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Editorial

The Need for Combination Antiviral Therapy for Effective Treatment of COVID-19

Misaki Wayengera*

Department of Immunology, Molecular Biology and Pathology, College of Health Sciences, Makerere University Kampala, Uganda

INTRODUCTION

The World Health Organization (WHO) declared coronavirus diseases 2019 (COVID19) on 30th January 2020. To date, infections with Severe Acute Respiratory Syndrome Coronavirus type II (SARS-CoV2) have reached pandemic levels. Despite several clinical trials, there is no specific effective treatment for COVID19.Among the many trialed drugs with demonstrated *in-vitro* anti-SARS-CoV2 effects, include: Hydroxyl-Chloroquine (HCQ), Azithromycin (AZ), Antivirals (remdesivir-RDV and lopinavir–ritonavir-LPV/r), and Ivermectin-IVM. Many of these have only been trialed as mono-therapies. Considering the low antiviral efficacy of each monotherapy and promiscuous vulnerability of the Replication Transcription Complex (RTC) of SARS-CoV2, it becomes necessary consider combinational therapies. We propose a new combinatorial regimen comprising of HCQ/RDV/LPV-r/IVM for clinical testing in the treatment of COVID-19. Other combinational therapy regimens need to be considered to optimize the desired combined *in-vivo* virocidal and virostatic.

The world is to-date held-hostage to the pandemic of Coronavirus Disease (Covid19) [1]. Covid19 is caused by Severe Acute Respiratory Syndrome Coronavirus type II (SARS-CoV2). Coronaviruses (CoVs) are enveloped, positive-stranded RNA viruses with a nucleocapsid [2]. SARS-CoV2 belongs to the beta category (betaCOV) of the Orthorcoronavirinae subfamily of the family *Coronaviridae* [2,3]. In genetic terms, Chan et al. have proven that the genome of SARS-CoV2 has 82% nucleotide identity with that of human SARS-CoV-1 [4].

CoVs generally replicate *via* a Replication-Transcription Complex (RTC) formed by virus RNA and the replicase-transcriptase (RdRp) complex. Unlike polymerases III, RdRp-like HIV-1's reverse transcriptase, lacks the proof reading mechanisms bestowed by the small polymerases (alpha-α, beta-β, gamma, Delta, Epsilon) and apurinic-apyramidinic endonuclease (APE). As a result, CoVs are prone to high mutational rates in course of several cycles [5].

In light of our longstanding experience with the treatment for HIV-1/AIDS, in which we evolved from absence of drugs, through monotherapy and finally several options of optimized Highly Active Antiretroviral Combinatorial Therapy (HAART) regimens, it suffices to consider combination antiviral therapy for SARS-CoV2/Covid19 as well [6,7].

This especially in light of repeated reports of resurgence of viraemia among COVID patients who had successfully been treated on monotherapy. It remains too early to determine whether resurgence issues from re-infection with a different strain of virus (which would suggest that protective immunity is very short lived or not ever attained among infected and recovered persons) or reactivation of virus concealed within sites in-accessed by monotherapy [8]. Regardless, the concept of combination SARS-CoV2 Antiviral Therapy (SARS- CoV2-ART) is to attain complete viral replication cycle inhibition and elimination, early in course of the infection before a potential reservoir if present, is established.

Despite several clinical trials, there is no specific effective treatment for CoVID19. Among the many trialed drug with demonstrated *in-vitro* antiviral effects, include: Hydroxyl-Chloroquine (HCQ), antivirals (remdesivir-RDV and lopinavir-ritonavir-LPV/r), and Ivermectin-IVM (Table 1) [9-12].

Table 1: List of drugs with demonstrated antiviral activity against SARS-CoV2 and benefit for treating COVID19.

Class	COVID19 therapeutic agent	Site of action*
Antimalarial, Quinolone	Hydroxychloroquine (HCQ)	pH mediated endocytosis
Antiviral(nucleotide analogue)	Lopinovir/Ritonivir (LPV/r)	RCT competitive inhibitor
Antiviral (virostatica)	Favipiravir, Penciclovir (FVP, PCV)	RdRp inhibitor
Anti-parasitic	Ivermectin (IVM)	None-specific innate system

*Several other highly-priced agents that are not readily available to all, but are known to inhibit various stages of the SARS-CoV2 replication cycle, can make this list.

Many of these have only been trialed as mono-therapies. Considering the low antiviral efficacy of each monotherapy and promiscuous vulnerability of the Replication Transcription Complex (RTC) of SARS-CoV2, it becomes necessary consider combinational therapies. We propose a new combinatorial regimen comprising of HCQ/RDV/LPV-r/IVM for clinical testing in the treatment of COVID19. Other combinational therapy regimens need to be considered to optimize the desired combined *in-vivo* virocidal and virostatic.

Correspondence to: Misaki Wayengera, Department of Immunology, Molecular Biology and Pathology, College of Health Sciences, Makerere University Kampala, Uganda, Email: wmisaki@yahoo.com

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CONCLUSION

In conclusion, we propose the use of at least a 3-drug combination regimen for the effective treatment of SARS-CoV2/COVID19. Several options are possible from the existing agents, which might enable us define a 1st line, 2nd line and 3rd line option of therapy.

REFERENCES

1. Perlman SJ. Netland. Coronaviruses post-SARS: Update on replication and pathogenesis. Nat Rev Microbiol. 2009; 7(6):439.
2. Chan JF, To KK, Tse H, Jin DY, Kuen KY. Trends Microbiol. 2013; 21(10):544-555.
3. Chen YQ, Liu D, Guo J. Emerging coronaviruses: Genome structure, replication, and pathogenesis. Med Virol. 2020; 92(4):418-423.
4. Chan JFK, Kok H, Zhu Z. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020; 9(1):221-236.
5. Mol CD, Izumi T, Mitra S. Nat. 2020; 403 (6768): 451-456.
6. Wayengera M, Kajumbula H, Byarugaba W. Harnessing pharmacogenomics to tackle resistance to the "nucleoside reverse trancripatse inhibitor" backbone of highly active antiretroviral therapy in resource limited settings. Open AIDS J. 2008; 2:78-81.
7. Wayengera M. Genomic-regulation of active retroviral elements as a model for HIV cure. J Antivir Antiretrovir. 2015; 7:069-075.
8. Wayengera M. HIV AIDS Review. 2011; 10(1): 1-8.
9. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020; 1: 105949.
10. Li G, De C. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020; 19(3):149-150.
11. Cao B, Wang Y, Wen D. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020.
12. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res. 2020; 104787.