Antivirals for the treatment of mild and moderate COVID-19 in South Africa

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While the majority of COVID-19 cases in South Africa (SA) are mild, patients with severe COVID-19 requiring hospitalisation present with significant morbidity and mortality and place a substantial burden on healthcare services. Given the low vaccine uptake in SA and other low- and middle-income countries in sub-Saharan Africa, the high prevalence of comorbidities and limited healthcare system capacity, evidence-based interventions that reduce the risk of severe disease and death should be considered for implementation. Several antiviral classes have been newly developed or repurposed to treat COVID-19 early after infection to retard progression to severe disease and reduce the risk of death, particularly in the elderly and/or in patients with comorbidities. COVID-19 antivirals such as remdesivir, nirmatrelvir/ ritonavir and molnupiravir are safe and cost-effective and have received either full approval or emergency use authorisation from regulators. Using a proposed test-and-treat strategy, judicious use of antivirals could be impactful.

The COVID-19 pandemic resulted in excessive loss of human life and destabilised healthcare systems, economies and social structures globally. Up to March 2023, over 680 million cases of COVID-19 had been reported globally, with an associated 6.8 million deaths.[1] The burden of COVID-19 has been heterogeneously distributed across countries and regions, largely driven by disparities in social, economic and environmental factors.[2] In Africa, as of March 2023, there have been ~9.5 million cases and ~175 000 deaths,[1] with South Africa (SA) reporting the highest number of cases and deaths on the continent, ~4 million and 100 000, respectively.[3]

The severity of COVID-19 infection ranges from mild to critical, with critical disease resulting in death in 0.5 - 2% of cases.[4] Early in the pandemic (December 2019 - February 2020; Wuhan-Hu-1), 81% of cases were reported as mild or moderate, 14% severe and 5% critical.[5] With the development of variants over time, disease severity associated with Alpha, Gamma and Delta variants was comparable, while Omicron infections were associated with less severe disease.[6] During the Omicron wave in SA, 8.3% of patients required hospitalisation, compared with 12.9%, 12.6% and 10.0% in the D614G (first), Beta (second) and Delta (third) waves. Of these admissions, 52.3%, 63.4%, 63.0% and 33.6% were severe or critical disease during the D614G, Beta, Delta and Omicron waves, respectively.[7] Severe and critical COVID-19 places a substantial burden on health systems owing to the need for hospitalisation, supplementary oxygen, organ support and pharmacotherapy.

Constrained resources and limited diagnostic capabilities have resulted in the true burden of COVID-19 in low- and middle-income countries (LMICs) being poorly characterised.[8] A retrospective data analysis (2020 - 2021) found that of an estimated 505.6 million infections in Africa, only 1.4% were reported.[9] Furthermore, modelling for excess mortality between 3 May 2020 and 27 March 2021 revealed 150 271 excess deaths, most of which were attributable to unreported COVID-19.[8] In SA, the economic cost of caring for a patient with severe COVID-19 was estimated at ZAR13 800 - ZAR14 300 daily.[10,11] Between May 2020 and December 2022, SA reported 22 968 intensive care unit (ICU) admissions related to

severe COVID-19.[12-14] In addition to financial and economic costs, the COVID-19 pandemic has had a significant impact on human resources, including medical staff, allied health professionals, nursing and support staff.[11] Furthermore, the World Bank reported that the disease has pushed between 88 million and 115 million people into extreme poverty.[15,16]

Although mitigation strategies such as vaccination, the use of personal protective equipment (PPE), general infection prevention and control measures and social distancing have played a role in the reduction of COVID-19 transmission, these strategies have significant limitations in LMICs. More than 80% of the population has probably been infected at least once since the start of the pandemic, evident by the high seroprevalence of SARS-CoV-2 antibodies.[17] Supply-chain and access-related challenges have limited the efficacy of vaccines and PPE as a strategy to curb the burden of COVID-19.[18] In addition, the efficacy of vaccines is limited in populations diagnosed with malignancies, particularly blood cancers, as well as immunosuppressed individuals.[19] Individuals with allergies to vaccine excipients and those who have experienced allergic reactions to the initial dose of the COVID-19 vaccine are unable to vaccinate, with those opting not to vaccinate also contributing to the unvaccinated population. As a result, we can no longer rely solely on vaccination, and so a 'vaccination plus' strategy must be adopted in order to reduce the global burden of COVID-19.[20] Vaccine hesitancy and refusal have grown, and vaccination levels have reached a plateau in LMICs such as SA.[21] Given the low vaccine uptake in sub-Saharan Africa, the high prevalence of comorbidities and the limited capacity of the healthcare system, existing mitigation strategies must be supplemented by other evidence-based interventions to reduce the risk of severe disease. One supplemental strategy is treatment of COVID-19 with effective oral antiviral agents to reduce the overall burden of disease, curtail transmission and retard progression to severe disease.[22]

Several antivirals have been developed or repurposed to treat COVID-19 early after infection is established.[23] Remdesivir, nirmatrelvir/ritonavir and molnupiravir are cost-effective and have

received either full approval or emergency use authorisation from regulatory authorities in most LMICs, and existing supply chain networks have been successfully established. In October 2021, Merck Sharp & Dohme (MSD) authorised a licence agreement with the Medicines Patent Pool (MPP) for molnupiravir that allowed 105 countries access to generic formulations of the antiviral for the treatment for mild to moderate COVID-19.[24] In November 2021, Pfizer authorised a licence agreement with the MPP to facilitate affordable access to nirmatrelvir/ritonavir. This allowed for access to generic antiviral products for the treatment of COVID-19 in 95 countries worldwide. The licensing agreements secured by MPP have enhanced global production, thus limiting supply shortages, and increased equitable access to therapeutics in LMICs, which in turn increases the global capacity to curb the transmission and progression of COVID-19, and therefore the morbidity and mortality.[25] In addition, licensing agreements allow for potential reduction in the cost of treatment, with generic formulations in LMICs and potential for exportation of generics from such countries to neighbouring countries. Other interventions include treatment with monoclonal antibodies, immunomodulating agents such as Janus kinase (JAK) inhibitors and convalescent plasma. While each intervention has shown sufficient levels of efficacy in the setting of high-income countries (HICs), limitations in LMICs such as costs, relevant regulatory body approval, supply chains, cold chain integrity and safety profile in a high HIV burden setting make these interventions difficult to implement. The implementation of oral antivirals for the treatment of COVID-19, however, may be the most pragmatic option in the LMIC setting.

Recent evidence also shows that in people with SARS-CoV-2 infection and at least one risk factor for progression to severe COVID-19, early treatment with antivirals (nirmatrelvir/ritonavir) during the acute phase of COVID-19 was associated with reduced risk (relative risk 0.74; 95% confidence interval (CI) 0.72 - 0.77) of post-COVID conditions (long COVID), including reduced risk of sequelae in the cardiovascular system (dysrhythmia and ischaemic heart disease), coagulation and haematological disorders (pulmonary embolism and deep vein thrombosis), fatigue and malaise, acute kidney disease, muscle pain, neurological system (neurocognitive impairment and dysautonomia) and shortness of breath.[26]

In support of a public health approach, therapeutic interventions in LMICs need to be designed for implementation at a nurse-driven, doctor-supported primary healthcare level, with minimal clinical monitoring and ease of administration being prioritised. Primary healthcare serves the majority of the population in LMICs and is easily available, accessible and affordable.[27] As a result, test-and-treat strategies should be aimed at this sector in order to be feasible, scalable, sustainable and have the greatest impact on the health of the population. A test-and-treat strategy to facilitate early administration of oral antivirals in a sub-saharan African setting could reduce hospitalisation and progression to severe illness, thus reducing the burden of COVID-19 on already resource-limited healthcare systems. The risk of progression from mild to critical disease is high in susceptible populations such as that of sub-Saharan Africa, where the healthcare system is ill-equipped to deal with such a burden, and the prevalence of comorbidities is high. Ideal interventions in this setting should be safe, effective, have a low potential for drug-drug interactions, be easy to administer and be economically and logistically feasible.

This review article provides information on presently available therapeutics for the treatment of mild/moderate COVID-19 as well as novel therapeutics in their developmental phases that could potentially be used to prevent the progression to severe disease in the sub-Saharan African setting.

Methods

We performed searches of Medline/PubMed, SCOPUS and the Cochrane Central Register of Controlled Trials from January 2020 to 31 March 2023. Publications in which the clinical evaluation of COVID-19 antiviral agents was reported were included. The search strategy included the following Medical Subject Heading (MeSH) terms in titles and abstracts: ('SARS-COV-2 OR 'coronavirus' OR 'COVID-19' OR 'COVID') AND ('antiviral' OR 'treatment' OR 'clinical trial' OR 'intervention'). Publications were limited to human studies in the English language. A review of all articles from the reference lists of identified articles was conducted to identify additional articles not found by the electronic search. We included all studies that described at least one antiviral agent, evaluated in at least one phase II, III or IV trial, and which reported clinical safety, efficacy outcomes, barriers to implementation, or enablers of implementation. Case reports, case series and review articles were excluded. We further restricted the search to oral antiviral agents with authorisation for use in at least one jurisdiction for use in the treatment of mild or moderate COVID-19. Studies that described the use of antiviral agents for prophylaxis only were excluded, while studies describing the effects of antiviral agents for COVID-19 on healthcare systems and infrastructure were included. In addition to published articles, COVID-19 treatment guidelines published by the World Health Organization (WHO), National Institutes of Health (NIH) and Centers for Disease Control and Prevention were also reviewed, as well as national government documents and policies.

Discussion

There are three antiviral agents that are available for use in SA (Table 1).[23,28-46] Currently registered antivirals for the treatment of COVID-19 include ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir (Lagevrio) and remdesivir (Veklury). While remdesivir has received full approval by the US Food and Drug Administration (FDA), ritonavir-boosted nirmatrelvir and molnupiravir have received emergency use authorisation (EUA).[28-32] Clinical investigations of ritonavir-boosted nirmatrelvir demonstrated a relative risk reduction in progression to severe disease of 89.1% in high-risk individuals.[33] Similar investigations show that molnupiravir is associated with a 30% reduction in COVID-19 hospitalisation or death in high-risk individuals.[34] In addition, a large-scale, real-world, retrospective cohort study during the Omicron (B.1.1.529) subvariant BA.2.2 wave demonstrated an overall reduction in mortality of 24% with molnuprinavir and 66% with ritonavir-boosted nirmatrelvir.[35-37] A SA cohort study investigating effectiveness of nirmatrelvir/ritonavir reported 79.6% effectiveness in preventing hospital admission or death within 30 days of a positive test if the patient received treatment 0 - 5 days after symptom onset. The effectiveness of treatment on patients who received the course on the day of their test was 89.6%. Effectiveness of treatment was 43.8% in patients who received the treatment >6 days after the onset of symptoms.[38] PANORAMIC, an open-label, platform-adaptive randomised controlled trial comparing the use of molnupiravir plus usual care v. usual care alone as early treatment for COVID-19 in high-risk adults reported that early addition of molnupiravir to usual care did not reduce hospitalisation or death. However, participants who received molnupiravir plus usual care recovered faster than those receiving only usual care, had a higher rate of early sustained recovery and had fewer general practitioner consultations.[39] A study published in February 2023 assessing the effectiveness of molnupiravir and nirmatrelvir/ritonavir in reducing hospitalisation and death in a real-world cohort of non-hospitalised patients reported that the use of either drug was not associated with lower risk of ICU admission, invasive mechanical ventilation and/or

Table 1. Summary of approved COVID-19 oral/injectable antiviral agents[23,28-46]

Characteristic	Product (generic/trade)		
	Molnupiravir (Lagevrio)	Nirmatrelvir + ritonavir (Paxlovid)	Remdesivir (Veklury)
MOA	Incorporation into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication.	Peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro)/3C-like protease (3CLpro).	SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) inhibitor (nucleoside prodrug of adenosine analogue).
Registration status			
SAHPRA	Section 21 item	Approved	Approved
FDA	Emergency use authorisation	Emergency use authorisation	Approved
EMA	Marketing authorisation evaluation	Authorised	Authorised
TGA	Provisional registration	Provisional registration	Provisional approval
Clinical trials phase	2/3	2/3	Completed
Efficacy	RR reduction = 30%	RR reduction = 88%	RR reduction = 87%
Safety/tolerability	Not recommended in pregnancy. Breastfeeding not recommended during treatment and 4 days after last dose. Theoretical risk of incorporation into host cell DNA and causing mutations – cancer/tumours.	Hypersensitivity reactions to any active ingredients. Co-administration with drugs affecting CYP3A liver enzyme. Contraindicated in hepatic impairment; GFR <30 mL/min (not recommended). Not recommended for use in pregnancy.	Insufficient data to evaluate associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No adverse effect on embryo-fetal development when administered to pregnant animals. Caution in patients with renal impairment.
Side-effect profile	Mild or moderate diarrhoea, nausea and dizziness.	Dysgeusia, diarrhoea, hypertension and myalgia.	Nausea, elevated ALT, elevated AST. Increased prothrombin time (no change in INR); hypersensitivity reactions.
Barriers to implementation	Has to be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms.	Many drug interactions due to ritonavir and needs to be initiated within 5 days. Potent CYP3A inducers reduce nirmatrelvir or ritonavir plasma concentrations.	Injectable dosage form poses a challenge as less convenient than oral. To be initiated within 7 days of symptoms.
Challenges in SA setting	Mutagenic – implications in HIV (structural similarities between the RNA polymerase in SARS-CoV-2 and HIV). Taking 4 capsules twice a day – pill burden. Severity of adverse reactions will also contribute to compliance. High prevalence of polypharmacy, especially with our high prevalence of NCDs. Since drug interaction studies have not been conducted there is a high risk of adverse events. Confirmation of COVID-19 required. Total cost of test and treatment is presently too expensive in SA setting. Cost: Unknown for the SA market. USA: cost is USD700 per course.	Many drug interactions because of the ritonavir boosting (CYP450 inhibition). Dose modifications for concomitant use with ARV regimens (see section on drug interactions). Sudden change in taste sensation could cause patients to stop medication – common misconception that the drugs are causing COVID-19. High prevalence of HIV, TB and NCDs in SA – large potential for drug-drug interactions. Added cost of treatment since contraception should be used in women of childbearing potential. NEML MAC does not recommend use (14 March 2022/20 July 2023). Single exit price: ZAR13 035.43 for a 5-day course.	Potential for drug interactions, especially within the SA setting, is concerning. High prevalence of HIV, TB and NCDs means that there is a high incidence of polypharmacy, which increases the chances of drug-drug interactions. Need to use contraceptives while on treatment – added cost to treatment. SA does not have the resources to facilitate home treatment with injectable antivirals. Patients will need to be admitted to hospital which adds to total cost of treatment. Approved but not recommended by MAC according to government gazette – limited access to medicine. Cost ZAR6 451.50 for 6 vials (4-day course).

MOA = mechanism of action; SAHPRA = South African Health Products Regulatory Authority; FDA = Food and Drug Administration; EMA = European Medicines Agency; TGA = Therapeutic Goods Administration (Australia); RR = relative risk; CYP3A = cytochrome P450, family 3, subfamily A; GFR = glomerular filtration rate; ALT = alanine transaminase; INR = international normalised ratio; NCD = non-communicable disease; SA = South Africa; CYP450 = cytochrome P450; TB = tuberculosis; NEML MAC = National Essential Medicines List Ministerial Advisory Committee; ARV = antiretroviral .

death as compared with patients who did not receive antivirals.[40] The use of nirmatrelvir/ritonavir, but not molnupiravir, was associated with a reduced risk of hospitalisation.[40] In addition, although nirmatrelvir/ritonavir use improves outcomes in high-risk patients aged >65 years, data in younger (between 50 and 64 years old) vaccinated patients are inconsistent.[41-44] While molnupiravir is a known mutagenic agent, a recent concern about the mechanism by which it works has been expressed, with the drug causing mutations that have been associated with onwards transmission.[45,46]

Several oral antivirals are currently under evaluation by relevant regulatory bodies and show promise as antivirals for the treatment of COVID-19 (Table 2).[47-57] Sabizabulin (VERU-111), a coronavirus microtubule disruptor, and baricitinib, a JAK inhibitor, have both received EUA by the FDA, while ensitrelvir, a C3-like protease inhibitor, is still under investigation. A phase III clinical trial assessing the benefit of oral sabizabulin in hospitalised adults with COVID-19 on supplemental oxygen reported a 55.2% relative reduction in mortality compared with placebo.[47] The COV-BARRIER study,

Table 2. Summary of COVID-19 oral antiviral agents under evaluation[47-57]

Characteristic	VERU-111 (Sabizabulin)	Ensitrelvir (Xocova)	Baricitinib (Olumiant)
	Product (generic/trade)		
MOA	Coronavirus microtubule disruptor	3C-like protease (3CLpro) inhibitor	Janus kinase inhibitor
Registration status			
SAHPRA	No approval	No approval	No approval
FDA	Emergency use authorisation	No approval	Emergency use authorisation
EMA	Company data review	No approval	No approval
TGA	Provisional determination	No approval	No approval
Clinical trials phase	3	2/3	3
Efficacy			
Absolute RR	24.9%	n/a	n/a
Relative RR	55.2%	n/a	n/a
Safety/tolerability	Safety in pregnancy has not been established. Refrain from prolonged exposure to the sun or use at least SPF 50 on all exposed skin throughout participation in the study.	Protease inhibitor – theoretically structurally similar to nirmatrelvir since works on the exact same protease. Should have a similar side-effect profile (theoretically).	Increased risk of allergic reactions, severe infections, cancer, thrombosis, stroke, myocardial infarction and death.
Side-effect profile	Consistent with patients with serious COVID-19 illness.	Transient decrease and increase in HDL and blood triglyceride levels as well as increase in total bilirubin and iron levels.	Deep vein thrombosis, pulmonary embolism and infections.
Barriers to implementation	Drug interactions and pregnancy and safety data lacking. Microtubule inhibitors have been shown to exhibit neurological symptoms in past studies. Estimated study completion date 21 September 2022.	Failed Japan approval due to insufficient data on drug efficacy.	Approval for oxygen-requiring hospitalised adults only. Risk of serious adverse events make outpatient use inviable option.
Challenges in SA setting	Not a lot of data on the effect on the inhibition of microtubule polymerisation on host cells. Inclusion/exclusion criteria for the study – the sample did not include those infected with HIV as a comorbidity. The duration of treatment is much longer than that of the current antivirals available for the treatment of SARS-CoV-2. Cost of treatment will be exceptionally high. Use of immunomodulators in the SA setting where there is a high prevalence of HIV/AIDS should be carefully considered.	Possibility of cross-sensitivity between HIV and SARS-CoV-2 to the protease inhibitor. Possibility of the development of cross-resistance between ARVs.	Increased risk of infection via neutropenia and lymphopenia effects is a concern in SA where deadly diseases such as HIV and TB are rife.

MOA = mechanism of action; SAHPRA = South African Health Products Regulatory Authority; FDA = Food and Drug Administration; EMA = European Medicines Agency; TGA = Therapeutic Goods Administration (Australia); n/a = not applicable; RR = relative risk; HDL = high-density lipoprotein; SA = South Africa; TB = tuberculosis.

a randomised, double-blind, placebo-controlled phase III trial assessing the efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19, reported a 38.2% reduction in 28-day all-cause mortality compared with placebo.[48] A recent study also reported that ensitrelvir demonstrates strong *in vitro* antiviral activity against SARS-CoV-2 Omicron subvariants BA.4 and BA.5.[49]

Fig. 1 presents a pipeline of treatments for COVID-19 in different phases of clinical trials and regulatory evaluation.[23, 28-31,52-57] Classes of drugs shown in the diagram include monoclonal antibodies, immunoglobulins, antivirals and JAK inhibitors, each with its corresponding route of administration, i.e. oral, intravenous, intramuscular, subcutaneous or intranasal. In the global fight against COVID-19, access initiatives such as the WHO's Access to COVID-19 Tools Accelerator (ACT-A) and the Global Accountability Platform to fight COVID-19 (COVID GAP) led by Duke University have been established to build global relationships to accelerate the end of the pandemic.[20,51] These initiatives focus on improving access to resources in settings where healthcare systems are ill-equipped to manage a high burden of severe disease. In addition to facilitating access to resources such as vaccines, the ACT-A strategic plan and COVID GAP outline strategies to improve testing capacity and enhance access to effective antiviral therapy to reduce the progression of disease and the overall burden of severe disease.

One initiative, the COVID Treatment Quick Start Consortium, a collaboration between Duke University, the Clinton Health Access Initiative (CHAI), COVID Collaborative and Americares, aims to support governments to increase access to novel COVID-19 antivirals in high-risk populations. It is one of the first initiatives to bring COVID-19 antivirals to low- and middle-income partner countries, including Ghana, Kenya, Laos, Malawi, Nigeria, Rwanda, SA, Uganda, Zambia and Zimbabwe.[58]

As of December 2022, Zambia became the first LMIC to receive a shipment of 1 000 courses of nirmatrelvir-ritonavir (Paxlovid), which is now available to patients for the treatment of mild-to-moderate COVID-19 in the implementation of a test-and-treat initiative in a vulnerable population.[59]

Various guidelines and policies for the treatment of mild to moderate COVID-19 have been implemented on a global scale. However, in the sub-Saharan African setting there have been many barriers to their implementation. The WHO's 'Therapeutics and COVID-19 Living Guidelines' as well as the NIH's 'Guidelines on Mild to Moderate COVID' are two examples of up-to-date scientific guides that recommend the use of novel oral antivirals for the treatment of mild to moderate COVID-19, including nirmatrelvir/ ritonavir (Paxlovid), remdesivir and molnupiravir.[60,61]

Test-and-treat strategy

With limitations to the current mitigation strategies to reduce COVID-19 morbidity and mortality in LMICs, the implementation of a test-and-treat strategy could play a key role in reducing transmission and progression of the disease (Fig. 2). Although there is a current lack of control trial data on the efficacy of a test-and-treat strategy for COVID-19, the approach itself has shown to be effective in other illnesses such as HIV and malaria (in endemic areas). Universal test-and-treat trials (UTT) conducted in LMICs such as sub-Saharan Africa demonstrated significantly improved population-level viral suppression and decreased HIV incidence and mortality associated with this strategy.[62,63] A model-based study estimating the potential need and impact of test-and-treat programmes in LMICs predicted a significant reduction in severe cases of COVID-19 and COVID-19-related deaths, provided testing rates are high enough to facilitate a test-and-treat programme.[64] A modelling study carried out in Wallis and Futuna suggested that a test-and-treat strategy may contribute to the mitigation of COVID-19 epidemic resurgences, particularly in populations with low immunity and high levels of comorbidities.[65] Furthermore, there is strong support for a test-and-treat strategy aimed at reducing progression to severe COVID-19 in children and elderly patients.[66] Home testing coupled with patient self-sampling
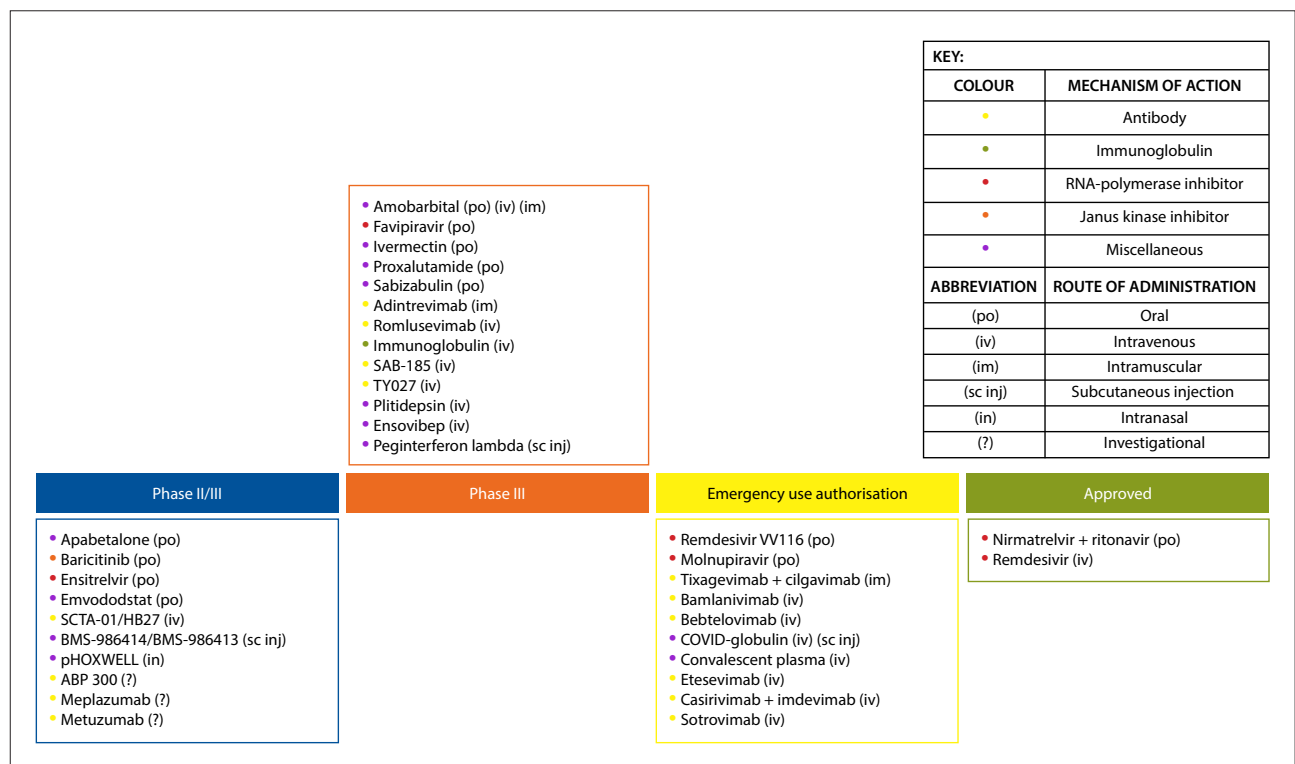

		KEY:	
		COLOUR	**MECHANISM OF ACTION**
		•	Antibody
		•	Immunoglobulin
		•	RNA-polymerase inhibitor
		•	Janus kinase inhibitor
		•	Miscellaneous
		ABBREVIATION	**ROUTE OF ADMINISTRATION**
		(po)	Oral
		(iv)	Intravenous
		(im)	Intramuscular
		(sc inj)	Subcutaneous injection
		(in)	Intranasal
		(?)	Investigational

Phase III:
- Amobarbital (po) (iv) (im)
- Favipiravir (po)
- Ivermectin (po)
- Proxalutamide (po)
- Sabizabulin (po)
- Adintrevimab (im)
- Romlusevimab (iv)
- Immunoglobulin (iv)
- SAB-185 (iv)
- TY027 (iv)
- Plitidepsin (iv)
- Ensovibep (iv)
- Peginterferon lambda (sc inj)

Phase II/III	Phase III	Emergency use authorisation	Approved
• Apabetalone (po)		• Remdesivir VV116 (po)	• Nirmatrelvir + ritonavir (po)
• Baricitinib (po)		• Molnupiravir (po)	• Remdesivir (iv)
• Ensitrelvir (po)		• Tixagevimab + cilgavimab (im)	
• Emvododstat (po)		• Bamlanivimab (iv)	
• SCTA-01/HB27 (iv)		• Bebtelovimab (iv)	
• BMS-986414/BMS-986413 (sc inj)		• COVID-globulin (iv) (sc inj)	
• pHOXWELL (in)		• Convalescent plasma (iv)	
• ABP 300 (?)		• Etesevimab (iv)	
• Meplazumab (?)		• Casirivimab + imdevimab (iv)	
• Metuzumab (?)		• Sotrovimab (iv)	

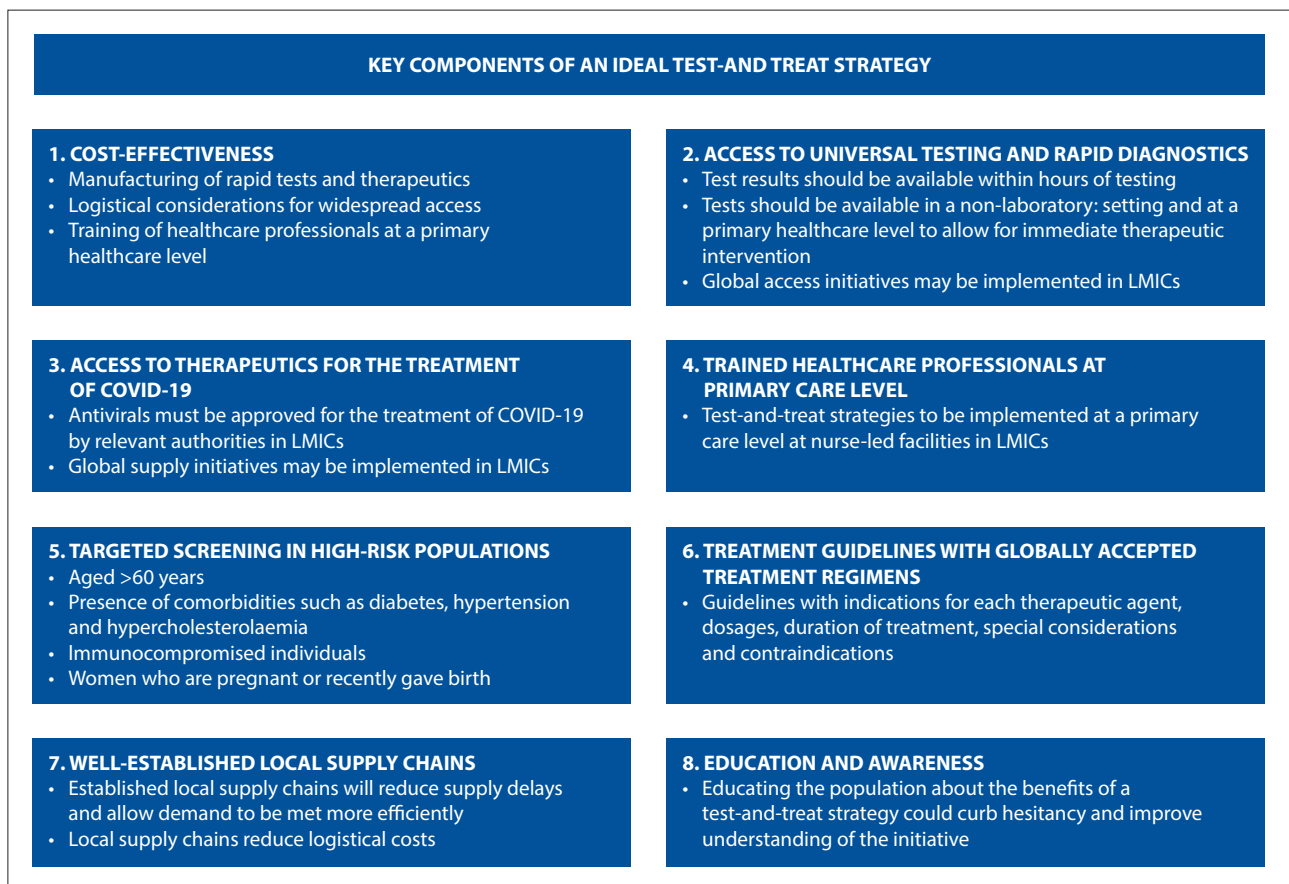*Fig. 1. The COVID-19 therapeutic pipeline*[23, 28-31,52-57]

Fig. 2. Key components of an ideal test-and-treat strategy.[62-71] *(LMICs = low- to middle-income countries.)*

may enhance testing the population using local regulator-approved test kits.[67] Delivery of therapeutics, including oral antivirals, to patients' homes may be a viable option that could be explored to improve access to treatment. The need for therapeutic trials in the outpatient setting of LMICs remains, and the high costs associated with these trials is a potential hurdle to the rollout of a test-and-treat programme.[66] However, implementation studies may succeed in filling this gap and offer an opportunity to nest ancillary research, including much-needed drug interaction studies among tuberculosis (TB)/HIV co-infected individuals and patients on statin therapy, and offers opportunities to assess the feasibility of COVID-19 home testing as examples of future research opportunities.

Studies assessing point-of-care testing in HICs, such as that for group A streptococcus in Wales, have shown not only clinical but cost-saving benefits as well.[68] A confirmed diagnosis before initiating treatment prevents overdispensing of medication and unnecessary prescribing of drugs. HICs such as the USA and the UK have proceeded to implement test-and-treat strategies for the management of COVID-19, despite the lack of clinical trial evidence. The implementation of a test-and-treat strategy in some HICs, such as New Zealand, allowed increased involvement of pharmacists in the prescribing and dispensing of antivirals for the treatment of COVID-19.[69] This allowed for increased access to the antivirals while requiring little to no additional training of healthcare workers. The importance of the pharmacy profession in test-and-treat initiatives should be considered. Local pharmacy clinics are ideal sites for administration of antivirals. The ideal test-and-treat strategy should include a multidisciplinary approach involving the healthcare professionals who are at community level (e.g. nurses, pharmacists, community healthcare workers, traditional healers) for greater access, convenience and coverage.[70]

The novel COVID-19 antivirals discussed in this review offer a promising approach in the treatment of mild to moderate COVID-19 when implemented as part of a test-and-treat strategy. Since these therapeutics must be initiated within 5 days of onset of symptoms, treatment must be closely linked to testing to reduce the burden of disease in a sub-Saharan African setting.[71] This implies a need for an increase in diagnostic capacity of healthcare systems in LMICs as well as increased access to oral antivirals, both of which may be accomplished by the intervention of previously mentioned global initiatives. Manufacturing of generic antiviral products has been slowed by regulatory processes and the need for high-quality bioequivalence data; therefore, access to effective biosimilars (biotherapeutics that have a high level of similarity to an already-approved 'reference' product) remains limited in most LMICs.[72,73]

Barriers and potential solutions for implementation

Access challenges

There is a limited supply of therapeutics, and although there are many global initiatives to provide access for LMICs to these drugs, HICs and high- to middle-income countries (HMICs) are often first to act. LMICs need to estimate their need for therapeutics prior to purchase to prevent misuse of resources. In the same way, sponsors, funders and other global initiatives require these estimates in order to purchase therapeutics on behalf of low-income countries (LICs) and LMICs to ensure supply on the basis of need in the face of global supply constraints. Forecasting the needs of LICs and LMICs depend on many variables, including testing capacity, capacity to get the therapeutics to the patients and hesitancy or lack of trust in the therapeutics.[20]

In order to overcome accessibility and supply barriers, countries in need of assistance in procuring and distributing these antivirals must work together with organisations and other countries in access initiatives such as ACT-A and COVID GAP. Pooled procurement of COVID-19 therapeutics to build treatment capacity is a strategy that can be utilised.[74] In addition to initiatives such as the COVID Treatment Quick Start Consortium, which is increasing access to COVID-19 antivirals to execute a test-and-treat approach, policy and guidelines on mobilisation and decentralisation of testing facilities must be developed.[75]

Global funding initiatives have been developed to ensure that countries in need are offered financial support for the procurement of COVID-19 tools including vaccines, treatment and test kits.[20,51,76] Reluctance to vaccinate or comply with treatment can be addressed with widespread education programmes that increase understanding and awareness of the test-and-treat strategy. Evidence-based communication strategies are key in reducing misunderstanding and promoting compliance.[77]

Local manufacturing of COVID-19 antivirals could also help to reduce cost and increase availability in a sub-Saharan African setting. Voluntary licences may be granted to generic manufacturers either directly from parent companies or via the MPP in order to increase production.[71]

Testing capacity

Oral antivirals for the treatment of COVID-19 need to be initiated within 5 days of symptom onset in patients with a confirmed diagnosis.[78] Access to rapid antigen tests in LMICs is limited compared with HICs, where at-home testing is easily accessible to confirm a diagnosis and initiate treatment. In many LMICs, testing facilities are inconveniently located, with many individuals having to travel long distances to clinics or hospitals. An assessment carried out in October 2021 by the WHO reported that only one in seven COVID-19 infections (14.2%) were being detected in Africa.[79] The implications of limited testing capacity include a greater burden of disease than estimated and inadequate clinical care of undiagnosed cases, leading to progression of disease.[80] An adequate testing capacity is one of the key components to a successful test-and-treat strategy, and initiatives such as ACT-A, CHAI and COVID GAP have facilitated an increased supply of tests to LMICs to be implemented at a primary healthcare level.

Capacity of the healthcare system

In many LICs and LMICs, such as those in sub-Saharan Africa, healthcare systems do not have the capacity to test patients timeously and simultaneously deliver therapeutics for the initiation of treatment. A large majority of cases go undetected, and since treatment must be closely linked to testing, this poses a great barrier in the global fight against COVID-19.[71] The test-and-treat strategy has been successful in HICs as a result of mobilisation of testing facilities as well as the supply of therapeutics on the basis of need. Healthcare workers need to be trained on how to test and treat effectively, and the population at large needs to be educated on how to use a home test kit. In addition, an authorised prescriber is needed in order to prescribe therapeutics following a positive COVID-19 diagnosis in mild/moderate disease, and patients need to be made aware of possible adverse reactions and to report to a healthcare facility should they experience such effects.[81] This is particularly important in a sub-Saharan African setting where the potential for drug-drug interactions is high owing to high rates of comorbidities. A proposed algorithm for a test-and-treat strategy is presented in Fig. 3.[78,82,83]

Literacy level of the population

Literacy, particularly COVID-19 health literacy, is a major driver of adherence to treatment as well as willingness to be treated.[84] The low literacy level of LMIC populations is expected to contribute to a higher reluctance to be treated with oral antivirals. In sub-Saharan Africa, the literacy levels are significantly lower than those in HICs, and so, although the population may benefit from treatment, many may opt not to take it. The lack of trust in therapeutics, however, is something that can be addressed with increased education and awareness, as seen from previous implementation of test-and-treat strategies for HIV in LMICs. Prescriber hesitancy, as seen in the early stages of vaccination rollouts worldwide, may be an additional hindrance to the success of a test-and-treat strategy in LMICs.[85]

Licensing issues

Access challenges result from limited production capacity due to delayed submission by licence holders following regulatory approval.[20] In addition, not all oral antivirals for the treatment of COVID-19 are registered in LMICs, presenting a major barrier to the implementation of treatment guidelines for mild/moderate COVID-19.[20] The United Nations-backed public health organisation, the MPP, is one organisation that aims to address these access challenges by signing agreements with patent holders to increase production and distribution of oral antivirals for the treatment of COVID-19 and COVID-19 technologies.[86] Voluntary licensing and patent pooling allow for LMICs to have rapid access to testing and treatment, thus making it not only possible but feasible to implement a test-and-treat strategy for COVID-19. The SA Health Products Regulatory Authority (SAHPRA) approved remdesivir and nirmatrelvir/ritonavir for the treatment of COVID-19, while molnupiravir was authorised as a section 21 item (to be prescribed on a patient-to-patient basis).

Risk of drug-drug interactions

According to Statistics SA, ~8.45 million people are living with HIV as of 2022 (mid-year statistics) in SA (13.9% of the total population).[87] According to the Joint United Nations Programme on HIV and AIDS (UNAIDS), ~74% of people living with HIV are on antiretroviral (ARV) therapy, and ~67% are virally supressed.[88] Paxlovid has the potential for drug-drug interactions with many therapeutics, including ARVs and drugs used to treat TB. In a population where HIV and TB are so prevalent, the effects of these potential drug-drug interactions on an individual's quality of life are currently unknown, and adverse drug events could result in poor compliance and treatment interruption, contributing to increased HIV and TB morbidity and mortality. However, the short treatment duration of most antivirals for COVID-19 provides some mitigation against this risk, and there are no known interactions expected between the current SA first-line ART, tenofovir/lamivudine/dolutegravir (TLD) and Paxlovid, while there is potential for interactions with second-line protease inhibitor-based regimens. For healthcare workers prescribing COVID-19 antivirals, the University of Liverpool COVID-19 drug interaction tracker is a valuable tool to guide clinical practice (https://www.covid19-druginteractions.org/checker).

Conclusion

This review sought to identify therapeutics that are effective at reducing progression of mild or moderate COVID-19 to severe disease, and to consider a test-and-treat approach that could be implemented in LMICs. In the SA setting, remdesivir, nirmatrelvir-
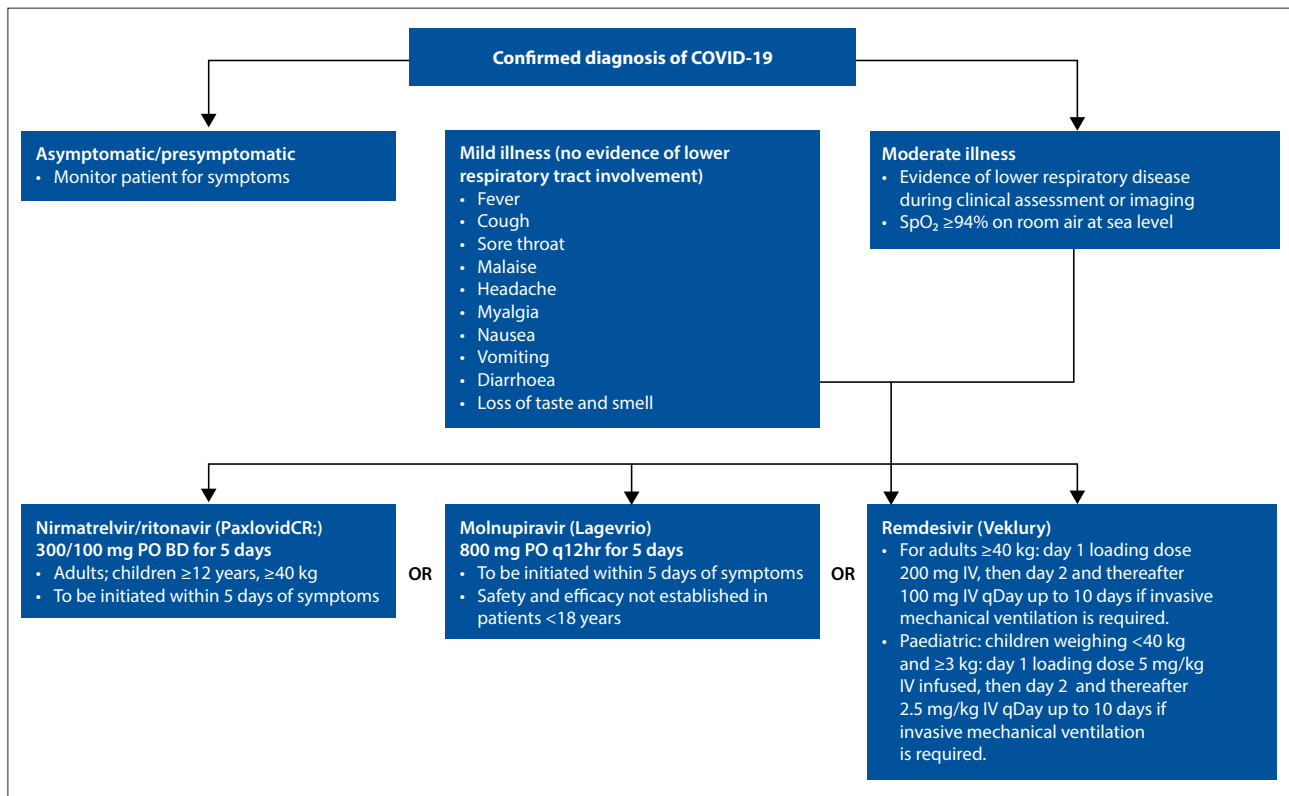
Fig. 3. Treatment algorithm for COVID-19.[78, 82,83] (PO BD = twice per day, orally; PO q12hr = every 12 hours, orally; IV = intravenous; qDay = once daily.)

ritonavir (Paxlovid) and molnupiravir are promising therapeutic agents. Other therapeutic agents, such as biologics and JAK inhibitors, remain in the therapeutic pipeline, but will likely be of limited use owing to their high cost and parenteral routes of administration. In a population where the prevalence of comorbidities such as hypertension, diabetes, hypercholesterolaemia, HIV and TB are high, strategies to reduce the burden of severe COVID-19 must be pursued to limit morbidity and mortality. Notwithstanding the significant challenges highlighted in this review, initiating a test-and-treat strategy with point-of-care testing and immediate administration of approved oral antivirals for the treatment of COVID-19 in high-risk patients may be a highly effective strategy in LMICs.

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