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1 Antimalarial artemisinin-based combination therapies (ACT) and COVID-19 in Africa: *In*
2 *vitro* inhibition of SARS-CoV-2 replication by mefloquine-artesunate
3
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18

19 **ABSTRACT**

20 *Objectives:* At the end of November 2019, a novel coronavirus responsible for respiratory
21 tract infections (COVID-19) emerged in China. Despite drastic containment measures, this
22 virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread in
23 Asia and Europe. The pandemic is ongoing with particular hotspot in Southern Europe and
24 America. Many studies predicted a similar epidemic in Africa as that currently seen in Europe
25 and the United States of America. However, reported data do not confirm these predictions.
26 One of the hypotheses that could explain the later emergence and spread of COVID-19
27 pandemic in African countries is the use of antimalarial drugs to treat malaria, and more
28 particularly artemisinin-based combination therapy (ACT).

29 *Methods:* The antiviral activity of fixed concentrations of ACT at concentrations consistent
30 with those observed in human plasma when ACT are administered at oral doses for
31 uncomplicated malaria treatment was evaluated *in vitro* against clinically isolated SARS-
32 CoV-2 strain (IHUMI-3) in Vero E6 cells.

33 *Results:* Mefloquine-artesunate exerted the highest antiviral activity with % inhibition of 72.1
34 \pm 18.3 % at expected maximum blood concentration (C_{max}) for each ACT drug at doses
35 commonly administered in malaria treatment. All the other combinations, artesunate-
36 amodiaquine, artemether-lumefantrine, artesunate-pyronaridine or dihydroartemisinin-
37 piperazine, showed antiviral inhibition in the same range (27.1 to 34.1 %).

38 *Conclusions:* Antimalarial drugs for which concentration data in lungs are available, are
39 concentrated from 10 to 160 fold in lungs than in blood. These *in vitro* results reinforce the
40 hypothesis that antimalarial drugs could be effective as anti-COVID-19 treatment.

41

42 **Keywords:** SARS-CoV-2, COVID-19, Antiviral, Antimalarial drug, *in vitro*, malaria

43 **Introduction**

44 In December 2019, a new severe acute respiratory syndrome coronavirus (SARS-CoV-2)
45 causing coronavirus diseases 2019 (COVID-19) emerged in Wuhan, China (Wu F et al.,
46 2020). Despite containment measures, SARS-CoV-2 spread in Asia, Southern Europe, then in
47 America and currently in Africa. Currently, 54 countries are affected in Africa with 332,820
48 cumulative confirmed cases and 8,733 reported deaths (June 25, 2020)
49 (<https://www.afro.who.int/health-topics/coronavirus-covid-19>). The five most affected African
50 countries are South Africa with 111,796 cases and 2,205 deaths, Nigeria with 22,020 cases
51 and 542 deaths, Ghana with 15,013 cases and 95 deaths, Cameroon with 12,270 cases and 313
52 deaths, and Algeria with 12,248 cases and 869 deaths. The first African cases are supposed to
53 have occurred on February 14, 2020 in Egypt and on February 27, 2020 in Nigeria for the
54 Sub-Saharan Africa. Gilbert et al. (2020) estimated that the countries at highest importation
55 risk of cases of COVID-19 from China were Egypt, Algeria, South Africa, Nigeria and
56 Ethiopia according to air travel flows from infected provinces of China to Africa and African
57 country's capacity to detect COVID-19. Another study estimated the number of cases of
58 COVID-19 in each African country, and more especially the timing of reporting 10,000 cases
59 for all African countries (Pearson et al., 2020). For instance, the timing of reporting 10,000
60 cases was between April 11 and 18 (6,129 cases on June 25, 2020) in Senegal, April 17 and
61 23 (12,270 cases) in Cameroon, May 7 to 21 (197 cases) in Angola and April 23 and May 3
62 (5,034 cases) in Ethiopia. The declared data to WHO indicated the spread of COVID-19 in
63 Africa but with lower confirmed cases than expected. Several hypotheses could explain the
64 later emergence and spread of COVID-19 pandemic in Africa, like delay in systematic SARS-
65 CoV-2 detection and appropriate epidemiological surveillance (Kobia and Gitaka, 2020),
66 quick implementation of lockdown measures, physical distancing and enhanced hygiene,
67 limited international air travel flows (Haider et al., 2020), climate conditions (Huang et al.,
68 2020; Wang et al., 2020), demographic conditions with less people above 65 years old (Diop

69 et al., 2020), genetic polymorphisms of the cell entry receptor for the SARS-CoV-2
70 (angiotensin converting enzyme 2, ACE-2) (Cao et al., 2020), cross-immunity to SARS-CoV-
71 2 (Grifoni et al., 2020; Katoh et al., 2020).

72 Another hypothesis that may explain this later emergence in Africa, and more particularly
73 in malaria endemic areas, would be the use of antimalarial drugs (Izoulet, 2020). Since 2002,
74 the World Health Organization (WHO) has recommended the use of artemisinin-based
75 combination therapy (ACT) in the treatment of uncomplicated falciparum malaria
76 (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine or
77 artesunate-mefloquine). The combination artesunate-amodiaquine is preferentially used as
78 first-line treatment in Burundi, Cameroon, Democratic Republic of Congo, Gabon, Ivory
79 Coast for instance, artesunate-mefloquine in Cambodia and Brazil, artemether-lumefantrine in
80 Benin, Central African Republic, Malawi and South Africa and dihydroartemisinin-
81 piperaquine in Thailand or Vietnam. Amodiaquine and mefloquine, two quinoline ACT
82 partners, were found to be active *in vitro* at micromolar concentration against SARS-CoV-1 at
83 2.5 μM and SARS-CoV-2 at 10 μM , respectively (Barnard et al., 2006; Fan et al., 2020).

84 Although *in vitro* activity is not necessarily linked to clinical efficacy, access of *in vitro*
85 effectiveness of ACT against SARS-CoV-2 may provide some answers if antimalarial use
86 may have been involved in the later emergence and spread of COVID-19 pandemic in Africa.
87 The aim of this study was to evaluate the antiviral activity of ACT at concentrations
88 consistent with those observed in human plasma when ACT are administered at oral doses for
89 uncomplicated malaria treatment.

90

91 **Methods**

92 *Antimalarial drugs*

93 All the drugs were provided by Sigma (Saint Louis, MO, USA). Stock solution of
94 pyronaridine and piperazine were prepared in water, in methanol for mefloquine,
95 desethylamodiaquine, and dihydroartemisinin and in DMSO for lumefantrine. All the stock
96 solutions were diluted in Minimum Essential Media (MEM, Gibco, ThermoFischer). Fixed
97 concentrations of drug combination were prepared according to human plasma concentrations
98 expected during oral intake of ACT. The expected maximum blood concentration (C_{max}) was
99 estimated from literature for each drug at doses commonly administered in malaria treatment.
100 The artemisinin compound (artemether, artesunate) C_{max} was determined as bioequivalent
101 concentration of its active metabolite, dihydroartemisinin. Indeed, artesunate or artemether
102 were metabolized rapidly in dihydroartemisinin after oral administration of fixed-dose
103 combinations (30min to 3h). A fixed dose of artesunate-amodiaquine led to plasma C_{max} of
104 dihydroartemisinin and desethylamodiaquine (200 mg/ 540 mg) around 802 and 879 ng/ml
105 (experimental fixed-dose estimated at 5 and 4 μ M) (Navaratnam et al., 2009). A fixed dose of
106 artemether-lumefantrine (80 mg/280 mg) led to plasma C_{max} of dihydroartemisinin and
107 lumefantrine around 126 ng/ml and 6.98 μ g/ml (experimental fixed-dose estimated at 1 and
108 33 μ M) (Ali et al., 2010; Ashley et al., 2007). A fixed dose of dihydroartemisinin-piperazine
109 (120 mg/960 mg) led to plasma C_{max} of dihydroartemisinin and piperazine around 387 ng/ml
110 and 539 ng/ml (experimental fixed-dose estimated at 3.1 and 1 μ M) (Hanboonkunupakarn et
111 al., 2019). A fixed dose of artesunate-mefloquine (250 mg/550 mg) led to plasma C_{max} of
112 dihydroartemisinin and piperazine around 698 ng/ml and 1392 ng/ml (experimental fixed-
113 dose estimated at 5 and 8.3 μ M) (Valea et al., 2014). A fixed dose of artesunate-pyronaridine
114 (180 mg/540 mg) led to plasma C_{max} of dihydroartemisinin and pyronaridine around 109
115 ng/ml and 130 ng/ml (experimental fixed-dose estimated at 1 and 0.5 μ M) (Jittamala et al.,
116 2015). ACT were evaluated *in vitro* at 0.5X, 1X and 2X of experimental fixed-dose estimated
117 for each combination.

118

119 *Virus and cells*

120 The clinically isolated SARS-CoV-2 strain (IHUMI-3) (Gautret et al., 2020) was
121 maintained in production in Vero E6 cells (American type culture collection ATCC® CRL-
122 1586™) in MEM with 4% of fetal bovine serum and 1% glutamine (complete medium).

123

124 *Antiviral activity assay*

125 Briefly, 96-well plates were prepared with 5.10^5 cells/mL of Vero E6 (200µL per well), as
126 previously described (Andreani et al., 2020). ACT concentrations were added 4 h before
127 infection. Vero E Cells were infected with IHUMI-3 strain at an MOI of 0.25. Controls 0%
128 (Vero E cell infected without drug) and 100% of inhibition (Vero E cell infected with 100 µM
129 of ferroquine, Sigma, Saint Louis, MO, USA) were included. After 48h post-infection, the
130 replication was estimated by RT-PCR using the Superscript III platinum one step with Rox kit
131 (Invitrogene) after extraction with the BIoExtract SuperBall kit (Biosellal, Dardilly, France).
132 The primers used were previously described (Amrane et al., 2020).

133

134 *Data analysis and interpretation*

135 The percentage of inhibition of SARS-CoV-2 replication was estimated for each
136 combination as following: $(\text{mean } CT_{\text{combination}} - \text{mean } CT_{\text{control 0\%}}) / (\text{mean } CT_{\text{control 100\%}} - \text{mean } CT_{\text{control 0\%}}) * 100$. Data were expressed as mean and standard deviation of 5 different
137
138 experimentations.

139

140 **Results**

141 Estimations of the % of inhibition of the SARS-CoV-2 replication by fixed-doses of ACT
142 were summarized in Table 1. Mefloquine-artesunate exerted the highest antiviral activity with

143 % inhibition of 72.1 ± 18.3 % at expected maximum blood concentration (C_{\max}) for each ACT
144 drug at doses commonly administered in malaria treatment. All the other combinations
145 showed antiviral inhibition in the same range (27.1 to 34.1 %).

146

147 **Discussion**

148 A patient, who is treated with fixed-doses of ACT at commonly recommended doses for
149 uncomplicated malaria, shows maximum blood concentrations (C_{\max}) of the two drugs which
150 are able to inhibit 27.1 to 72.1 % of the Vero E Cells infected with the SARS-CoV-2 IHUMI-
151 3 strain. Treatment with artesunate-amodiaquine, artemether-lumefantrine, piperazine-
152 dihydroartemisinin or artesunate-pyronaridine leads to replication inhibition around 30%.

153 Additionally, some of these antimalarial drugs are concentrated in lungs. A single oral dose of
154 2 mg (10 mg/kg) of pyronaridine in rats led to a blood C_{\max} of 223 ng/ml and a lung C_{\max} of
155 36.4 $\mu\text{g/g}$ (163 more concentrated in lung than blood) (Park and Pradeep, 2010). About 0.07%
156 of the administered oral dose (8.6 mg/kg) of amodiaquine was found in rat lung (Winstanley
157 et al., 1988). Treatment with artesunate-mefloquine (expected blood C_{\max} at 8.3 and 1 μM)
158 leads to replication inhibition above 70%. This is consistent with the *in vitro* antiviral activity
159 of mefloquine previously reported at 10 μM (Fan et al., 2020). A study on postmortem human
160 cases showed that mefloquine levels are 10 times higher in lung than in blood (concentration
161 can go up to 180 mg/kg in the lung) (Jones et al., 1994). No data is available on drug
162 accumulation in lungs for the other antimalarial drugs, and more particularly
163 dihydroartemisinin. The data on pyronaridine and mefloquine suggest the concentrations
164 expected in lungs allow a 100% replication inhibition of SARS-CoV-2.

165 Additionally, artesunate exerts anti-inflammatory effects by decreasing the secretion of
166 various pro-inflammatory cytokines including interleukin 6 (IL6), tumor necrosis factor-alpha
167 (TNF), interleukin 1 beta (IL1beta) and interleukin 6 (IL6) through inhibition of nuclear

168 factor kappa B (NF-kB) (Xu et al., 2007). The secretions of IL1beta, IL6, interferon gamma
169 (INF γ) were considerably increased in the cytokine storm due to COVID-19 (Huang et al.,
170 2020; Qin et al., 2020). The combination of antiviral activity and anti-inflammatory effects
171 could allow a better clinical efficacy of mefloquine-artesunate.

172 These *in vitro* results reinforce the hypothesis that antimalarial drugs could be effective as
173 anti-COVID-19 treatment. Based on our results, we would expect that countries which
174 commonly use ACT report fewer cases and deaths during malaria season. It could be
175 necessary now to evaluate clinically the ACT efficacy to treat COVID-19, and more
176 particularly that of mefloquine-artesunate, and the potential prevention of ACT against
177 SARS-CoV-2 by comparing the antimalarial use and the dynamics of COVID-19 country by
178 country.

179

180 **Contributors**

181 MG carried out *in vitro* and molecular investigations, analyzed the data, and participated in
182 drafting the paper. ID participated in cellular and viral cultures. MB carried out molecular
183 investigations. OD participated in *in vitro* and molecular investigations. PJ, MLB, JA and CR
184 participated in virus isolation and its maintenance in culture. IF, JM and SH participated in *in*
185 *vitro* investigations. BLS supervised the study and participated in drafting the paper. BP
186 designed and supervised the study, analyzed the data and drafted the manuscript.

187

188 **Declaration of interest**

189 M Boxberger received a PhD grant supported by L'Occitane Society. All the other authors
190 have no conflict of interest to declare.

191

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196

197 **Ethical approval**

198 No ethical approval is required.

199

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285

Table 1

Estimation of the % of inhibition of the SARS-CoV-2 replication by fixed-doses of ACT (1x corresponds to expected maximum blood concentration (C_{max}) for each ACT drug at doses commonly administered in malaria treatment)

Combination	Inhibition % at 2x plasma C_{max}		Inhibition % at 1x plasma C_{max}		Inhibition % at 0.5x plasma C_{max}	
	Concentrations	Mean \pm SD	Concentrations	Mean \pm SD	Concentrations	Mean \pm SD
Mefloquine-dihydroartemisinin	8.3-5 μ M	99.6 \pm 0.7	4.1-2.5 μ M	72.1 \pm 18.3	2.0-1.25 μ M	30.9 \pm 14.1
Desethylamodiaquine-dihydroartemisinin	4.0-5.0 μ M	85.8 \pm 9.9	2.0-2.5 μ M	32.3 \pm 9.9	1.0-1.25 μ M	17.2 \pm 6.5
Pyronaridine-dihydroartemisinin	0.5-1.0 μ M	38.2 \pm 5.7	0.25-0.5 μ M	34.1 \pm 7.1	0.12-0.25 μ M	16.3 \pm 5.0
Lumefantrine-dihydroartemisinin	33.0-2.0 μ M	37.7 \pm 3.4	16.5-0.5 μ M	27.1 \pm 6.0	8.2-0.25 μ M	12.3 \pm 4.4
Piperaquine-dihydroartemisinin	1.0-3.1 μ M	29.7 \pm 16.8	0.5-1.5 μ M	29.3 \pm 4.6	0.25-0.75 μ M	14.0 \pm 4.2

SD = standard deviation