A Preliminary Study on Various Types of 4-Aminoquinolines for Pre- or Post-Exposure Prophylaxis and for Treatment in Severe COVID-19

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Case Report

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Abstract

Background: LiveWell Initiative LWI is a self-funded nonprofit social enterprise that thrives on innovation. The organization has, for 5 years, supervised MPH and DrPH Practicums for the Harvard T. H. Chan School of Public Health, Harvard University, Boston USA. It also supervises the PhD thesis at the University of Helsinki, Finland. At the inception of COVID-19, LWI designed and compiled three (3) sets of study protocols in response to the COVID-19 response in Africa with a goal to arrive at a practical and affordable solution to the pandemic using 4-aminoquinolines.

Method: A concurrent cohort/descriptive study of observation in patients exposed to HCQ/CQ prophylaxis and treatment with HCQ/CQ and quinine with categorization as specified as not critically ill, critically ill but not on a ventilator and critically ill on a ventilator. One hundred and twenty-three (123) subjects were categorized into shelter-in-place, self-quarantine and self-isolation (not critically ill, critically ill but not on a ventilator and critically ill on a ventilator). The 4-aminoquinolines were administered macrolide and zinc sulfate as appropriate for a defined duration and dose.

Results: The preliminary study of the 123 subjects covering all categories listed above resulted in 100% positive outcomes: Nil death, Nil relapse in symptomatic persons and total recovery with no relapse after 6 weeks lockdown, and asymptomatic persons post-prophylaxis after 6 weeks lockdown. The results have been gathered principally from Clinician Reported Outcomes with a few Patient Reported Outcomes.

Conclusion: These repurposed drugs with unique strengths—chloroquine and its analogue Hydroxychloroquine as well quinine—hold sway in the treatment of COVID-19.

Introduction

[1] stated Coronavirus to be an enveloped, positive single-strand RNA virus that belongs to the Orthocoronavirinae subfamily, as the name, it possesses the characteristic “crown-like” spikes on their surfaces.

[2] stated that alongside SARS-CoV, bat SARS-like CoV and others, it also falls into the genus beta-coronavirus.

COVID-19 enters the cell by using the S spike on its surface to bind onto an ACE2 receptor through glycolysis. Once in the cell, the virus RNA uses the host cell ribosome to synthesize more RNA and protein. The protein is used to form the virus the capsule that protects the genetic material RNA. After
making a million copies of itself using the host ribosome, it then assembles new viral particles and leaves the cell to find a new host.

The immune system, which is a complex interconnection of molecular interactions across the cell, nucleus and cytoplasm, sometimes overreacts because of its weakened and dysfunctional state during the process of infection, releasing cytokines than required, resulting in a cytokine storm. As of present, there is yet to be an ideal treatment for COVID-19, and the treatment is mainly supportive.

The 3 sets of protocols designed by the LiveWell Initiative have undergone professional debates among physicians, researchers and pharmacists for hypothesis testing over 5 weeks. Thereafter, the team presented a Global Webinar on April 15th 2020 at which the Panelists were the Country Rep WHO Nigeria Dr Fiona Braka, The FIP Vice President, EMROPHARM Secretary-General, AFRO Lead at FIP, UN Ambassador of Goodwill Dr Corinne Shenouda and A Clinician at Mayo Clinic, Dr Michael Leise. The webinar series was thereafter taken along with the Nigeria National COVID-19 THINKTANK, and a third webinar was held with the medical community in Nigeria, hosted by GSK.

The study protocols are currently undergoing random Physician-Patient Trials at the discretion of Prescribing Clinicians and Clinical Researchers, and they are as recommended in a compilation of recent findings by LiveWell Initiative LWI on COVID-19. LiveWell Initiative LWI, a nonprofit organization, takes no liability for damage from the use of the above-suggested STUDY PROTOCOLS FOR COVID-19 RESPONSE IN AFRICA. It is a Study Protocol designed to ‘evolve’ as an African Solution to COVID-19 Response.

This document is not intended for non-physicians, non-researchers or non-pharmacists. It is strictly meant for research, as we look towards a cure for the Pandemic. The outcomes of the empirical data are encouraging, as there has been 100% recovery from COVID-19 on 11 patients at an Isolation Center in Oyo State Nigeria, and a patient in faraway Canada recovered under the ventilator with the protocols. The study is to be scaled through prospective partnership or collaboration. This is also an open call for partnerships to scathe COVID-19 REPONSE IN AFRICA and the DIASPORA.

Materials And Methods

SOME KEY FACTS:

- There is a dose-response relationship
- Those on HCQ/CQ prophylaxis are less likely to develop SARS-CoV-2 infection compared to those who were not on it
- This does not, however, believe the need for PPEs and must not confer an undue sense of overprotection

Inclusion Criteria

- Shelter-in-place: a healthy individual who chose to stay at home just to limit the spread of the virus
• Self-quarantine: are those who must have come in contact with someone who tested positive for coronavirus. They may be immune active or immunocompromised
  - Asymptomatic healthcare workers working in non-COVID hospitals/non-COVID areas
  - Asymptomatic healthcare workers involved in containment and treatment of COVID-19
  - Asymptomatic frontline workers,
  - Asymptomatic household contacts of laboratory-confirmed cases.

• Self-isolated: Those who tested positive for COVID-19
  - Symptomatic self-isolated persons
  - Symptomatic Hospital isolated persons
  - Symptomatic critically ill persons

Exclusion Criteria

• The drug is contraindicated in persons with a known case of
  1. Retinopathy, 2. Hypersensitivity to HCQ or 4-aminoquinoline compounds
  3. G6PD deficiency
  4. Pre-existing cardiomyopathy and cardiac rhythm disorders
• The drug is not recommended for prophylaxis in children under 15 years of age and in pregnancy and lactation.

DOSES:

1. Shelter-in-place: 1.5G chloroquine, 1.2G hydroxychloroquine and 0.7G azithromycin maximum.
   - Chloroquine 500 mg daily for three days
   - Hydroxychloroquine 400 mg daily for three days
   - Azithromycin 250 mg daily for three days

2. Self-Quarantine: 2.5G Chloroquine, 2.0G Hydroxychloroquine; and 1.5-2G Azithromycin
   - Chloroquine 500 mg 12 hourly stat, then 500 mg daily for three days
   - Hydroxychloroquine 400 mg 12 hourly stat, then 400 mg daily for seven days
   - Azithromycin 250 mg daily for five to seven days

3. Self-Isolation: 1.8G Quinine; 1.5-2G Azithromycin Maximum.
(Not critically ill)
- Quinine 600 mg 8 hourly for five days
- Azithromycin 500 mg daily for seven days
- Zinc sulfate 220 mg daily for seven days

(Critically ill)
- Quinine intravenously with dextrose saline 8 hours for five days
- Azithromycin 500 mg intravenously
- Zinc sulfate 220 mg daily for seven days
- Generous fluid

4. Treatment doses below 4G were sustained due to the ionophoric effect of zinc on chloroquine, which makes lower doses of chloroquine more efficacious due to enhanced tissue binding affinity and uptake by the viral cell. Other mechanisms of action of HCQ/CQ offer additional protection to the host. HCQ/CQ alters the pH of the ACE2 receptor, thus making it difficult for the virus to penetrate the host cell. In addition, it breaks the polymerase chain, and in advanced COVID-19, it exhibits its Haemozoin inhibitor action, thus disabling the virus from engulfing food vacuoles of deris and dead blood cells. Quinine is highly soluble and crosses the blood brain barrier, penetrating advanced COVID-19 patients into the alveoli and dislodging the viruses. Thus, the usefulness of the 4-aminoquinolines ends to end in COBVID-19.

USE BEYOND 7 WEEKS:

For its use beyond 7 weeks on weekly dosage with strict monitoring of clinical and ECG parameters, which would also ensure that the therapy is given under supervision. This is ideally for IPT intermittent prophylactic therapy post-recovery, as the virus is still shed through the bowels after recovery. For further research, we recommend the bowel infiltrates of the virus for possible vaccine development, as it is believed to be the attenuated virus.

SAFETY AS A MAJOR CONCERN:

The safety of chloroquine or hydroxychloroquine is premised on the use of a dose below the 4G cumulative total loading dose. This is carefully titrated at LWI. As long as HCQ/CQ is used at therapeutic concentrations, it remains a very safe drug with a broad therapeutic margin. Even quinine, used in advanced COVID-19, remains very safe with no requirements for TDM within the specified therapeutic concentrations where side effects are self limiting and reversible, namely, reversible ototoxicity.

AFFORDABLE, REPLICABLE, SCALABLE:
The remedy is affordable, scalable and replicable for all low-income economies. It is hereby strongly recommended.

Results And Discussion

OUTCOMES OF PRELIMINARY STUDY:

A preliminary study of 123 subjects covering all categories listed above resulted in 100% positive outcomes: Nil death, Nil relapse in symptomatic persons and total recovery with no relapse after 6 weeks lockdown, and asymptomatic persons.

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>CLASSIFICATION</th>
<th>PREP</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Protocol</td>
<td>Inpatient</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEP</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PrEP</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICU Patient (Treated on Quinine i.v.)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grand Total</td>
<td>123</td>
<td></td>
</tr>
</tbody>
</table>
As seen in Table 1, 62% of respondents took the 4-aminoquinolines prophylactically, and 27% were administered the drugs because of their contact with positive COVID-19 patients.

**TABLE 2: Age of respondents**

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35</td>
<td>65</td>
</tr>
<tr>
<td>36-55</td>
<td>55</td>
</tr>
<tr>
<td>&gt;55</td>
<td>3</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>123</strong></td>
</tr>
</tbody>
</table>

From table two, 52.85% of the respondents were adults, while 2.4% were above 55 years.

**TABLE 3: Gender of respondents**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>123</strong></td>
</tr>
</tbody>
</table>

Table 3 shows that 69% were males, while 31% were females.

**TABLE 4 – LABORATORY TESTING FOR COVID-19:**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>LABORATORY TESTED (n)</th>
<th>NON-TESTED (n)</th>
<th>ONLINE TESTED - AWAITING LABORATORY TESTING (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP</td>
<td>NIL</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>PEP</td>
<td>NIL</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>OutPatient (U.K. Nurse)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inpatient / Isolation Center (Oyo State Isolation Center)</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Critical Care / Ventilator Patient (Canada) *treated on Quinine Injection i.v.</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>13</strong></td>
<td><strong>106</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>
TABLE 5– SYMPTOM OUTCOMES ASSESSMENT BEFORE AND AFTER USE OF CHLOROQUINE AND HYDROXYCHLOROQUINE FOR COVID-19 PROPHYLAXIS:

<table>
<thead>
<tr>
<th>SYMPTOMS &amp; TESTING STRATIFICATION</th>
<th>Number (n)</th>
<th>Comments - AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPTOMATIC, ONLINE TESTED, Awaiting Laboratory Test</td>
<td>3</td>
<td>General Public – Awaiting Laboratory Test for 3 weeks but now symptom-free</td>
</tr>
<tr>
<td>SYMPTOMATIC NOT LABORATORY TESTED</td>
<td>8</td>
<td>4 Frontline Workers, 4 Frontline Healthcare Workers. No Symptoms</td>
</tr>
<tr>
<td>SYMPTOMATIC, LABORATORY TESTED POSITIVE</td>
<td>13</td>
<td>1 inpatient in Canada, 1 Self Quarantined HCW in the UK, 11 Isolation Center inpatients in Nigeria. No Symptoms.</td>
</tr>
<tr>
<td>TOTAL</td>
<td>24</td>
<td>COVID-19 Free 100% NIL mortality NIL morbidity</td>
</tr>
</tbody>
</table>

TABLE 6– OUTCOMES OF PRE-EXPOSURE PROPHYLAXIS USING CHLOROQUINE / HYDROXYCHLOROQUINE FOR COVID-19 PRE EMPTIVE-THERAPY:

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PrEP Pre Exposure Prophylaxis (n)</th>
<th>Post-Lockdown/6 weeks after</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRONTLINE HEALTHCARE WORKER FHCW</td>
<td>4</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free</td>
</tr>
<tr>
<td>HEALTHCARE WORKER HCW</td>
<td>2</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free</td>
</tr>
<tr>
<td>FRONTLINE WORKER FW</td>
<td>42</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free (22-man Cohort of Security men and 20 Bankers)</td>
</tr>
<tr>
<td>GENERAL PUBLIC /FAMILY MEMBERS</td>
<td>28</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free</td>
</tr>
<tr>
<td>TOTAL on PrEP</td>
<td>76</td>
<td>Post-PrEP Post-Lockdown Symptom-free after 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 7– OUTCOMES OF POST EXPOSURE PROPHYLAXIS USING CHLOROQUINE / HYDROXYCHLOROQUINE FOR COVID-19 PROPHYLAXIS
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PEP Post Exposure Prophylaxis</th>
<th>Post-Lockdown/6 weeks after</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRONTLINE HEALTHCARE WORKER FHCW</td>
<td>3</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free (3 Isolation Center Staffers)</td>
</tr>
<tr>
<td>HEALTHCARE WORKER HCW</td>
<td>15</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free (15 Community Pharmacists)</td>
</tr>
<tr>
<td>FRONTLINE WORKER FW</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>GENERAL PUBLIC</td>
<td>16</td>
<td>NIL SYMPTOMS</td>
<td>COVID-19 Free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* 2 persons awaited Laboratory Testing after symptoms but are now symptom-free</td>
</tr>
<tr>
<td>TOTAL on PEP</td>
<td>34</td>
<td>Post-PEP Post-Lockdown Symptom-Free after 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

As of present, there is yet to be a validated and consensus treatment for COVID-19, and the treatment is mainly supportive. However, repurposed drugs with unique strengths, such as chloroquine and its analogue hydroxychloroquine, as well as quinine, from time immemorial have been largely touted as possessing anti-inflammatory and immunomodulatory properties, hence their use in the treatment of systemic lupus erythematosus (SLE) and other rheumatism[3]. As the mechanisms of action of the 4-aminoquinolines have been further elucidated, it is believed to distort the ACE2 receptor by altering glycan attachment, thereby preventing the attachment of SARS-COV2. It is also believed to decrease the pH of the cell, thereby inhibiting viral replication, altering the viral particle assemblage and stopping the cytokine storm [4], [5], [6]. Researchers have even reported both prophylactic and therapeutic advantages of CQ for SARS-CoV infection [7]. However, other researchers have reported in a retrospective study with no defined administration time that no evidence in the use of hydroxychloroquine either with or without azithromycin reduced the risk of a mechanical ventilator in patients hospitalized with COVID-19 [8].

[9] in an open-label nonrandomized clinical trial concluded that hydroxychloroquine showed a significant association with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by azithromycin. In a randomized controlled trial in China of 62 patients who were positive for COVID-19 and hospitalized, Chen reported that 31 patients received hydroxychloroquine 400 mg per day, and the remaining 32 received a placebo. Chen concluded that pneumonia improved in 81% of patients compared to 55% of controls [10].
The LWI study protocols have undergone hypothesis testing among physicians, researchers, pharmacists and clinicians, with online debates on several professional health platforms.

The results in this preliminary study are based on preliminary data gathered from Physician-Patient recommendations of Prophylaxis using the 4-Aminoquinolines in COVID-19 Treatment and Prophylaxis. It also recognises some self-medicating individuals who took advantage of the non-prescription remedy.

The LWI study protocols are currently being used in Kaduna State, Bauchi State, and some other states in Nigeria. The unique thing about the Study Protocols, the 4-Aminoquinolines offer an end-to-end care in COVID-19, from CQ/HCQ in Pre and Post Exposure to Mild and Moderate COVID-19 and escalating into QUININE I.V. for Critical Care in COVID-19.

**Conclusion**

CQ and HCQ prophylaxis works as none of the 110 clients placed on prophylaxis has progressed into COVID-19 in 6 weeks post-lockdown; none of them is symptomatic.

CQ/HCQ is relevant for ambulatory care as the Laboratory Tested Positive Healthcare Worker on Self Quarantine who was treated with CQ is fully recovered, up to 6 weeks post-lockdown with no relapse, and having tested negative twice post-treatment.

CQ/HCQ is also relevant for inpatient care, as the 11 Laboratory Tested Positive Patients placed on admission at the COVID-19 Isolation Center who were treated with CQ are all fully recovered, up to 6 weeks post-lockdown with no relapse, and having tested negative twice post-treatment.

Quinine works in advanced COVID-19 as the Single Laboratory Tested Positive client on the ventilator, has fully recovered after treatment with I.V. Quinine and is still symptom-free 6 weeks post-lockdown.

**Declarations**

**Ethical approval was obtained from the hospitals' Health and Human Research Committee (HHRC) before proceeding with the study.**

**Informed consent was sought from each respondent before administering the medicaments.**

**The privacy, dignity, and autonomy of the respondents were maintained accordingly throughout the conduct of the study**

**That the authors declare no competing interests.**

**References**


**Figures**
Figure 1
Designation of respondents

Figure 2
Age of respondents
Figure 3

Gender of respondents

Figure 4

LABORATORY TESTING FOR COVID-19
Figure 5

SYMPTOM OUTCOMES ASSESSMENT BEFORE AND AFTER USE OF CHLOROQUINE AND HYDROXYCHLOROQUINE FOR COVID-19 PROPHYLAXIS:

PrEP Pre Exposure Prophylaxis (n)

- FRONTLINE HEALTHCARE WORKER FHCW: 4
- HEALTHCARE WORKER HCW: 2
- FRONTLINE WORKER FW: 42
- GENERAL PUBLIC / FAMILY MEMBERS: 28
Figure 6

OUTCOMES OF PRE-EXPOSURE PROPHYLAXIS USING CHLOROQUINE / HYDROXYCHLOROQUINE FOR COVID-19 PRE EMPTIVE-THERAPY:

Figure 7

OUTCOMES OF POST EXPOSURE PROPHYLAXIS USING CHLOROQUINE / HYDROXYCHLOROQUINE FOR COVID-19 PROPHYLAXIS