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Randomized clinical trial of nitazoxanide or sofosbuvir/daclatasvir for the prevention of SARS-CoV-2 infection

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Background: The COVER trial evaluated whether nitazoxanide or sofosbuvir/daclatasvir could lower the risk of SARS-CoV-2 infection. Nitazoxanide was selected given its favourable pharmacokinetics and *in vitro* antiviral effects against SARS-CoV-2. Sofosbuvir/daclatasvir had shown favourable results in early clinical trials.

Methods: In this clinical trial in Johannesburg, South Africa, healthcare workers and others at high risk of infection were randomized to 24 weeks of either nitazoxanide or sofosbuvir/daclatasvir as prevention, or standard prevention advice only. Participants were evaluated every 4 weeks for COVID-19 symptoms and had antibody and PCR testing. The primary endpoint was positive SARS-CoV-2 PCR and/or serology ≥7 days after randomization, regardless of symptoms. A Poisson regression model was used to estimate the incidence rate ratios of confirmed SARS-CoV-2 between each experimental arm and control.

Results: Between December 2020 and January 2022, 828 participants were enrolled. COVID-19 infections were confirmed in 100 participants on nitazoxanide (2234 per 1000 person-years; 95% CI 1837–2718), 87 on sofosbuvir/daclatasvir (2125 per 1000 person-years; 95% CI 1722–2622) and 111 in the control arm (1849 per 1000 person-years; 95% CI 1535–2227). There were no significant differences in the primary endpoint between the treatment arms, and the results met the criteria for futility. In the safety analysis, the frequency of grade 3 or 4 adverse events was low and similar across arms.

Conclusions: In this randomized trial, nitazoxanide and sofosbuvir/daclatasvir had no significant preventative effect on infection with SARS-CoV-2 among healthcare workers and others at high risk of infection.

Introduction

In early 2020, when the SARS-CoV-2 epidemic was first spreading worldwide, it was unclear if or when an effective vaccine would be developed.[1,2] At the time, health systems and health workers were under severe strain, exacerbated by widespread lack of access to personal protective equipment (PPE). Antiviral and other drugs had previously been shown to be effective prophylactic agents in preventing HIV infection.[3–5] Clinical trials were therefore established to evaluate similar efficacy of antiviral agents in the prevention of SARS-CoV-2 infection. Early candidates for prevention were not effective, including hydroxychloroquine,[6,7] ivermectin[8,9] and tenofovir.[10] Other direct-acting oral antivirals (molnupiravir, nirmatrelvir/ritonavir) and monoclonal antibodies are being evaluated as preventative drugs more recently.[11–13]

Subsequently, SARS-CoV-2 vaccines have demonstrated significant protection against severe disease, but less against infection transmission. Traditionally, vulnerable and immune-compromised groups have diminished vaccine-induced protection and remain at high risk for severe disease and death. Together with groups at high risk of recurrent infections, these populations may benefit from the use of a prophylactic medication administered during future waves of infection transmission.[14–16]

To date, South Africa has experienced four waves of the COVID-19 pandemic. The original wave peaked in mid-2020, the Beta wave in late 2020, the Delta wave in mid-2021 and the Omicron wave in late 2021/early 2022.[17] A peak of 37,875 new daily cases were reported during the Omicron wave and a peak of 844 new daily deaths were reported during the Beta wave.[17]

Globally, healthcare systems have experienced immense pressure during the COVID-19 pandemic. The treatment burden has been exacerbated by high rates of infection, quarantining, isolation and resultant hospitalization in healthcare workers (HCWs) and community health workers.[18] Limited access to PPE in South Africa, and inadequate infection control systems within facilities, raised fears of high infection rates in HCWs and subsequent transmission to their families and communities.

In South Africa, scalable therapeutic pharmaceutical interventions were seen as an urgent requirement while awaiting an efficacious preventive vaccine. Vaccine uptake has subsequently been slow, with 47.86% of the adult population having received at least one vaccine dose more than a year after vaccines were first made available in the country.[19] Ideally, prophylactic pharmaceuticals, an appealing alternative to some, and as a supplemental agent for high-risk groups, should already be approved for other indications, and hence immediately available as quality-assured generics.

The COVER trial was set up in April 2020 to evaluate whether nitazoxanide or sofosbuvir/daclatasvir could lower the risk of SARS-CoV-2 infection in HCWs and others at high risk of infection. Nitazoxanide, an already widely available affordable generic anti-protozoal agent, was selected for evaluation as a preventative drug, given its favourable pharmacokinetics relative to its *in vitro* activity compared with other drugs that had been screened by April 2020.[20,21] It should be noted that early pharmacokinetic analysis suggested that a higher dose than that used in the COVER trial would be required to achieve antiviral concentrations in plasma across the dosing interval, and a dose of 1500 mg twice daily is currently under evaluation in the AGILE Phase I/IIa platform treatment trial.[22] Sofosbuvir/daclatasvir, widely used to treat hepatitis C infection and again available as an affordable co-formulated generic, had shown favourable results in early clinical trials and evidence of antiviral effects against SARS-CoV-2.[23] However, it was not clear whether therapeutic levels of this drug combination could be achieved at standard human doses[24,25] and subsequent studies indicated sofosbuvir would be unable to achieve target concentrations whereas much higher doses of daclatasvir may or may not be supported.[26]

Methods

Trial design and randomization

COVER is an investigator-led, randomized, three-arm open-label study in inner-city Johannesburg, South Africa, initiated on 8 December 2020, during the peak of the Beta wave. The trial enrolled participants thought to be at high risk for SARS-CoV-2 infection by virtue of their profession (high-risk HCWs, front-facing workers).

HCWs were deemed high risk if they were doctors, nurses, nurse aids, radiographers, physiotherapists, phlebotomists, technicians, porters, cleaners, laboratory or other personnel identified as being at high risk of exposure (such as those collecting and processing samples for PCR testing). Other high-risk, front-facing workers (essential services employees such as firefighters, law enforcement officers, grocery store employees and those using public transport at least three times a week) were added as high-risk groups in subsequent iterations of the protocol, as the high rate of infection during both the Beta and Delta waves was recognized in the broader community.

Key inclusion criteria included being at least 18 years of age, usage of reliable contraception and minimum weight of 45 kg. Key exclusion criteria included current symptoms or PCR and/or serological evidence of current or previous SARS-CoV-2 infection, vaccination against SARS-CoV-2, significant renal, cardiac or hepatic conditions, and pregnancy or breastfeeding, all of which were contraindications to coadministration of the study drug. Detailed eligibility criteria are listed in the clinical trial registry, available at ClinicalTrials.gov NCT04561063.

Randomization was overseen by the study statistician. The study was open label to participants and study personnel. Participants were enrolled and randomized 1:1:1 to one of the three treatment arms: (i) nitazoxanide 500 mg taken orally twice daily for 1 week and 1000 mg twice daily thereafter; (ii) sofosbuvir/daclatasvir 400 mg/60 mg orally once daily; or (iii) no pharmacological intervention. Study treatment was taken daily until the end-of-study visit (Week 24). All participants were encouraged to use PPE and/or standard prevention advice in accordance with national guidelines and employment institution provisions and regulations. At the screening phase, laboratory tests were used to exclude participants with underlying renal or liver disorders.

Participants were followed up for a maximum of 24 weeks. They visited the study site every 4 weeks for virological and serological testing for SARS-CoV-2, and for safety assessments. As participants were at high risk of exposure, they engaged in weekly check-in visits with site personnel using telemedicine, telephone or text/direct messaging as far as was possible. Participants were asked to contact the study team if they developed symptoms suggestive of COVID-19 and underwent additional virological testing at the time. Adherence to the intervention products was assessed using pill count and self-report. Compliance level below 80% based on pill count, and self-reported missed doses in the last 4 days prior to a study visit were defined as non-adherent.

Adaptations to the protocol were made to accommodate several factors, including significantly delayed approvals due to COVID-19 lockdown restrictions, the implementation of the expedited vaccine programme among health workers and subsequently extension to the general population after recruitment had commenced. In addition, a major fire and shutdown at the recruiting health care institution resulted in the temporary suspension of recruitment efforts and the need for innovative follow-up strategies for enrolled HCWs who were distributed to work in other hospitals outside of the catchment area. These strategies included the use of mobile research sites to reach those who were posted far from the primary research site, and the extension of research site working hours to include weekends. Accrual was further adversely affected by staffing reductions resulting from SARS-CoV-2 infections (and subsequent isolation) during the third and fourth waves, unpredictable lockdown regulation changes restricting movement of both staff and potential/enrolled participants, and a spate of social unrest in the inner city of Johannesburg.

As it became apparent that inner-city populations were at very high risk for infection, entry criteria were relaxed for inclusion, to include 'front-facing' workers, as detailed in the adapted entry criteria.

Ethics

The trial conformed to international and local guidelines based on the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation, as well as legally mandated South African clinical trial conduct guidelines.[27]

The trial was approved by the local ethics committee [the Human Research Ethics Committee (HREC)] at the University of the Witwatersrand (HREC reference number 200613B), the South African Health Products Regulatory Authority (SAHPRA), relevant provincial health and facility regulatory bodies, as well as initial and subsequent revisions by WHO's *ad hoc* Ethics Review Committee for COVID-19 (WHO ERC reference number CERC.0005).[28] Willingness to participate in the clinical trial, including subsequent 4 weekly and *ad hoc* swabbing, to use

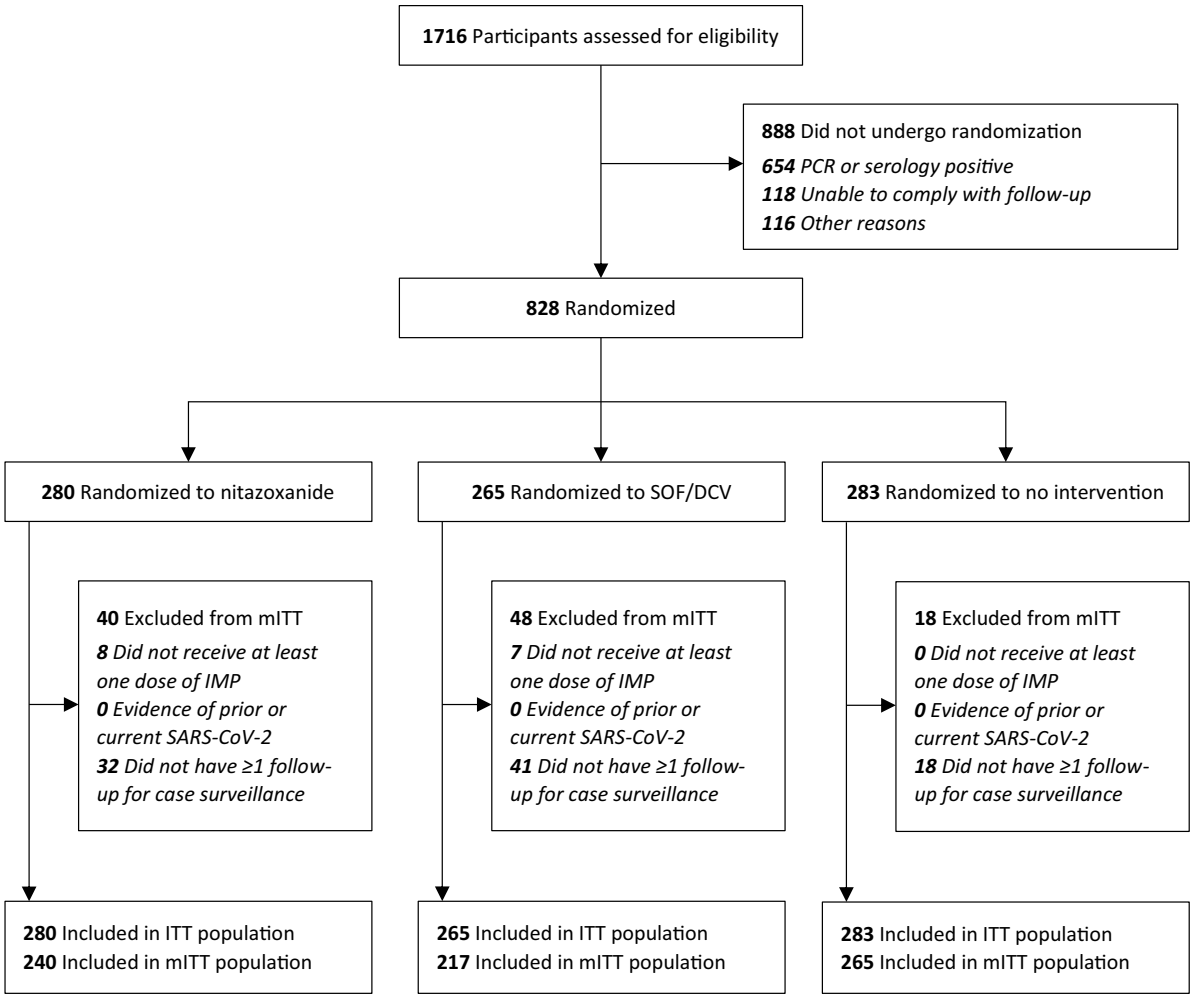

Figure 1. Study flowchart. SOF/DCV, sofosbuvir/daclatasvir; IMP, investigational medicinal product.

study drugs and to comply with all study procedures, was assessed prior to enrolment. Written informed consent was obtained prior to any study procedures.

Oversight

Oversight was maintained through a data and safety monitoring board, with approval and regular reporting to the HREC and SAHPRA.

Authors, sponsors and donors were involved in the original trial design and execution, as well as in conceiving this manuscript preparation and finalization. Written informed consent was obtained from all the participants. Safety oversight was provided by the principal investigator (PI) and an inhouse safety management committee comprising a safety physician, lead clinician, and a regulatory officer. Analysis of data was performed by all authors, with the first author responsible for overall trial management and the last author for manuscript submission oversight. All authors assure the completeness and accuracy of the data and adherence of the trial to the protocol.

Endpoints

The primary endpoint was the efficacy in preventing COVID-19 infection occurring at least 7 days post randomization (infections defined as the first occurrence of virological and/or serologically confirmed SARS-CoV-2, with or without symptoms). The secondary efficacy endpoint was symptomatic virological and/or serologically confirmed COVID-19 cases occurring at least 7 days after randomization.

Other secondary endpoints were related to severity and symptoms associated with COVID-19 cases identified over the study period. These were peak score on the FLU-PRO Plus©[29] (successfully used in other COVID-19 studies) and maximum disease severity using the WHO Ordinal Scale for Clinical Improvement. For each symptomatic infection, the modified FLU-PRO was completed daily by the study participant during the symptomatic phase of illness. Maximum WHO Ordinal Scale was recorded by the study personnel for each confirmed SARS-CoV-2 infection. Adverse events were recorded throughout the study and reviewed at each study visit. A full list of endpoints can be found in the study protocol.

Statistical analysis

Sample size was calculated assuming that 10% of participants in the control arm would develop COVID-19 infection defined as above. A total of 650 participants per arm would have 80% power to detect a reduction in infection rate to 5% in either experimental arm, with a significance level of 5% and allowing for a 10% dropout or baseline positivity. In an

Table 1. Baseline characteristics of participants

Characteristic	Nitazoxanide ($n=280$)	SOF/DCV ($n=265$)	No intervention ($n=283$)
Age (years), median (IQR)	24 (21–36)	24 (20–34)	24 (20–36)
Age >50 years	18 (6)	8 (3)	12 (4)
Female sex	148 (53)	126 (48)	125 (44)
Black	277 (99)	264 (100)	279 (99)
Obese (BMI ≥30 kg/m^2)	62 (22)	54 (20)	57 (20)
Self-reported comorbidities			
Any listed below	48 (17)	29 (11)	34 (12)
Hypertension or increased blood pressure	29 (10)	17 (6)	22 (8)
Chronic lung disease[a]	6 (2)	6 (2)	6 (2)
HIV infection	11 (4)	3 (1)	2 (1)
Diabetes	5 (2)	1 (0)	3 (1)
Other[b]	3 (1)	3 (1)	5 (2)
Occupation			
Nurse, midwife or HCW	17 (6)	19 (7)	18 (6)
Other hospital or clinic-based[c]	86 (31)	75 (28)	89 (31)
University/college student	120 (43)	120 (45)	135 (48)
Other	57 (20)	51 (19)	41 (14)

Data are *n* (%) unless otherwise stated. Percentages may not total 100% because of rounding. Characteristics at screening visit prior to study enrolment. SOF/DCV, sofosbuvir/daclatasvir.

[a]Includes asthma, bronchiectasis, COPD and pulmonary embolism.

[b]Other medical conditions as listed by the CDC as conditions associated with higher risk for severe disease, excluding obesity, previous/current smoker and substance-use disorders.

[c]Includes other individuals who were recruited as working in a hospital setting, including administrative staff, laboratory staff, pharmacists, domestic workers, security or catering staff, and others.

amendment to the analysis plan, interim analyses were planned after 25% and 50% of the original sample size, with futility stopping rules based on conditional power. As planned in the protocol, the primary efficacy analysis was triggered once at least 65 participants in the control arm (or 165 participants in the entire study) had developed confirmed SARS-CoV-2 infection.

Efficacy analysis included all participants who had no immunological or virological evidence of COVID-19 at enrolment, who received at least one dose of the study medication, and who had at least one follow-up visit for case detection [modified ITT (mITT) population]. Confirmed COVID-19 incidence per 1000 person-years was calculated by arm and presented with the corresponding 95% CI. Poisson models were used to estimate the incidence rate ratios of confirmed COVID-19 between each experimental arm and the control group (i.e. two separate models). Models included the natural logarithm of the person-time at-risk (constrained to one) to account for different follow-up times. Participants were censored at the earliest date of COVID-19 vaccination, early treatment or study discontinuation, or the date of their last visit.

Secondary COVID-19 severity endpoints were evaluated through review of maximum WHO Ordinal Scale and/or peak total FLU-PRO score for all COVID-19 infections and symptomatic COVID-19 infections, respectively. These analyses included all cases from randomization through to the end of the study and as such, multiple, discrete occurrences of COVID-19 could be included for a single participant.

Safety analyses included all randomized participants. Participants were evaluated in the treatment groups to which they were assigned. Missing data were not imputed. Data analysis was done using Stata (version 16.1) and an α level of 0.05 was deemed significant. The analysis was triggered at the prerequisite number of infections and the cut-off date for inclusion in the analysis was 22 January 2022.

Results

Between 8 December 2020 and 29 November 2021, 1716 individuals were screened for eligibility and 828 were randomized. Most exclusions were due to evidence of SARS-CoV-2 infection. Those randomized were: 280 to nitazoxanide, 265 to sofosbuvir/daclatasvir and 283 to no pharmaceutical intervention (Figure 1). At the data cut-off, 722 were included in the mITT population for the primary efficacy analysis; exclusions were due to early discontinuations prior to starting treatment or to any further study visits and were higher in the two treatment arms. By arm, the mITT populations were 240 in the nitazoxanide group, 217 in the sofosbuvir/daclatasvir group and 265 in the no-intervention group.

Baseline demographic characteristics were largely balanced between the three groups (Table 1). The median age was 24 years (IQR 20–34) and 5% of participants were older than 50 years of age. Most participants were black (99%), 48% were female, 21% were obese and 13% had at least one other coexisting condition putting them at risk for severe COVID-19. Participant disposition changed over time, reflecting changes in recruitment strategies, but changes were similar across arms.

At the data cut-off (22 January 2022), average person-time at risk in the mITT population was longer in the control arm (median 11 weeks, IQR 5–17) compared with the nitazoxanide (median 8 weeks, IQR 4–14) and sofosbuvir/daclatasvir arms (median 8 weeks, IQR 4–15). For the primary endpoint, a total of 298 individuals had confirmed COVID-19 at least 7 days after randomization and prior to treatment discontinuation or COVID-19 vaccination: 100 in the nitazoxanide arm (2234 per 1000 person-years; 95% CI 1837–2718), 87 in the sofosbuvir/daclatasvir arm (2125 per 1000 person-years; 95% CI 1722–2622) and 111 in the control arm (1849 per 1000 person-years; 95% CI 1535–2227). Compared with the control arm, there was no significant effect of either intervention arm on incidence of confirmed COVID-19 (Table 2). Findings were similar for the secondary endpoint, evaluating confirmed symptomatic COVID-19 cases, with no significant differences in case incidence observed. Overall, 78 symptomatic cases meeting eligibility criteria were identified: 23 in the nitazoxanide group (514 per 1000 person-years; 95% CI 342–773), 18 in the sofosbuvir/daclatasvir group (440 per 1000 person-years; 95% CI 277–698) and 37 in the no-intervention group (616 per 1000 person-years; 95% CI 447–851).

Two individuals had a maximum WHO Ordinal Scale greater than two (indicating hospitalization); both were in the no-intervention arm. One required hospitalization with no oxygen therapy (WHO score 3) and one had COVID-19 infection resulting in death (WHO score 8). FLU-PRO results were available for 48 (62%) symptomatic infections. Total FLU-PRO score for symptomatic infections did not vary significantly between treatment arms.

Table 2. Primary efficacy results in the mITT population

	Nitazoxanide ($n=240$)	SOF/DCV ($n=217$)	No intervention ($n=265$)
Confirmed COVID-19 at least 7 days after randomization			
No. of cases	100	87	111
Total person-years (median person-weeks at risk)[a]	44.8 (8)	40.9 (8)	60.0 (11)
Incidence rate per 1000 person-years (95% CI)	2234 (1837–2718)	2125 (1722–2622)	1849 (1535–2227)
Incidence rate ratio (95% CI)[b]	1.21 (0.29–1.58)	1.15 (0.87–1.52)	Ref
Confirmed symptomatic COVID-19 at least 7 days after randomization			
No. of cases	23	18	37
Total person-years (median person-weeks at risk)[a]	44.8 (8)	40.9 (8)	60.0 (11)
Incidence rate per 1000 person-years (95% CI)	514 (342–773)	440 (277–698)	616 (447–851)
Incidence rate ratio (95% CI)[b]	0.83 (0.50–1.40)	0.71 (0.41–1.25)	Ref

Analyses were conducted in the mITT population, including all randomly assigned participants with no serological or virological evidence of SARS-CoV-2 at baseline, who received at least one dose of study medication, and had at least one follow-up for case surveillance.
[a]The time period for case accrual is from randomization to the end of the surveillance time. Participants are censored at the earliest of COVID-19 vaccination, early discontinuation of investigational medicinal products (IMP) or the study, death, or the latest study assessment visit. In the analysis of symptomatic infections, individuals with non-symptomatic COVID-19 were censored at the time of infection.
[b]The incidence rate ratios were estimated using Poisson models comparing the treatment group with the no-intervention group, with the natural logarithm of the at-risk time as an offset.

Table 3. Safety summary

	Nitazoxanide ($n=280$)	SOF/DCV ($n=265$)	No intervention ($n=283$)
Subjects with AEs, *n* (%)			
Any AEs	213 (76)	166 (63)	202 (71)
Grade 3 or higher AEs	1 (0)	2 (1)	5 (2)
Grade 3 or higher AEs excluding COVID-19 events	1 (0)	2 (1)	4 (1)
SAEs	1 (0)	1 (0)	3 (1)
SAEs excluding COVID-19 events	1 (0)	1 (0)	1 (0)
Deaths	0	0	1 (0)
WHO Ordinal Scale ≥3, *n*	0	0	2
Modified FLU-PRO			
Symptomatic cases with FLU-PRO results, *n*	17	11	20
Total score, median (IQR)	0.26 (0.09–0.59)	0.12 (0.06–0.21)	0.21 (0.10–0.35)

AE, adverse event. Includes all participants enrolled in the study. Number of subjects with AEs are number of participants reporting at least one occurrence of the specified event category.

Adverse events are shown in Table 3. Overall, five serious adverse events were observed, including one each in the nitazoxanide and sofosbuvir/daclatasvir arms and three in the no-intervention arm. One serious adverse event in the sofosbuvir/daclatasvir arm was deemed at least possibly related to study treatment (the participant experienced a miscarriage). One death occurred in the study; the death was in the no-intervention arm and was due to severe COVID-19 infection leading to hospitalization and subsequent death. The frequency of grade 3 or higher adverse events was low and similar across arms.

Discussion

In this randomized trial of 828 HCWs and others at high risk of SARS-CoV-2 infection, there was no significant protective effect detected for either nitazoxanide or sofosbuvir/daclatasvir. Confirmed infections were detected for 100/280 for nitazoxanide (35.7%), 87/265 for sofosbuvir/daclatasvir (32.8%) and 111/283 for the control arm (39.2%). There was no significant difference in the primary endpoint between the treatment arms. The frequency of grade 3 or higher adverse events was low and generally similar across arms.

Earlier small studies suggested a treatment benefit of sofosbuvir/daclatasvir in a meta-analysis.[30] One of the included trials, however, was non-randomized.[24] Other emerging evidence from a case–control study suggested that early treatment of mild to moderate COVID-19 with sofosbuvir/velpatasvir, also used for the treatment of hepatitis C, may promote faster viral elimination and prevent disease progression.[31] The randomized, placebo-controlled DISCOVER trial, however, showed no benefits of

sofosbuvir/daclatasvir in patients hospitalized for COVID-19.[32] Nitazoxanide has shown a range of results when used for treatment and prevention in other trials. A randomized, double-blind pilot trial in Brazil showed nitazoxanide to be superior to placebo in treating moderate COVID-19 in mean time to hospital discharge (6.6 versus 14 days, $P=0.021$) and negative PCR at Day 21 ($P=0.035$).[33] A prospective study from 2020 showed a decrease in hospitalizations in healthcare personnel presenting with COVID-19 symptoms when treated with nitazoxanide.[34] The NACOVID trial conducted in Nigeria showed no evidence of efficacy of nitazoxanide at 1000 mg twice daily combined with atazanavir/ritonavir, but the trial was terminated early due to lack of enrolment and resultant low participant numbers.[35] An evaluation of the nitazoxanide concentrations as part of the NACOVID trial also demonstrated extremely low drug penetration into saliva, suggesting that the penetration into other tissues required for sterilizing prophylaxis may therefore also be low. Recently, acceptable safety was confirmed in the AGILE Phase I/IIa platform trial at a higher (1500 mg twice daily) dose in healthy volunteers, with Phase 1b evaluations assessing its role in treatment of COVID-19 currently ongoing in South Africa.[36] Neither nitazoxanide nor sofosbuvir/daclatasvir demonstrated any clinical benefit in the prevention of SARS-CoV-2 infection in the COVER trial.

The COVER trial was relatively small compared with standard randomized trials of vaccines, which represent the bulk of preventative COVID-19 trials. In contrast to typical vaccine trials, which evaluate the risk of infection in the general population, COVER evaluated those at high risk of infection. This strategy was reflected in the rate of SARS-CoV-2 infection, which was markedly higher than that reported in vaccine trials. A significant proportion of these occurred in the fourth wave, driven by the highly transmissible Omicron variant, and increasing pandemic fatigue.[37] Since the statistical power of COVER was prospectively based on the number of infections, the final sample size was smaller than originally planned.

The primary endpoint definition, a combination of positive results by either PCR or antibody testing irrespective of symptoms, also contributed to the high rate of detected infection. In standard vaccine trials, an endpoint of symptomatic infection is typically used. For HCWs enrolled in COVER, it was considered important to prevent any infection, whether symptomatic or asymptomatic, and hence lower the risks of onward transmission, important in the healthcare environment. Nonetheless, it should be acknowledged that it is not possible to determine with certainty whether either intervention would have had an impact on symptomatic infection.

Only 32% (95% CI 27%–36%) of participants in the COVER trial were vaccinated during the study, despite being actively offered vaccination and regularly encouraged by study staff to become vaccinated.[38,39] Even among frontline HCWs who were prioritized in Phase 1 of the country's vaccine rollout, the uptake rate was relatively low at 32%. Vaccination rates in South Africa are significantly behind the global average, with just 27.9% of the population being full vaccinated.[40,41] Development of an effective drug against SARS-CoV-2 transmission and infection therefore continues to be important in the local setting and in global at-risk groups, and may enhance transmission blocking of available vaccines, especially as we face new variants of SARS-CoV-2.[42]

Other drug candidates are still being evaluated for transmission prevention. For example, the antiviral drug molnupiravir is being evaluated in the Phase 3 randomized placebo-controlled MOVe-AHEAD trial for prevention of COVID-19.[43] This study is testing the preventative efficacy of molnupiravir in participants residing with an individual infected with COVID-19. Other antivirals are also being studied for post-exposure prophylaxis (PEP). In September, Pfizer initiated the Phase 2/3 EPIC-PEP study to evaluate the efficacy and safety of nirmatrelvir/ritonavir in adults exposed to SARS-CoV-2 through a household member. Monoclonal antibodies have also been evaluated, but these present challenges in terms of scaling up use and access.

The search for preventative drugs effective against SARS-CoV-2 should remain a priority.

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Transparency declarations

There are no conflicts of interest to declare.

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