AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

An Africa-focused Report on Safety Data of COVID-19-related Products, May 2020
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Introduction

The urgency to mitigate the mortality and morbidly rates due to COVID-19 pandemic has resulted in accelerated product development, re-purposing of formulations, off-label use of therapeutics and dedicated search for preventive and case management interventions. Emergencies such as COVID-19 call for a safety surveillance for relevant products throughout the product life cycle to make up for the safety issues that may have been overlooked.

The African Union Smart Safety Surveillance **(AU-3S)** programme of the **AUDA-NEPAD** is engaged in ensuring the characterization of the safety profile of all COVID-19 related products used in Africa. The process entails aggregation of data and establishment of a database on adverse events resulting from such medicinal products during trials involving new and re-purposed approved medicines including vaccines, medicines, herbal products, as well as medical devices.

Some countries have given Emergency Use Authorization (EUA) for re-purposed medicines for use in the treatment of COVID-19. Some consider this a trial while others as compassionate use. National Medicines Regulatory Authorities (NMRAs) need to ensure that adequate data on adverse events are collected to enhance the characterization of the product safety profile for COVID-19 therapy.

There are reports of trials on-going or planned in Africa, prominent among them are the SOLIDARITY trials coordinated by the World Health Organization (WHO). This report will highlight the landscape of therapeutic agents and medical devices used in some African countries and safety concerns reported on the globe but relevant to the African context. In the future, this report will focus on safety reports from active and spontaneous reports from African countries as appropriate.

Trials

As at the time of this publication, there is no reported clinical trial of any vaccine on Africa. There are, however, on-going and planned trials for re-purposed medicines. The African Union's Africa Centres for Disease Control (CDC) has outlined on-going trials for COVID-19, as part of the continent's stride for the quest for treatment and vaccination for the virus. In total, different trials were on-going in Egypt, Zambia, Nigeria, Tunisia and South Africa. The Africa CDC indicates that comparatively few treatments have been tested on the continent.

WHO Solidarity trials

The World Health Organization (WHO) is coordinating an international randomized trial of additional treatments for COVID-19 in hospitalized patients. They are receiving the local standard of care referred to as the SOLIDARITY trials. Globally, over 100 countries have expressed interest in engaging on Solidarity Trials, including more than 25 African countries.

So far, at least six (6) African countries have made progress with satisfying required criteria to participate in the global trial. Products involved in these trials include Chloroquine Phosphate or hydroxychloroquine; Remdesivir; Lopinavir (given with ritonavir); and Interferon (b1a).

Review of COVID-19 therapy-related Adverse Events (AEs)

Knowledge of the comprehensive profile of products will help countries make regulatory decisions on what to use. Globally, there are confirmed/reported and suspected adverse events associated with re-purposed medicines. A comprehensive profile of the specific case of Africa for the solidarity trials will be more meaningful when an active case search of retrospective data is conducted when COVID-19 has subsided.

In this regard, a recent comparison analysis on some products (remdesivir, favipiravir, hydroxychloroquine, chloroquine and azithromycin) in the treatment of coronavirus disease 2019 COVID-19 affirms that thorough monitoring of adverse events may be helpful.

Below are some of the adverse events worth monitoring.

Remdesivir: A review of 3 medical publications, two regulatory agency communications and one company communication revealed increased liver enzymes, liver dysfunction, renal dysfunction/impairment, multiple organ dysfunction syndromes, septic shock, acute kidney injury, increased aminotransferase levels, acute respiratory failure, diarrhoea, rash, hypotension, sweating, tremor, shivering, and gastrointestinal symptoms, including nausea, vomiting, gastroparesis and rectal bleeding as adverse events suspected or confirmed/reported with the use of Remdesivir. The alert phases included clinical trials, compassionate use and post-marketing. [Augustin M. et al. (2020), Grein J, et al. (2020), Kujawski, S.A. et al. (2020), PMDA package insert, FDA 2020, and Gilead (company) communication (2020)]*

Lopinavir/Ritonavir: Previous adverse drug reactions and serious adverse events reported in AU members states including Ghana and Nigeria in the course of using Lopinavir/ritonavir HIV indication include the overactive immune system, abnormal protrusion (progressively increasing abdominal growth), itching, rash, nausea, abdominal pain, loss of appetite, vomiting, fatigue, diarrhoea, which in 1 case caused/prolonged hospitalization. Concomitant drugs used during the medication period were Tenofovir, Lamivudine, Efavirenz (EFV, EFZ), and Cotrimoxazole. The alert phase was post-marketing. [NAFDAC (2017, 2018),

Interferon-beta 1a: Omrani and Memish (2015)***** reported depression (psychiatric disorder) as an adverse event observed following the use of interferon beta 1a in the treatment of Middle East respiratory syndrome coronavirus infection. The alert phase for this observation was post-marketing.

Chloroquine: 4 medical publications, three individual case safety reports (ICSRs) submitted to NAFDAC (2017, 2018) and information from Ghana FDA indicated prolonged electrocardiogram QT, haemoglobin decrease, increased creatinine, increased creatine phosphokinase, increased creatine phosphokinase-MB, ventricular tachycardia, rash, swollen facial area, itching as reported adverse events. Two of the medical publications revealed that severe rhabdomyolysis and ventricular tachycardia were suspected to be related to adverse events. Individual case safety reports were based on the use of chloroquine for the treatment

of malaria, while the publications were based on COVID-19 therapy. Concomitant drugs used, as reported by one of the publications, are azithromycin and ceftriaxone. The alert phases considered included clinical trials (3 publications) and post-marketing (3 ICSRs and one publication). [Borba MGS et al. (2020), van den Broek MPH et al. (2020), Garcia-Cremades M et al. (2020) and Borba MGS et al. (2020)]*

Hydroxychloroquine: Garcia-Cremades M et al. (2020)* reported related adverse events in the treatment of COVID-19 to include retinopathy and gastrointestinal disorder.
Similarly, findings by Garcia-Cremades M et al. (2020)* showed that prolongation of electrocardiogram QT (by hERG blockage) is a suspected adverse event. The alert phase considered for both sources was post-marketing.

Chloroquine and **hydroxychloroquine:** The use of chloroquine and hydroxychloroquine have been studied. One of such studies conducted in a post-marketing alert phase revealed that adverse events related to the use of these drugs in the treatment of COVID-19 include psychiatric effects, arrhythmia and sudden death. Regulatory Agency communications have also indicated the use of these drugs in the treatment of COVID-19. These communications clearly stated related adverse events to include arrhythmia (Cardiac disorders), ventricular fibrillation, ventricular tachycardia, death, prolonged electrocardiogram QT, hypoglycaemia, liver disorder, nervous system disorder, renal disorder and seizure. The adverse events were observed with azithromycin as a concomitant drug. 2 of the communications are based on findings from the clinical alert phase. In contrast, the 3rd is based on results from both clinical and post-marketing alert phases. [Moore N. (2020), Health Canada (2020), FDA (2020) and EMA (2020)]*

Azithromycin: In a study by Damle B. et al. (2020)*, electrocardiogram repolarization abnormality, prolonged electrocardiogram QT, Torsade de Pointes (Cardiac disorders) and vomiting (gastrointestinal disorder) were confirmed adverse events while urticaria (skin and subcutaneous tissue disorders) was suspected Urticaria (Skin and subcutaneous tissue disorders) related to the treatment of COVID-19 during the clinical alert phase.

Next step:
As African countries are engaged in COVID-19 Solidarity and other trials, AUDA-NEPAD, through the AU-3S project, will facilitate the aggregation of COVID-19 therapy-related adverse events, provide a continental repository of such data and develop/disseminate Africa-focused safety reports to enhance informed regulation and decision-making in Africa.

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