



ACT-ACCELERATOR CSO REPRESENTATIVES

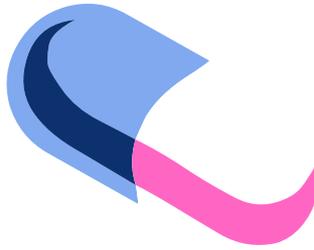
WHITEPAPER

COMMUNITY-BASED TEST-AND-TREAT

This white paper grew out of the policy conversations and policy priorities identified by the communities and civil society representatives to the Diagnostic and Therapeutic pillars of the ACT-Accelerator. As such, this document captures challenges and demands that have been consistently highlighted by representatives during their engagement in various ACT-A fora. For more information on the work of Community and Civil Society Representatives of the ACT-Accelerator, please visit www.covid19advocacy.org

LEAD

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Introduction

Since the beginning of the COVID-19 pandemic, civil society activists have been focused on the possibility of an outpatient therapy that would help address devastating waves of infection, disease progression, hospitalization, and death. The first outpatient treatment, Gilead's remdesivir, was borderline efficacious, expensive, and difficult to administer, requiring multiple infusions.¹ Soon thereafter, promising monoclonal antibody treatments were discovered, but they too, though more efficacious, were not only expensive and infusion-based but in relatively short supply, guarded by multiple intellectual property barriers, and required much more complex and scarce biologic manufacturing capacity. Finally in late 2021, promising outpatient antiviral therapies have been developed, including Merck's molnupiravir and Pfizer's Paxlovid (co-packaged nirmatrelvir with a ritonavir booster). These are both small molecule medicines that can be more easily produced and scaled up by a wide base of generic manufacturers. Moreover, they will be cheap to produce, easily stored, and administered in pill or tablet form; but they must be taken early in infection, typically within 5 days of symptom onset. In addition, there are counter-indications (pregnancy risk for molnupiravir and ritonavir drug interactions for Paxlovid) and use restrictions (at present prioritizing on older patients and patients with underlying risks, including obesity, diabetes, heart disease, and immuno-suppression). In addition to these antivirals, fluvoxamine, a selective serotonin reuptake inhibitor, is available affordably from multiple generic producers and has been found to be effective as an immune modulator that reduces the risk hospitalization. WHO treatment guidance on all three medicines is expected in February 2022.

These and other antiviral therapies when combined with early testing promise significant benefits to patients and the community at large. Early viral suppression will reduce the risk of disease progression, lower viral load, and shorten the period of active infection. These therapeutic benefits will, in turn, potentially reduce infectivity, especially when matched by post-testing isolation and contact tracing.²

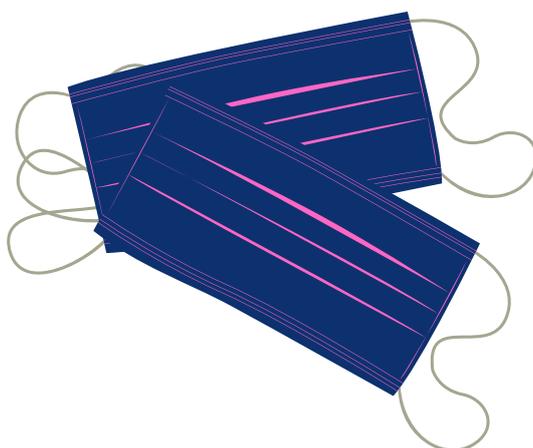
¹ A more recent study has shown outpatient efficacy in reducing risk of hospitalization and an oral formulation is under development.

² As testing increases there will be increased touchpoints with patients more opportunities for 1) contact tracing; 2) source investigation, outbreak identification, and identification of unvaccinated pockets; 3) counseling and education; and 4) more sequencing and variant surveillance.

They might also reduce the risk of mutations and possibly, like vaccines, positively affect the incidence and/or severity of long covid. Test-and-treat has potential to improve community trust in health systems. There are social benefits accompanying clinical benefits. Patients will be able to return to economic, family, and social activity more quickly, and demands on health services, especially in-patient hospitalizations and ICUs, will be reduced. Given the positive impacts of post-test isolation and early treatment on disease transmission, prevention efforts will also be strengthened and overall social and economic disruptions reduced. Although therapeutics will not be a substitute for vaccination, they will be an important complement for those who are unvaccinated or who experience break-through infections, especially given the legacies of vaccine apartheid.

At the same time that activists have been awaiting viable out-patient therapies, they have been eager for increased access to COVID-19 testing, especially in underserved LMICs. Although there has been a global preference for gold-standard molecular or polymerase-chain-reaction tests, constricted capacity for lab-based testing and long turn-around times for PCR test results in many LMICs have resulted in a renewed focus on antigen rapid diagnostic tests (Ag RDTs) that can be administered at the community level or even at home and give reasonably accurate results in 15 minutes. However, supply and uptake of Ag RDTs in LMICs has been low and slow, partially as a result of delay and a lack of clarity in WHO Ag RDT use-case guidance. It is activists' firm conviction that demand for community-based- and self-testing will significantly increase with the arrival of effective outpatient therapies.

The combination of these two tools – rapid diagnostic tests and effective outpatient therapies – give rise to the imperative of a robust test-and-treat strategy delivered at the community-level. Although activists inside and outside the ACT-Accelerator have been beating this drum for a year or more, the ACT-Accelerator, including its lead agencies, especially Unitaid and FIND, are finally beginning to work more proactively. Nonetheless, the WHO seems recalcitrant and key activities and analytical work are being delayed. The remainder of this White Paper will outline civil society's vision for a community-based, test-and-treat strategy and the advocacy steps needed to accelerate its effective rollout and scaleup.





TESTING

Expanding and quantifying community-based and self-testing

There is no doubt that testing will need to be scaled-up to implement an effective test-and-treat strategy, but there are still multiple questions and barriers that must be addressed. The first issue concerns use cases for Ag RDTs, which will in turn affect quantity demands beyond the projected global target on 1 test per 1000 people per day, which would roughly mean on one in three people being tested in LMICs in any given year. This meager goal, far less than testing rates in high-income and upper-middle-income countries with much higher rates of vaccination, was set without calculating supply needs for test-and-treat testing.

There are several conceivable use cases for broader Ag RDT deployment. Some proponents, if money were no obstacle, would recommend regular population testing on a weekly basis, regardless of symptoms. Such frequent testing is regularly deployed in schools, universities, and workplaces in the rich countries and is often subsidized with government funding. Broad-based and regular testing has the advantage of detecting infections even in people who are asymptomatic but who are otherwise still infectious. This early detection allows quarantine/isolation to protect family and others, but is resource intensive given costs of tests and difficulties of supply and distribution.

Other proponents urge a focus on regular testing for higher risk populations only (older people and people with underlying risk factors) and higher risk places (public facing worksite, congregate housing, transportation facilities, etc.). Yet another strategy is emphasizing early testing of people with covid symptoms. Of course, covid symptoms overlap with cold, influenza, TB, and other respiratory, gastrointestinal, and fever conditions. Although differential testing would be ideal, even covid testing alone could identify people early enough in infection to make a difference.

There is no doubt that testing could/should take place at the community or facility level and that it can be implemented not only at primary care health facilities, but more broadly through community testing supported by trained community health workers, trained peers, school nurses, and others. Such deployment would depend on availability of tests, minimal wait times, and ease of access to wide population groups, a requirement that is more difficult in hard-to-reach and rural populations. Supervised testing, if all cadres are well trained, could result in more accurate test results and capture of results to inform local and national surveillance.

However, facility-based, supervised testing can and should be supplemented with self-testing. With well-designed instructions, first-use training, and easy-to-use tests, the general population could easily be able to self-test. The viability of self-testing has already been established in other contexts, pregnancy, HIV, malaria, HCV, and even flu. The idea that people will not know how to self-test, or that they will not respond appropriately to positive test results is exaggerated and frankly insulting. In addition to wanting to take steps to protect families and others, we can expect that self-testers can also be sensitized to the need to report results, especially positive results, and to the critical importance of connecting to care.

These different use cases can reasonably be expected to result in different quantification needs. The ACT-Accelerator Diagnostics Pillar and others will need to move quickly to identify the quantities needed under different scenarios so that advance planning can occur.

Expanding supply base, lowering prices, and reducing/eliminating out-of-pocket costs

The global supply of Ag RDTs is too low, especially for significantly expanded testing in LMICs. Moreover, the cost of testing is too high both in terms of price per test and the costs of testing borne by users. The current price for Ag RDTs secured by the ACT-Accelerator is roughly \$2.50@. However, Ag RDTs in high quantities are available much more cheaply in certain high-income countries including the UK and Germany where the cost of tests is reported to be as low as \$1@. Every effort should be made to lower the prices of tests through bulk procurement and sustainable competition in the market with a goal of achieving \$1 a test or less.

Efforts to expand and diversify the supply base need to be undertaken as quickly as possible. Realistically, 100s of millions of tests will be needed on a monthly basis. Most manufacture of diagnostics is concentrated in a few countries, but that too needs to change. Although recent ACT-Accelerator agreements with suppliers provide for licensing, much more is needed to disperse and expand manufacturing in LMIC regions. Not only will there need to be resource support, tech transfer, and technical support to expand manufacturing capacity, but there will also need to be increased support for quicker regulatory approval, strengthened supply chains, and improved distribution channels.

To ensure equity and broader uptake, tests, including self-tests, must be widely available in multiple venues. Although some system of controlled distribution might be required and tests certainly should be made available in retail settings, equity requires non-retail distribution so that out-of-pocket costs for end users can be avoided. Poor people simply will not be able to afford even \$1 tests for themselves and their families. Although subsidizing tests will add costs to governments, the payoff in reduced health systems costs and decreased economic and social disruption will more than pay for itself.

WHO must speed up its test guidance and regulatory processes

The WHO has still not issued concise and clear guidance on community-based testing and has signaled a very protracted process of evidence gathering before it will consider self-test guidance. In this regard, the WHO is significantly behind the curve because countries are already planning on using new testing strategies in light of anticipated availability of out-patient therapies. Studies by FIND and others signal wide acceptance of self-testing by community members and health workers even before easily deployed outpatient therapies were identified. WHO should already be highlighting the need for expanded use cases, including self-testing, with communities and countries even in advance of its formal guidance procedures, and those too must be accelerated. WHO plays a key normative role for many countries that are often reluctant to follow break-through strategies absent a WHO stamp of approval.

In addition to speeding up testing use-case guidance, WHO must expedite emergency use listing of Ag RDTs and facilitate rapid regulatory approval at the national level. As of this writing, the WHO has only issued EULs for three Ag RDT manufacturers that have grossly insufficient capacity to meet expanded LMIC demand. Although many of the PQ applicants lack prior regulatory experience and thus have difficulty in putting together the dossiers that WHO requires, the WHO and others need to be more proactive in capacitating those applicants to better comply with regulatory requirements and WHO must speed up its own internal deliberative processes. Thereafter, countries will need support, including reliance on WHO Collaborative Registration procedures, to accelerate national regulatory approval.





CONNECTION TO CARE

Testing needs to be tightly connected to care. Not only should test results be reported, but people who test positive should be immediately connected to care where their individual clinical need can be further assessed and where they can initiate out-patient treatment as soon as possible within the short, 5-day treatment window post-first-symptoms. If testing is conducted in a facility, connection to care should be relatively seamless with patients immediately being assessed for treatment and given a prescription or medicines directly.

Non-health-facility testing will present a slightly more complicated scenario. One similar option would be to have trained community health workers and other community testers assist the covid-positive patient to connect with care. In some settings, we might even imagine community health workers being able to directly provide therapies to patients under strict screening, reporting, and treatment protocols, as has been done with malaria. Obviously, it will be more complicated to connect people who self-test to care. For this purpose, clear instructions accompanying the test kit and hot-lines and websites can be used to facilitate connection to care. One complication will be the advice that people isolate upon a positive test and thus safe transportation to treatment providers and prescribers may be much more complicated. Thus, effective connection to care might require health systems to dispense medicines to family members or other supporters, including CHWs. Some countries are already discussing having online prescribing systems and rapid treatment delivery systems, both of which are great ideas, but that much more complicated in resource poor and peri-urban/rural settings.





TREATMENT

Expanding, quantifying, and prioritizing treatments

Just as with diagnostics, it will be necessary to expand the supply base of antiviral therapies and to quantify needed quantities (note: this will not be as significant an issue for generic fluvoxamine). However, given the pipeline of medicines, it may also be necessary to prioritize antiviral access based on time to market, efficacy and safety, cost, and the need for combination therapies to prevent the development of viral resistance and to help address hyper immune system activation.

Both Merck and Pfizer have taken some steps to expand their own internal manufacturing capacity and to license generic licensees to supply designated markets. Merck was an early mover in this regard and selected 8 Indian generic manufacturers who were licensed to supply 105 countries via a tightly controlled bilateral agreement. Merck has since entered into a more transparent license with the Medicines Patent Pool, but it is still geographically limited to 105 countries, leaving 30+ LMICs outside the license and with a total 46% of the global population within its exclusive control. Subsequently, in November, Pfizer too entered into a voluntary license with the MPP with a geographical scope of 95 countries, keeping 47% of the global population for itself. Both companies have recently expanded their projected manufacturing capacity for 2022, but it is still not clear that they will be able to supply their exclusive territories. Of course, they certainly can enter into contract manufacturing agreements, including with their MPP licensees, but supply might still be less than demand, depending on how broad patient-use authorization turns out to be. Not only is supply likely to be constricted, but once again rich countries are running to the front of the line to secure preferential access to the new antivirals. The US has already secured access to 3.1 million courses of molnupiravir and 10 million courses of Paxlovid and many other HICs and UMICs are not far behind.

Equally troubling, however, will be both Merck and Pfizer's commitment to tiered pricing in their reserved territories, where they will be free to set their price according to their commercial interests. One troubling signal in that regard is that Merck has already charged Thailand \$300 for a course of treat of molnupiravir, approximately 40% of what it had first charged the U.S.

Regardless of geographical restrictions in voluntary licenses and limitations in supply capacity quantification of treatment needs is complicated by two other factors. The first is that the number of recent infections, confirmed by PCR tests, is likely to be only a fraction of actual infections, especially in Africa and other regions where testing rates are low. Relying on excess mortality to estimate infections results in infection estimates as much as 10 times higher than official numbers in some countries. Without doubt, more testing will result in more diagnoses, but exactly how many more needs further quantification. The second factor complicating quantity need calculations is which patients will be eligible for treatment. Final clinical trial results reported thus far involve treatment of patients with underlying high-risk factors such as age, obesity, diabetes, heart disease, and immune suppression. If treatment were limited to this high-risk population, the number of treatments needed would be significantly reduced. However, trials are ongoing on Pfizer's Paxlovid in patients with normal health risks and people who have been previously vaccinated, and interim readouts show a 70% reduction in hospitalization and no deaths in these populations. If treatment is ultimately authorized for broader patient groups by stringent regulatory authorities and/or the WHO Prequalification Programme, we could see a quantitative leap in demand. Even without formal authorization, as the ACT-Accelerator has estimated, we can expect some significant degree of off-label use as all covid-infected patients come to expect or demand access to effective therapies.

The presence of promising pipeline therapies with different safety and efficacy profiles and different time-to-market complicates treatment planning and treatment rollout. The first available antiviral is molnupiravir, whose reported efficacy paradoxically dropped between interim and final analysis from 50% to 30% in terms of reducing risk of hospitalization and death. Moreover, its safety profile is complicated because of mutagenic risks, which means that people who are pregnant, people who can become pregnant and are not practicing birth control, and possibly even men who might impregnate others, might be excluded or cautioned. On the plus side, however, molnupiravir might come to market relatively quickly, especially given \$120 million in support from the Gates Foundation for regulatory and manufacturing assistance and early advancement market commitments. Although likely to be delayed compared to Merck's molnupiravir, Pfizer's Paxlovid has significantly increased efficacy for high-risk patients – as high as 89% if treatment is initiated within 3 days of first symptoms and 88% if initiated within 5 days. As discussed previously, there are also interim results finding 70% efficacy in reducing hospitalization and no deaths in normal risk and vaccinated patients. Unfortunately, this product too comes with some safety-related contraindications arising from its complementary use of ritonavir. How to plan for and prioritize shorter term and longer-term access to these two antiviral candidates (let alone others in the pipeline) is obviously a significant issue that must be addressed.

Two final issues that must be addressed are the need to prevent/reduce viral resistance and also how to combine antivirals with other out-patient therapies, including immune modulators. Molnupiravir and Paxlovid have not been tested together for dual use, and originators are generally unwilling to test regimens as part of their product development and clinical trial plans. In any event, the risk of resistance intensifies the need for patients to understand the importance of completing their entire course of treatment.

Ensuring access in countries outside of existing voluntary licenses

As suggested in the section above, special attention will be needed to meet the needs of MICs excluded from Merck's and Pfizer's voluntary licenses. In addition to advocating for expanded geographic coverage and/or non-enforcement of relevant intellectual property protections, including patents and data exclusivity rights, support should be provided to companies willing to produce at risk outside the licenses and countries where generic access is blocked by granted or pending patent applications and regulatory exclusivities. Activists are already promoting the idea of a Defiance Campaign to support independent producers and excluded countries, but the ACT-Accelerator and particularly Unitaid could help facilitate access by supporting coordinated compulsory licensing strategies, patent oppositions (most likely to be success for molnupiravir because of its weak patents), and implementation of a TRIPS waiver if passed or a domestic IP national security waiver under TRIPS Art. 73. In any event, it would be unconscionable for the global response to allow intellectual property rights to stand in the way of expanded access to outpatient therapies for populations in countries excluded from voluntary licenses.

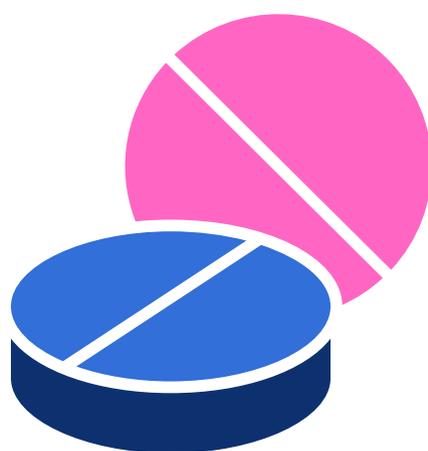
Expanding supply, lowering prices, and eliminating out-of-pocket expenses

As with diagnostics, there is a compelling need to expand the supply of promising outpatient medicines. During the initial treatment phase when the originator medicines first enter the market and generics may lag a bit behind because of product development and regulatory delays, it will be important to secure doses for LMICs on a proportionate basis and to preempt vaccine nationalism and rich country hoarding. Interventions might take the form of advance market commitments such as those promised by the Gates Foundation and previously deployed by the ACT-Accelerator. There are already plans by UNICEF and the Global Fund to procure supplies of molnupiravir, though the details of those transactions are not yet known.

Antiviral rightholders, Merck and Pfizer, are already announcing plans to scale up their internal manufacturing capacity and there are also signs that they will enter into contract manufacturing agreements as well. Merck has recently tapped Thermo Fisher in Canada as a contract manufacturer and it has reserved rights to enter into contract manufacturing agreements with its MPP licensees as well. Even so, given the scale of anticipated future infections, especially with the more transmissible omicron variant, there is reasonable concern that Merck and Pfizer might not be able to meet antiviral demand in the huge population centers it has reserved for its own exclusive and higher priced supply.

Historically, allowing for robust generic competition has been the preferred pathway to simultaneously increase supply capacity and to lower prices. The correlations between increased generic supplies and lower prices for HIV antiretrovirals has been pronounced over time. Thus, a key component of a successful campaign to increase supply and lower price for COVID-19 antivirals and other outpatient meds would similarly be to promote generic entry and competition between companies that can market in all LMICs. Although the cost-of-manufacture for the new antivirals is still being quantified, there is every reason to believe that optimized manufacturing and supply chains and achieving economies-of-scale could result in production costs below \$10 per course of treatment for both molnupiravir and Paxlovid. Ensuring low-cost generic production and competition will require aggregating markets, which has partially been achieved via the MPP licenses, but there also needs to be a further aggregation of excluded MIC markets. Coordinated compulsory licenses in both exporting and importing countries as discussed in the preceding subsection could play a key role in this regard. These licenses should also override any data exclusivity claims so that regulatory approval can be promptly initiated.

It will be important that patients do not have to pay co-pays or other out-of-pocket expenses for outpatient medicines. Ability to pay should not affect an individual's access to antivirals and other outpatient medicines nor the community scale-up needed to reduce disease burden and its impacts on fragile health systems and economic and social life.



Speeding up regulatory processes for generic medicines

Fortunately, abbreviated regulatory pathways are well established for small molecule medicines, but that doesn't mean that even greater alacrity is not needed to expedite access to originator and generic therapies. Emergency use authorizations by stringent regulatory authorities should be prioritized as should complementary emergency use listing by WHO Prequalification. The Gates Foundation has already promised to use part of its \$120 million funding to capacitate MPP-licensed generic applicants and to expedite submissions of fulsome dossiers sufficient for accelerated regulatory review. The same kinds of investments will be needed to support regulatory approval for generic producers of Paxlovid and also for generic companies operating outside of the licensed MPP territories. Countries should be encouraged to rely upon or reference SRA EUAs and marketing approvals or WHO EULs or prequalification decisions. In addition, all originators and generic entrants should be encouraged to use WHO Collaborative Registration procedures to expedite emergency use authorizations and marketing approvals at the national level, and additional countries should be urged to join the Collaborative Registration mechanism.

TEST-AND-TREAT HEALTH LITERACY AND HEALTH WORKER TRAINING

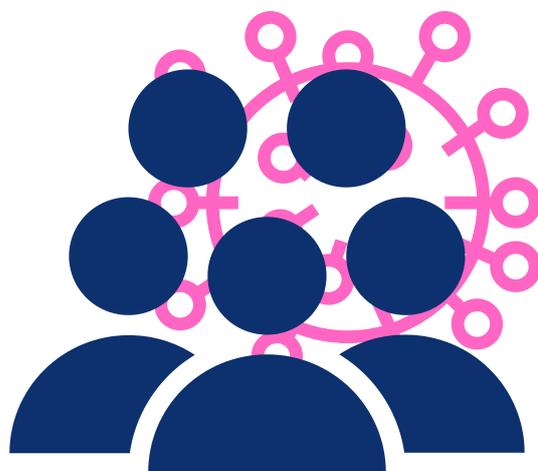
Test-and-treat strategies simply cannot succeed if people and communities are not provided with culturally competent test-and-treat health literacy that emphasizes:

- (1) the importance of regular testing and especially early testing at first covid symptoms;
- (2) the importance of reporting test results, but most especially positive results, and isolating and cooperating with contact tracing efforts;
- (3) the imperative of connecting to care as quickly as possible to be assessed for clinical appropriateness of antiviral and other therapies, including counseling on possible side effects and safeguards, e.g., contraception to prevent pregnancy if accessing molnupiravir; and
- (4) the necessity of immediate access to medicines and patients taking medicines as directed and completing their course of treatment to reduce the risk of resistance.

We know that test-and-treat preparedness and health literacy works. The remarkable success of antiretroviral therapy rollout rests in no small part on the dedicated work done at community level by community health workers, peer educators, and treatment activists who ended up helping to empower community members to be the central players in their own health and well-being. The Treatment Action Campaign in South Africa is the best-known practitioner of this grassroots work, but there are many other community groups eager and willing to work with their neighbors to share the information and skills needed to operationalize successful test-and-treat programs. Resourcing this work and preparing materials to support it will be absolutely essential to the scale-up and success of test-and-treat.

Other forms of test-and-treat health communication can also help test-and-treat rollout. Government officials, health workers, religious and community leaders should all be capacitated and motivated to deliver test-and-treat messaging. Radio and TV programming, community billboards, health pamphlets, and text and whatsapp messages will help show people how to test, connect to care, and comply with treatment. As much as possible materials and messages should be made available in local as well as official languages.

In addition to focusing on health literacy, proponents of test-and-treat will also have to convince governments to strengthen diagnostics and medicines procurement and supply chains and also train the health workforce, including community health workers and peer educators, to deliver the early testing, quick connection to care, and immediate initiation of therapy needed for test-and-treat programming. Health workers will need to be sensitized to this importance of speedy and compassionate test-and-treat service delivery that makes patients partners in test-and-treat uptake.



COMMUNITY BASED SERVICE DELIVERY

To be effectively implemented, covid-outpatient test-and-treat must be delivery at the primary health and community level. Many places will be able to leverage existing community screening and linkage-to-care activities by integrating covid programming and using existing referral pathways and messaging techniques. Nonetheless, connecting people who test positive to treatment will be the trickiest part of health and community service delivery, as the optimal programming will require quick delivery of medicines, immediately at the time of treatment or through direct delivery of medicines to patients by their designated proxies, peripheral health workers, or in some contexts courier service. Inferior service delivery with delayed appointments, long waiting lines, and wide gaps between testing, connection-to-care, and treatment will doom test-and-treat to failure. In contrast, efficient and interconnected test-and-treat services at the primary health care and community level will guarantee success. Text messaging may be particularly useful in connecting people to community-based health services, though the digital divide means that person-to-person communication strategies will also be needed.



CONCLUSION

Successful adoption and implementation of outpatient test-and-treat for covid is not a given. It will require advocacy, resources, and ambition. The first step is for ACT-Accelerator, the WHO, and civil society activists to immediately connect with countries and communities to begin sensitizing them to the promise of test-and-treat and to get input from both to strengthen planning and buy-in. Simultaneously, it will be necessary to address upstream structural barriers to test-and-treat including intellectual property and regulatory barriers to expand supplies, lower prices, and ensure equitable distribution. The time to start test-and-treatment consultations and country planning was yesterday, but today will have to do.