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# Quinine in Covid-19 Repurposing for Impact

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## Abstract

Quinine repurposing for use in moderate to severe COVID-19 is empirically utilized on a physician-patient basis, adduced from the (LWI) study protocols for COVID-19 Response, a monologue of protocols which had been hypothesis-tested, and debated for 6 weeks prior. The three (3) sets of study protocol S6 were compiled with a goal to arriving at a practical and affordable solution to the pandemic. Having undergone debates and hypothesis testing among physicians, researchers and virologists, they are still undergoing random physician-patient trials at the discretion of prescribers and researchers.

They are study protocols designed to 'evolve' as a solution to COVID-19 response. Having tested for the repurposing of Chloroquine and Hydroxychloroquine. 1 in moderate to severe COVID-19 with little success, their use is now assigned to prophylaxis, for a future study. The LWI study protocols strongly suggest the use of Quinine for COVID-19 treatment in moderate to advanced disease, recommending intravenous infusion of Quinine for critical care in COVID-19.

In conclusion, although the sample size of the preliminary study was small, Quinine is impactful with positive outcomes for severe or advanced COVID-19 especially after the cytokine storm, with 5-7 days total recovery after the onset of the cytokine storm. Our preliminary study also found that CQ/HCQ may be very useful for prophylaxis and pre-emptive treatment in COVID-19. In furtherance to this study, we are recommending strongly that a full study should be commissioned to establish and quantify the impact of Quinine on thousands in a given population, and to avert the cytokine storm which is the killer in COVID-19.

**Keywords:** Quinine; Chloroquine; Hydroxychloroquine; Haemozoin Inhibition; Immunomoduulation; Blood Brain Barrier

## Introduction

On 11th March, 2020 by World Health Organization (WHO) declared a pandemic, which arose from the new coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2), leading to a disease known as COVID-19 (Coronavirus Disease discovered in late 2019) [1-3].

In Africa, the first case of coronavirus disease 2019 (COVID-19) was reported in 25th February, 2020 in Algeria [2]. All member states have since been affected with the exception of Lesotho where there have been no official reports of confirmed COVID-19 cases to date. The virus has spread to dozens of countries within weeks. Governments and health authorities across the continent are striving to limits widespread infection [3].

As of 7th August, 2020 the number of confirmed Covid-19 cases from Africa has exceeded 1 million cases [1], of which more than half of that number is in South Africa. There have been over 20,000 deaths and over 600,000 recovered cases [1]. Chan J et al. stated that it is a beta-coronavirus and it may have mild diverse biologic characteristic and virulence. Whether or not this is true is yet to be proven as the virus continues to ravage across the continents [4,5].

There is no known cure for COVID-19 and although it was thought initially to affect only the elderly and chronically ill people, it is believed now, as the strains unfold, to affect all age groups [1,3]. However, most COVID-19 patients are found in the 30-69 years age group. Pre-existing chronic disease is an inclusion criteria for high pre-disposability to COVID-19 [4].

## Live Well Initiative (LWI)

Live Well Initiative (LWI) [6,7] a non-profit public health NGO in Nigeria, with the mission to improve the health status of the people, responded to COVID-19 by developing some pragmatic interventions to mitigate its effect on people, healthcare system and the general communities at large.

## Hypothesis Testing of a Study Protocol

The organization designed Study Protocols 1(Smart), 2(Generic) and 3(Community Health Workers and Low-income settings), which involves the combinatorial use of Chloroquine/Hydroxychloroquine with Azithromycin [6] in appropriate doses (Figures 1 and 2). The (LWI) study protocols have undergone hypothesis testing among physicians, researchers, pharmacists and clinicians as Pre-Exposure Prophylaxis (PrEP), Post Exposure Prophylaxis (PEP), ambulatory care, in-patients care, critical care and post-discharge Intermittent Prophylactic Therapy (IPT) [6,7].

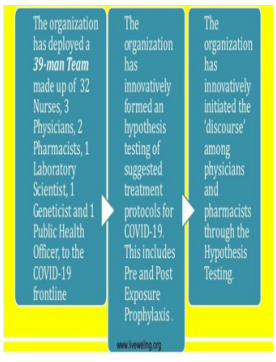


**Figure 1:** LWI COVID-19 corporate response.

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**Figure 2:** Etiology, Pathophysiology of SARS-COV2.

## Covid-19 Reponse Team, Crt

CLWI set up about 39 men team of healthcare professionals from different field of expertise to work as frontline officers with government and stakeholders central to tackling the COVID-19 diseases [6,7].

## The Case for Covid-19 Treatment with Quinine

### Background

Initially at inception, COVID-19 Response was mostly focused on Chloroquine and Hydroxychloroquine, repurposing the drugs for COVID-19 Response, for the following reasons. They are 4-Aminoquinolines; a class of drugs which have been proven to have 7 modes of action against the SARS-COV2 [8,9]. Namely they are Anti-inflammatory, Anti-parasitic, Antiviral, Anti-haemozoin, Immunomodulatory and pH modulation, ionophoric in catalytic relationship with zinc, Antimutagenic, and Polymerase chain inhibition [10,11].

To overcome the shortage of Quinine during the 2nd world war, Quinacrine was developed, which was extensively used during the war to treat malaria. However, the need for a more effective and safer antimalarial for was pressing. Examination of the structural framework of Quinine and Quinacrine revealed that the common feature in the two drugs is the presence of a 4-substituted Quinoine skeleton which was probably responsible for evoking the antimalarial response. Not wanting to lose the key fact in the finding, the 4-Amino Quinoline Structure present in Quinine and Quinacrine was captured as a framework for future Anti-malarials.

Thus the name 4-Amino Quinoline, emerged. To date, Quinine and Quinacrine are interchanged and substituted one for the other.

The above rationale was amply exploited by scientists working in Germany and the Soviet Union resulting in the development of two drugs with the 4-Aminoquinoline structure, namely Chloroquine (CQ) and Sontoquine [10]. The USA then developed a large number of 4-aminoquinolines finally screened emerging chloroquine as the most effective and least toxic drug. There after Hydroxychloroquine (HCQ) was developed by inserting a Hydroxy chain in the Chloroquine moiety. Same properties but the Hydroxy chain attenuated the histamine-1 receptor release [10].

### Efficiency of Cq/Hcq-Pre-Emptive COVID-19 therapy

It is strongly believed that COVID-19 Pre-emptive therapy will benefit greatly from the use of CQ/HCQ. However for the purpose of this study, the history of CQ/HCQ in COVID-19 depicts some hope if therapy is instituted pre emptively or early. A controlled trial study at Renmin Hospital of Wuhan University, Wuhan, China, where 62 patients randomized to take either placebo or HCQ 200 mg twice daily for 5 days from the onset of admission alongside the observation of other standard treatment protocols; from the collated data, it was shown that after treatment with HCQ for 5 days, symptoms exhibited by COVID-19 patients reduced. Also, most of the patients with pulmonary inflammation experienced partial absorption in the HCQ treatment group, thus, HCQ significantly exhibits immune modulatory and Anti-inflammatory properties in viral diseases [12]. Quinine is the Mother of All Amino quinolines and the only naturally occurring one, obtained from the bark of Cinchona [10]. The structure of 4-aminoquinoline is based on the natural crystalline alkaloid Quinine [10], found in Cinchona bark with the Amino chain (NH) at ring 4. In 1934 the drug Chloroquine was synthesised for the first time [11], and it became first in class of the Quinine-based drugs termed as 4-aminoquinolines. The structure of 4-aminoquinoline is based on Quinine, found in Cinchona bark. The Amino chain can also be in ring 8, like Piperaquine which is an 8-Aminoquinoline [10].

In our understanding the viral replication takes place during hibernation. The virus enters the host quietly and hibernates for 10-14 days, replicating and becomes a trojan horse with multiples of copies (trillions) of hidden enemies' viable new viruses (Figure 3).

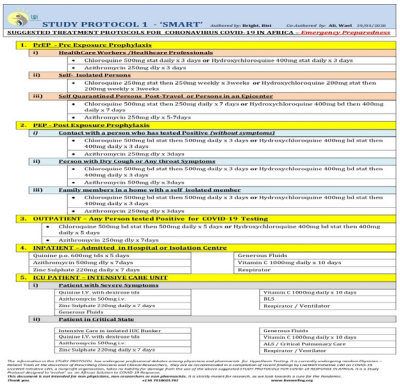


**Figure 3:** ELWI Study Protocol 1 for COVID-19 response in Africa -a solution to the pandemic.

## The storm

This leads to a post hibernation release of trillions of viable viruses in the lungs and they find their way into the alveoli [8,9,13,14], by 'plucking out' the heme iron, thus displacing ferrous and ferric ions and disabling oxygen uptake or ion exchange (ferrous to ferric exchange impeded) and the viruses are then uptake (instead of oxygen uptake) so instead of gaseous exchange, the alveoli are occupied by viruses, causing the typical glass-ground opacity in advanced covid-19. At this stage the viruses are viable in the lung tissue and they are fed by engulfing debris of the dead blood cells, as their food vacuoles.

They are engaging in the Haemozoin Activity [1,4], and they are kept viable through continued haemozoin activity, so the more the hemolysis, the more the 'food' (dead blood cells). The host's body responds with exaggerated immune-defence response of exaggerated Cytokine production, now harming itself by producing too much Cytokines and there is a storm, a total disequilibrium which then enables the viruses to get totally out of hand and like in metastatic cancer, the Storm leaders to a self-attack of host by host defence mechanism, and the exaggerated immunogenic response is described as the Cytokine Storm.

## Managing the 'storm' quinine in COVID-19

CQ/HCQ cannot cross the membranous barrier into the Alveoli, but Quinine can. Quinine, because of its solubility and permeability will cross into the alveoli [15], and its first action on the viruses is to inhibit the Haemozoin activity, thus disrupting the viruses. Secondly it breaks the polymerase chain and alters the overall pH so the viruses start to break off from the alveolar walls and are no longer viable. That way the glass ground opacity gradually clears up after Quinine multi-pronged action and, aided through enhanced phagocytosis mediated by the macrolide antibiotic, intravenously administered Azithromycin (Figure 4). If the patient is L-Phenotype, he or she will benefit from corticieroids but if not, Aspirin alone would do. Over time, and within 3 days, the alveoli will be clear [16], there will be enhanced oxygen uptake, conversion of ferrous to ferric ions, gaseous exchange at the alveoli, exit of $CO^2$ and a general restoration of airway equilibrium, with non-viable viruses which would be attenuated and cleared out of the system through enhanced phagocytosis. That is why in post-COVID-19 patients, the viral shedding through the bowel, is the attenuated non-viable virus. It takes 3-6 days of critical care, to discharge for Quinine. Quinine is only useful in moderate to advanced covid-19 while CQ/HCQ is useful in pre-covid, as well as mild to moderate covid-19.

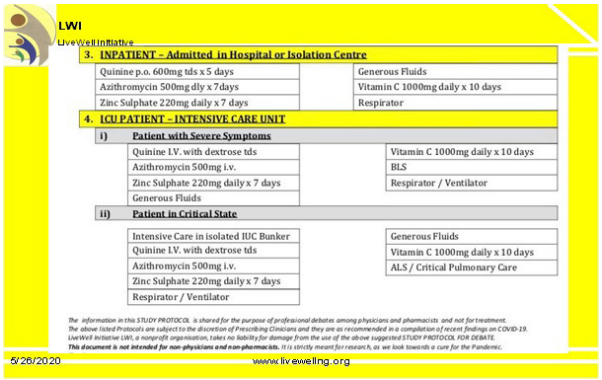


**Figure 4 :** LWI Study Protocol 1 for COVID-19 response in Africa-showing the role of QUININE IN COVID-19.

## Quinine in COVID-19 our preliminary study

Our only case study was a sickle cell patient aged 67 years placed under the ventilator in faraway canada. She recovered fully, with IV Quinine intervention. Within 2 days she was taken off the ventilator and within 5 days she was discharged hone. This was over 7 weeks ago and she is still doing fine. Although this is alone case study it is significant because she was aged, and suffering from a significant comorbidity.

## Why qukeep in sentensinine?

Zinc ionophoric action, pH modulation, PCR inhibition, and Haemozoin Inhibition. It is a well-known fact that the 4-Amino quinolines [10], are very potent in eliminating the virus. In fact, in a study by Martin, J et al. (2005) [17], CQ appears to possess forceful antiviral return on SARS-CoV infection of primate cells. Its action will be seen when the cells are treated with the CQ either pre or post exposure to the virus. However the action is limited because CQ cannot cross membranous barriers. This shows that it is favorable as both prophylaxis and therapeutic substance. CQ also exhibits other advantages like elevating endosomal pH and interfering with the end glycosylation of endosomal receptor, Angiotensin-Converting Enzyme 2 (ACE2).

This may adversely influence the virus-receptor binding and abolish the infection, with further implication by the increase of vesicular pH, resulting in the inhibition of infection and spread of SARS CoV at clinically admissible concentrations [11,15,16]. CQ/HCQ has proven not to have much efficacy in moderate to severe COVID-19 due to their inability to cross the BBB (Bloodbrainbarrier). In addition, because Quinine crosses the blood brain barrier [10], it will therefore cross into the membranous alveoli in COVID-19 and clear out the viruses in situ as well as clear out the virus in other distal or membranous tissues in the body.

## Repurposing the amino-quinolines

The 'repurposing', of drugs such as Quinine, leaves us with new uses for such old drugs, it saves the system the cost of researching for new moieties, and allows for a 'Jump' directly phasing 2 or phasing 3 trials as safety is already proven with an original pior indication having successfully used it to treat several other infectious diseases. In the case of the 4-Aminoquinolines [10], as earlier said they have Anti-inflammatory, Immunomodulating, Anti-infective properties and are now being used as Anti-thrombotics, and with metabolic effects. Among the newer biological effects of Quinine, it is important to highlight its Anti-mutagenic, Anti-autophagy and Anti-proliferative capacities, thus extending widely its reach and newer uses [10] (Figure 5).

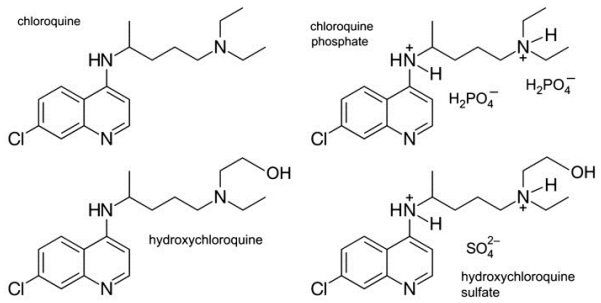


**Figure 5 :** Chemical structure of 4-Amino quinolines CQ/HCQ.

## Treatment outcomes with COVID-19

The prognosis has been very good with patients severely ill with COVID-19 recovering within 5-6 days of commencement of treatment with Quinine; and, they are able to test negative twice to the RT-PCR test [16], within 24 hours of taking samples nasopharyngeal, oropharyngeal and sputum samples.

Health Care Workers (HCWs) and Frontline Healthcare Workers (FHCWs) recruited in the preliminary study were asymptomatic before and after exposure after CQ/HCQ prophylaxis, however patients with severe COVID-19 benefitted more from oral Quinine while critically ill patients benefitted from Intravenous Quinine (Figure 6).

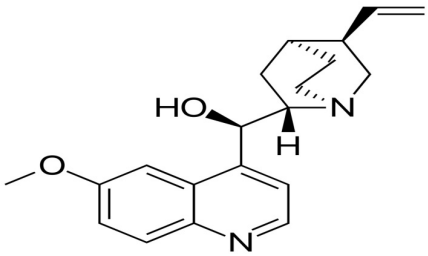

**Figure 6 :** Chemical structure of Amino quinolines showing the mother Quinine.

## Mechanism of action-quinine

Quinine, a 'wonder drug', has a multiple modes of action on the

virus namely:

• As a zinc ionophore it ensures penetration of zinc into the viral cell, altering the pH.

• Zinc also potentiates Quinine action, and enhances its tissue binding affinity and uptake.

• At the entry point in the ACE2 receptors and spikes, it prevents the virus from penetrating the host cell using its S protein and Protease.

• It breaks the polymerase chain and prevents viral replication [10].

• Quinine suppresses the exagerrated Immunoglobulin response IgG and IgM through Immunomodulation and therefore also exerts.

• It has an anti-inflammatory action and deters the release of mediator substances.

• Since it is a highly soluble and more potent 4-Amino quinoline, it will cross the blood brain barrier and dislodge viruses in the alveoli.

• Quninine will disseminate the glass ground opacity, restore heme iron and normalcy which will then lead to air exchange and oxygen uptake.

• As a Haemozoin inhibitor, Quinine will starve the virus of its food vacuoles so it cannot thrive .

• In addition, Quinine is a muscle relaxant and a non-narcotic analgesic, taking care of the accompanying severe muscle pain which characterizes severe COVID-19 through its Anti-myalgic action.

• It is an all-round mediator for reversal of viraemia in COVID-19 (Figure 7).

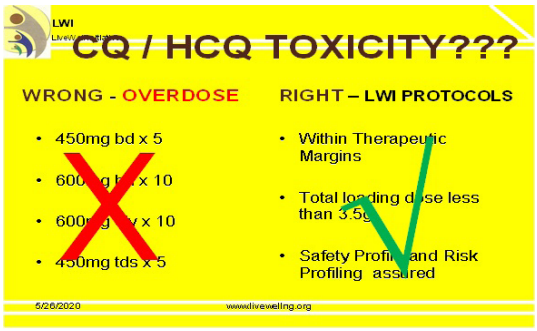


**Figure 7 :** Observed overdose comparison of Amino quinolines and resultant negative outcomes.

## Recommended regimen of quinine for use in COVID-19

• Moderate COVID-19-Oral Quinine Sulphate, 600 mg t.i.d. for 5 days

• Severe COVID-19-Intravenous Quinine Infusion, dose-determined by physician

• Acute Severe COVID-19-ICU Patient-Intravenous Quinine Infusion, dose-determined by physician

Administration of Ancillary medications for Ancillary symptoms may be as guided in LWI study protocols 1,2 and 3. These ancillary therapies include anti-inflammatory, antibiotic anticoagulant, and bronchodilator medications are an essential additive component of care to be used per in severe COVID-19 Patients. Please refer to Figures 1 and 4. [18,19].

## Is the remedy affordable, replicable, and scalable?

Yes, Quinine is affordable, realistic, and its use is scalable and replicable for all economies.

• The remedy is affordable, scalable and replicable for all low-income economies.

• It is hereby strongly recommended.

## Conclusion

Quinine is the answer to COVID-19 and its junior derivatives are useful in early or pre-emptive care in COVID-19 bordering principally on prophylaxis. This is for a future study. However, the re-purposing of Quinine, is a benchmark for the management of moderate to severe COVID-19, and therefore completes the treatment curve for COVID-19 in today's modern scientific world. It should be commenced through clinical trials and repurposed use by physicians all over the world, for their patients.

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