunological pathways shared by both diseases, as angiotensin-converting enzyme 2 (ACE2) is involved in heart function and the development of hypertension and diabetes mellitus, risk factors frequently observed in patients with CCC. ACE2 levels can be increased by the use of ACE inhibitors and/or angiotensin receptor blockers (ARBs) which are frequently used for the management of CCC. There is no evidence to date to support discontinuation of either ACE or ARBs based on the theoretical potential of increasing the susceptibility to COVID-19 infection. Most cardiovascular societies including ESC, ACC, AHA, CCS, and the IASC have indicated that these medications should be continued regardless of the presence of concomitant COVID-19 manifestations. This should also be true in patients with CCC.

Other potential interactions may occur in patients with CCC currently treated for cardiac arrhythmias such as atrial fibrillation or life-threatening ventricular arrhythmias receiving amiodarone, as the potential for increased QT interval with treatments that have been proposed for COVID-19 such as hydroxychloroquine and/or azithromycin may increase the risk of torsade de points.

Patients with CCC must continue their usual treatments during the COVID-19 pandemic. Outpatient clinics may use telehealth if available, to avoid putting these vulnerable patients at risk of COVID-19 infection. With proper hygiene and self-care measures, cardiac tests like EKG, echo, stress tests or Holter may be performed or slightly delayed, always weighting risk-benefit and regional SARS-CoV-2 circulation status. If a patient with CCC develops new arrhythmias, stroke, or acute or worsening chronic heart failure, hospitalization must not be
delayed. As hospitals in some regions may be severely strained by COVID, care of these acute events may be compromised, putting CCC patients at risk.

Table 2 lists potential interactions between cardiovascular drugs used to treat CCC and some proposed COVID-19 treatments.

**Table 2: Potential Interactions between COVID-19 Treatments under Investigation and CCM Drugs**

| Drug                        | Interaction                                                                 |
|-----------------------------|-----------------------------------------------------------------------------|
| Chloroquine-hydroxychloroquine | Inhibits CYP2D6 (increasing half-life of most of the beta blockers (73) and amiodarone), and inhibits and downregulates P-gP (74). They do not interact with NOACS or VKAs (75). |
| Protease inhibitors (lopinavir-ritonavir) | By inhibiting CYP3A4, they increase plasma levels of most of CV drugs. May lower the effect of VKAs by induction of CYP2C19 and increase plasma levels of NOACs. Also may increase amiodarone levels (76). |
| Azithromycin | Increases levels of warfarin/acenocoumarol, these anticoagulants should be withdrawn during Azithromycin treatment. Due to PgP inhibition, dose reduction of NOACs may be required. |
| Atazanavir | Increases levels of VKA’s and NOACs (should be discontinued). May increase amiodarone levels and effect. May increase digoxin levels. Mild increase in atenolol levels (beta blocker) (76). |
| Remdesivir | No relevant interactions. |
| Favipiravir, Bevacizumab, Eculizumab, Fingolimod, Pirfenidone, Interferon Methylprednisone | No relevant interactions. |
| Tocilizumab | May lower effect of anticoagulants. |
| Nitazoxanide | May increase VKAs levels; do not use concomitantly. |
| Sarilumab | It is a CYP3A4 inducer, but dose modifications are not recommended. |
### Interferon and Methylprednisolone
- Reduction of VKAs is advised.

### Ribavirin
- Interferes with the absorption of VKAs, possibly increasing the dose. Enalapril and other ACE2-is may provoke dry cough as well as ribavirin (77).

### Ivermectin
- May decrease the effect of warfarin and dicoumarol. Risk of myopathy with captopril (78).

### Oseltamivir
- No CYP interactions with CV drugs. However, case reports and series show some increase in the effect of VKAs (75).

### Arbidol (Umifenovir)
- May decrease metabolism of labetalol (beta-blocker) (79).

### Canakinumab
- No known drug interaction, but upregulation of CYP enzymes may further modify metabolism of CV drugs (80, 81).

### Anakinra
- No drug interactions.

### Emapalumab
- No known drug interaction, but upregulation of CYP enzymes may further modify metabolism of CV drugs (82).

### Siltuximab
- Vitamin K antagonist interaction through CYP3450. Close monitoring (83).

### Cyclosporin A
- Cyclosporin may increase in Digoxin levels. Amiodarone, losartan and valsartan increase cyclosporine levels; ACE inhibitors increase nephrotoxicity (84, 85).

### Sirolimus
- Serious warning; may increase risk of ACE inhibitors angioedema. CYP450 and PgP interactions (86).

### Darunavir/cobicistat
- Drugs metabolized by CYP3A4, CYP2D6, or that use the transporters P-glycoprotein, BCRP, MATE1, OATP1B1 or OATP1B3, may have interactions (87). Anticoagulants, beta blockers, and digoxin should be used with caution.

### Future Needs
Our current understanding of the potential interrelations between CD and COVID-19 is still limited; there are substantial needs for future research. The recommendations provided in this document should be considered preliminary and may require refinement and adjustment as
our understanding of both diseases develops. Table 3 lists some of the most important gaps in our current clinical knowledge. Research from other disciplines will also be needed to better understand the epidemiology of both diseases, the social and psychological impacts of the pandemic on people with CD, new access barriers that emerge in the context of the pandemic and the economic dislocation it causes, and the particular contexts of vulnerable populations including migrants and indigenous communities.

Table 3: Understanding the Interaction of COVID-19 and Chagas Disease: Gaps and Needs

| Disease interaction                                      | Clinical questions                                                                 | Drug development needs                                                                 |
|----------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| ● How is the natural history of Chagas disease affected by COVID-19? | ● What cautions are necessary regarding COVID-19 treatment in CD patients?        | ● What are the antiviral effects of antiparasitic drugs for CD (benznidazole and nifurtimox)? |
| ● Can the cytokine storm trigger reactivation of parasitemia?      | ● What are the hemodynamic and arrhythmic risks of COVID-19 in patients with CCC? | ● Can anti-inflammatory drugs improve host response to COVID-19 and complement antiparasitic treatment of CD? |
| ● Does the cytokine storm trigger disease progression?             | ● What is the impact of delaying CD treatments during COVID-19 infection?          | ● Can allopurinol or colchicine help delay or avoid thrombotic complications?          |
| ● Do viral and parasitic immune response pathways cross react?   | ● What is the impact of delays in access to CD diagnosis and cardiac evaluation?  | ● Is full anticoagulant therapy useful for COVID-19 (88) and CD (89)?                  |
| ● Does the chronic inflammatory state of CD lead to more severe COVID-19 disease | ● What is the impact of possible health system collapse on quality of care of CD patients with symptomatic disease? | ● Could cardiovascular CD treatments such as amiodarone treat COVID-19?                  |
| ● Does the prothrombotic state from both diseases behave synergistically? |                                                                                       |                                                                                        |
Conclusion

While global in scope and indiscriminate in whom it infects, COVID-19 poses a particular risk to people with CD. Both diseases are more prevalent in marginalized populations, whose access to appropriate care is limited, and whose exposure to risk factors is proportionally higher. COVID-19 is more lethal in individuals with cardiac disease, and/or other cardiac risk factors, such as diabetes and obesity, which are also prevalent in individuals with CD. The mechanisms of COVID-19 disease, while not completely understood, theoretically pose a risk of both exacerbation of cardiac dysfunction from CD and acute reactivation of CD due either to disease-induced immunomodulation or therapeutic immunosuppression. The economic impact of the pandemic hits hardest in the lowest socioeconomic strata, further complicating the ability of many individuals with CD to obtain the care that they need for either illness. Efforts to mitigate the spread of COVID-19 by limiting medical facilities to all but the most urgent care complicates efforts to diagnose, treat, and monitor patients with CD, which may lead to clinical deterioration, increased maternal fetal transmission, and underdiagnosis, all of which were significant concerns even before the onset of the pandemic.

Roadblocks to accessing proper care for CD were recently described in the WHF-IASC Roadmap on CD (5). Using a similar framework, Table 4 assesses the potential effect of the pandemic on key roadblocks to CD healthcare.
Table 4. Potential Impact of COVID-19 on Chagas Disease Healthcare Roadblocks

| Area                                      | Potential Impact of SARS-CoV-2 on Roadblocks                                                                 |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Prevention                                | • Reduced commitment from governments  
• Diversion of clinical research to COVID-19  
• Public health resources diverted to COVID-19  
• Lower media interest in neglected diseases  
• Limitations on health fairs, campaigns, and community events. |
| Diagnosis                                 | • Decreased visits to healthcare facilities out of fear of contagion  
• Testing/laboratory resources strained by COVID-19 |
| Etiological Treatment                      | • Decreased visits to healthcare facilities out of fear of contagion  
• Healthcare personnel strained by COVID-19  
• Lack of knowledge on drug interactions with COVID-19, or with COVID-19 drugs |
| Diagnosis and treatment of clinical complications | • Limited knowledge of interaction between COVID-19 and chronic Chagas cardiomyopathy (CCC)  
• Potential impact of COVID-19 drugs on CCC  
• Strains on health facilities’ ability to manage CCC |
| Psychosocial                               | • Increasing poverty due to economic impact of pandemic  
• Isolation from support networks  
• Fears about susceptibility to COVID-19 because of CD diagnosis |

The end of the pandemic in Latin America is still far from sight and its full impact on healthcare and healthcare access, in particular, remains to be seen. CD has long been a hidden disease, with low awareness among healthcare professionals and people at risk, and limited commitment from governments. In the short-term, as public health resources are intently focused on mitigating the pandemic, it could become even more of a challenge to bring awareness to CD. At the same time, the pandemic could serve as an opportunity to strengthen public concern for addressing comorbid conditions and meeting the healthcare needs of underserved populations. Still, the current reality requires us to rethink traditional approaches to CD and other neglected diseases, to ensure we continue to make progress toward their eradication even as new public health challenges emerge. Ultimately, neither CD nor COVID-19 can be separated from its socioeconomic context, and winning the struggle against both diseases will involve implementing comprehensive programs that focus on strengthening the healthcare rights and access of the marginalized people who are currently most impacted.
Contributions
All authors contributed to the drafting and review of the manuscript.

Conflicts of Interest
None.

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References

1. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. The Lancet. 2010;375(9723):1388–402.
2. Johns Hopkins Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2020 [updated June 30, 2020. Available from: https://coronavirus.jhu.edu/map.html.
3. World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates Weekly Epidemiological Record. 2015;90(6):33-44.
4. World Health Organization. Fourth WHO Report on Neglected Tropical Diseases. Geneva; 2017.
5. Echeverría LE, Marcus R, Novick G, Sosa-Estani S, Ralston K, Zaidel EJ, et al. WHF IASC Roadmap on Chagas Disease. Glob Heart. 2020;15(1):26–.
6. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MOC. Diagnosis and management of Chagas disease and cardiomyopathy. Nature Reviews Cardiology. 2012;9(10):576-89.
7. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. European journal of clinical investigation. 2009;39(7):618-25.
8. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovascular Research. 2020;116(6):1097-100.
9. Rassi A, Amato Neto V, de Siqueira AF, Ferrioli Filho F, Amato VS, Rassi Júnior A. [Protective effect of benznidazole against parasite reactivation in patients chronically infected with Trypanosoma cruzi and treated with corticoids for associated diseases]. Revista da Sociedade Brasileira de Medicina Tropical. 1999;32(5):475-82.
10. dos Santos-Neto LL, Polcheira MF, Castro C, Lima RA, Simaan CK, Corrêa-Lima FA. [Trypanosoma cruzi high parasitemia in patient with systemic lupus erythematosus]. Revista da Sociedade Brasileira de Medicina Tropical. 2003;36(5):613-5.
11. López L, Arai K, Giménez E, Jiménez M, Pascuzzo C, Rodríguez-Bonfante C, et al. [C-reactive protein and interleukin-6 serum levels increase as Chagas disease progresses towards cardiac failure]. Revista espanola de cardiologia. 2006;59(1):50-6.
12. Keating SM, Deng X, Fernandes F, Cunha-Neto E, Ribeiro AL, Adesina B, et al. Inflammatory and cardiac biomarkers are differentially expressed in clinical stages of Chagas disease. International journal of cardiology. 2015;199:451-9.
13. Benziger CP, do Carmo GAL, Ribeiro ALP. Chagas Cardiomyopathy: Clinical Presentation and Management in the Americas. Cardiology clinics. 2017;35(1):31-47.
14. Tanowitz HB, Machado FS, Spray DC, Friedman JM, Weiss OS, Lora JN, et al. Developments in the management of Chagas cardiomyopathy. Expert review of cardiovascular therapy. 2015;13(12):1393-409.
15. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020.
16. Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nature reviews Immunology. 2020;20(5):271-2.
17. de Araújo FF, Lima Torres KC, Viana Peixoto S, Pinho Ribeiro AL, Vaz Melo Mambrini J, Bortolo Rezende V, et al. CXCL9 and CXCL10 display an age-dependent profile in Chagas patients: a cohort study of aging in Bambui, Brazil. Infectious diseases of poverty. 2020;9(1):51.
18. Dutra WO, Menezes CA, Magalhães LM, Gollob KJ. Immunoregulatory networks in human Chagas disease. Parasite immunology. 2014;36(8):377-87.
19. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart rhythm. 2020.
20. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020;75(23):2950-73.
21. Pinazo MJ, Posada Ede J, Izquierdo L, Tassies D, Marques AF, de Lazzari E, et al. Altered Hypercoagulability Factors in Patients with Chronic Chagas Disease: Potential Biomarkers of Therapeutic Response. PLoS neglected tropical diseases. 2016;10(1):e0004269.
22. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. Circulation. 2018;138(12):e169-e209.
23. Sosa-Estani S, Cura E, Velazquez E, Yampotis C, Segura EL. Etiological treatment of young women infected with Trypanosoma cruzi, and prevention of congenital transmission. Revista da Sociedade Brasileira de Medicina Tropical. 2009;42(5):484-7.
24. Fabbro DL, Danesi E, Olivera V, Codebó MO, Denner S, Heredia C, et al. Trypanocide treatment of women infected with Trypanosoma cruzi and its effect on preventing congenital Chagas. PLoS neglected tropical diseases. 2014;8(11):e3312.
25. Regueiro A, García-Álvarez A, Sitges M, Ortiz-Pérez JT, De Caralt MT, Pinazo MJ, et al. Myocardial involvement in Chagas disease: insights from cardiac magnetic resonance. International journal of cardiology. 2013;165(1):107-12.
26. Nunes MCP, Badano LP, Marin-Neto JA, Edvardsen T, Fernández-Golfín C, Bucciarelli-Ducci C, et al. Multimodality imaging evaluation of Chagas disease: an expert consensus of Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI). European heart journal cardiovascular Imaging. 2018;19(4):459-60n.
27. Torreão JA, Ianni BM, Mady C, Naia E, Rassi CH, Nomura C, et al. Myocardial tissue characterization in Chagas' heart disease by cardiovascular magnetic resonance. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2015;17:97.
28. Barros ML, Ribeiro A, Nunes Mdo C, Rocha MO. [Association between left ventricular wall motion abnormalities and ventricular arrhythmia in the indeterminate form of Chagas disease]. Revista da Sociedade Brasileira de Medicina Tropical. 2011;44(2):213-6.
29. Furtado RG, Frota Ddo C, Silva JB, Romano MM, Almeida Filho OC, Schmidt A, et al. Right ventricular Doppler echocardiographic study of indeterminate form of chagas disease. Arquivos brasileiros de cardiologia. 2015;104(3):209-17.
30. Cianciulli TF, Saccheri MC, Papantoniou A, Méndez RJ, Gagliardi JA, Prado NG, et al. Use of tissue doppler imaging for the early detection of myocardial dysfunction in patients with the indeterminate form of Chagas disease. Revista da Sociedade Brasileira de Medicina Tropical. 2020;53:e20190457.
31. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69(6):1002-9.
32. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997-1001.
33. Nath A. Neurologic complications of coronavirus infections. Neurology. 2020;94(19):809-10.
34. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg. 2020;194:105921.
35. Howard EJ, Xiong X, Carlier Y, Sosa-Estani S, Buekens P. Frequency of the congenital transmission of Trypanosoma cruzi: a systematic review and meta-analysis. BJOG: an international journal of obstetrics and gynaecology. 2014;121(1):22-33.
36. Kaplinski M, Jois M, Galdos-Cardenas G, Rendell VR, Shah V, Do RQ, et al. Sustained Domestic Vector Exposure Is Associated With Increased Chagas Cardiomyopathy Risk but Decreased Parasitemia and Congenital Transmission Risk Among Young Women in Bolivia. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;61(6):918-26.
37. Carlier Y, Altcheh J, Angheben A, Freilij H, Luquetti AO, Schijman AG, et al. Congenital Chagas disease: Updated recommendations for prevention, diagnosis, treatment, and follow-up of newborns and siblings, girls, women of childbearing age, and pregnant women. PLoS neglected tropical diseases. 2019;13(10):e0007694.
38. Buekens P, Alger J, Bréart G, Cafferata ML, Harville E, Tomasso G. A call for action for COVID-19 surveillance and research during pregnancy. The Lancet Global health. 2020;8(7):e877-e8.
39. Sartori AM, Ibrahim KY, Nunes Westphalen EV, Braz LM, Oliveira OC, Jr., Gakiya E, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Annals of tropical medicine and parasitology. 2007;101(1):31-50.
40. Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and Cancer: a Comprehensive Review. Current oncology reports. 2020;22(5):53.
41. Zingone F, Savarino EV. Viral screening before initiation of biologics in patients with inflammatory bowel disease during the COVID-19 outbreak. The lancet Gastroenterol & hepatology. 2020;5(6):525.
42. Manne-Goehler J, Umeh CA, Montgomery SP, Wirtz VJ. Estimating the Burden of Chagas Disease in the United States. PLoS neglected tropical diseases. 2016;10(11):e0005033.
43. Martins-Melo FR, Ramos AN, Jr., Alencar CH, Heukelbach J. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. Acta tropica. 2014;130:167-74.
44. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-62.
45. Verity R, Okell LC, Dorogati I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious diseases. 2020;20(6):669-77.
46. Centers for Disease Control. CDC COVID Data Tracker 2020 [updated June 30, 2020. Available from: https://www.cdc.gov/covid-data-tracker/index.html#demographics.
47. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical research in cardiology : official journal of the German Cardiac Society. 2020;109(5):531-8.
48. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama. 2020;323(11):1061-9.
49. Moccia F, Gerbino A, Lionetti V, Miragoli M, Munaron LM, Pagliaro P, et al. COVID-19-associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. GeroScience. 2020.

50. Imam Z, Odish F, Gill I, O’Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. Journal of internal medicine. 2020.

51. Alves RM, Thomaz RP, Almeida EA, Wanderley Jda S, Guariento ME. Chagas' disease and ageing: the coexistence of other chronic diseases with Chagas' disease in elderly patients. Revista da Sociedade Brasileira de Medicina Tropical. 2009;42(6):622-8.

52. Oliveira Junior LR, Carvalho TB, da Costa ÉAPN, Marques Pereira PC, Kurokawa CS. Cardiovascular comorbidities in patients with chronic Chagas disease. AME Medical Journal. 2018.

53. Jackson Y, Castillo S, Hammond P, Besson M, Brawand-Bron A, Urzola D, et al. Metabolic, mental health, behavioural and socioeconomic characteristics of migrants with Chagas disease in a non-endemic country. Tropical medicine & international health : TM & IH. 2012;17(5):595-603.

54. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020.

55. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. Jama. 2020;323(18):1775-6.

56. Centers for Disease Control. Provisional Death Counts for Coronavirus Disease 2019 (COVID-19): Race and Hispanic Origin 2020 [updated June 24, 2020. Available from: https://www.cdc.gov/nchs/ncs/vsrr/covid_weekly/index.htm#Race_Hispanic.

57. Batista A AB, Faveret G, Peres I, Marchesi J, Cunha JP, Dantas L, Bastos L, Carrilho L, Aguilar S, Biaoo F, Macaira P, Hamacher S, Bozza F. Análise socioeconômica da taxa de letalidade da COVID-19 no Brasil. Nucleo de Operacoes e Inteligencia em Saude (NOIS); 2020 May 27, 2020. Contract No.: Nota Tecnica 11.

58. Baqui P BI, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. The Lancet Global Health. 2020.

59. Viotti R, Vigliano CA, Alvarez MG, Lococo BE, Petti MA, Bertocchi GL, et al. The impact of socioeconomic conditions on chronic Chagas disease progression. Revista espanola de cardiologia. 2009;62(11):1224-32.

60. United Nations. World Economic Situation and Prospects as of mid-2020 New York, NY; 2020.

61. Pessoa-Amorim G, Camm CF, Gajendragadkar P, De Maria GL, Arsac C, Laroche C, et al. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. European Heart Journal - Quality of Care and Clinical Outcomes. 2020.

62. Reza N, DeFilippis EM, Jessup M. Secondary Impact of the COVID-19 Pandemic on Patients With Heart Failure. Circulation: Heart Failure. 2020;13(5):e007219.

63. Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. J Clin Virol. 2020;128:104395-.

64. Alvar J, Alves F, Bucheton B, Burrows L, Büscher P, Carrillo E, et al. Implications of asymptomatic infection for the natural history of selected parasitic tropical diseases. Semin Immunopathol. 2020;42(3):231-46.

65. Pan American Health Organization. Guidelines for the diagnosis and treatment of Chagas disease Washington, DC; 2019.
66. Urbina JA. Ergosterol biosynthesis and drug development for Chagas disease. Memorias do Instituto Oswaldo Cruz. 2009;104 Suppl 1:311-8.
67. Bern C, Montgomery SP, Herwaldt BL, Rassi A, Jr., Marin-Neto JA, Dantas RO, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. Jama. 2007;298(18):2171-81.
68. Sperandio da Silva GM, Mediano MFF, Hasslocher-Moreno AM, Holanda MTd, Sousa ASd, Sangenis LHC, et al. Benznidazole treatment safety: the Médecins Sans Frontières experience in a large cohort of Bolivian patients with Chagas’ disease—authors’ response. Journal of Antimicrobial Chemotherapy. 2018;73(4):1115-6.
69. Pinazo MJ, Muñoz J, Posada E, López-Chejade P, Gállego M, Ayala E, et al. Tolerance of benznidazole in treatment of Chagas' disease in adults. Antimicrobial agents and chemotherapy. 2010;54(11):4896-9.
70. Forsyth CJ, Hernandez S, Olmedo W, Abuhamidah A, Traina MI, Sanchez DR, et al. Safety Profile of Nifurtimox for Treatment of Chagas Disease in the United States. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(8):1056-62.
71. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259-60.
72. Libby P. The Heart in COVID-19: Primary Target or Secondary Bystander? JACC: Basic to Translational Science. 2020;5(5):537-42.
73. Shin J, Johnson JA. Pharmacogenetics of beta-blockers. Pharmacotherapy. 2007;27(6):874-87.
74. Salaroglio IC, Gazzano E, Abdullrahman A, Mungo E, Castella B, Abd-Elrahman G, et al. Increasing intratumor C/EBP-β LIP and nitric oxide levels overcome resistance to doxorubicin in triple negative breast cancer. Journal of experimental & clinical cancer research : CR. 2018;37(1):286.
75. Zaidel E WQF, Sosa Liprandi A, Mendoza I, Marquez MF, Nunez E, Barbosa M, Baranchuk A. Hidroxicloroquina. Mensajes desde la cardiología en tiempos de pandemia por coronavirus [Hydroxychloroquine: Cardiology’s viewpoint in times of coronavirus pandemic]. Medicina (B Aires). 2020;80(3):271-4.
76. University of California-San Francisco. Interactions with Amiodarone and Antiretrovirals 2019 [Available from: http://arv.ucsf.edu/insite?page=ar-00-02&post=8&param=116.
77. Milazzo L, Cattaneo D, Cheli S, Ferraris L, Colella E, Clementi E, et al. ACE inhibitors and ribavirin-associated cough: a common undefined predisposing factor? European journal of clinical pharmacology. 2013;69(3):743-5.
78. DrugBank. Ivermectin 2020 [updated June 30, 2020. Available from: https://www.drugbank.ca/drugs,DB00602.
79. DrugBank. Umifenovir 2020 [updated June 12, 2020. Available from: https://www.drugbank.ca/drugs,DB13609.
80. Chakraborty A, Tannenbaum S, Rordorf C, Lowe PJ, Floc’h D, Gram H, et al. Pharmacokinetic and Pharmacodynamic Properties of Canakunumab, a Human Anti-Interleukin-1β Monoclonal Antibody. Clinical Pharmacokinetics. 2012;51(6):e1-e18.
81. Novartis Pharmaceuticals Corporation. ILARIS (canakinumab) Full Prescribing Information2012.
82. Patheon Italia. GAMIFANTTM (emapalumab-lzsg) injection, for intravenous use. 2018.
83. Janssen Biotech. SYLVANT. Full Prescribing Information2014.
84. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporin. An update. Clin Pharmacokinnet. 1996;30(2):141-79.
85. Lill J, Bauer LA, Horn JR, Hansten PD. Cyclosporine–drug interactions and the influence of patient age. American Journal of Health-System Pharmacy. 2000;57(17):1579-84.
86. Pfizer Inc. RAPAMUNE. 2017.
87. Janssen Pharmaceutical Companies. PREZCOBIX (darunavir and cobicistat) tablets, for oral use. 2019.
88. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. Journal of the American College of Cardiology. 2020;76(1):122-4.
89. Sousa AS, Xavier SS, Freitas GR, Hasslocher-Moreno A. Prevention strategies of cardioembolic ischemic stroke in Chagas’ disease. Arquivos brasileiros de cardiologia. 2008;91(5):306-10.