

The impact of the COVID-19 response on the supply chain, availability and cost of generic antiretroviral medicines for HIV in low- and middle-income countries



Scope

The objective of this report is to assess the situational landscape during mid-May 2020 surrounding the value chain of the production and distribution of generic antiretroviral medicines in low- and middle-income countries and to provide recommendations on mitigating the risks of potential disruptions.

The assessment of the situational landscape is based on two sources:

1. Intelligence collected from eight generic manufacturers of antiretroviral medicines in India that together account for more than 80% of generic antiretroviral medicine production worldwide.
2. A survey sent to seven additional countries that produce generic antiretroviral medicines domestically.

Together, those countries account for most of the production of generic antiretroviral medicines in low- and middle-income countries. They also are large buyers of generic antiretroviral medicines. Government departments were contacted through UNAIDS offices in Brazil, Indonesia, Kenya, South Africa and Thailand to respond to UNAIDS' May 2020 survey; responses are awaited from Egypt and Uganda.

Challenges to the availability, affordability and accessibility of generic antiretroviral medicines

COVID-19 is spreading across countries and regions at a rapid pace (1). Lockdowns, border closures and restrictions on the movement of people and goods have caused a huge impact on the value chain of production and consumption across different economic sectors.

KEY POINTS

- Lockdowns have impacted both the transport of goods across the value chain of production and the distribution of HIV medicines.
- Barriers to the supply chain and a forecasted economic shock indicate a possible fluctuation in the availability of antiretroviral medicines and an increase in cost.
- Manufacturers are facing logistics issues that may indicate a potential disruption in the next few months.
- Countries should identify the risk level for the stock of all antiretroviral medicines.
- Coordinated action by governments is necessary to ease the supply chain and the distribution of medicines to facilities.
- Buyers (both donors and domestic governments) should enhance transparent and timely communication between countries and suppliers.

By the end of 2018, 24.5 million people were on antiretroviral treatment. Domestic funding—and official development assistance from bilateral and multilateral agencies—have contributed to increased treatment coverage of people living with HIV, thereby significantly reducing AIDS-related mortality. Antiretroviral medicines have been instrumental in saving millions of lives from AIDS-related illnesses.

Disruptions to the regular taking of HIV medicines places millions of lives at risk and risks a surge in new HIV infections and deaths. A modelling group convened by the World Health Organization and UNAIDS estimated that if efforts are not made to mitigate and overcome interruptions in health services and supplies during the COVID-19 pandemic, a six-month disruption of antiretroviral therapy could lead to more than 500 000 additional AIDS-related deaths, including from tuberculosis, in sub-Saharan Africa in 2020–2021 (2, 3).

Several partners are actively working to mitigate this impact. The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) is providing immediate funding of up to US\$ 1 billion to help countries respond to COVID-19 and is expanding the use of its procurement platform (WAMBO) to non-Global Fund recipients in order to mitigate the impacts on life-saving HIV, tuberculosis and malaria programmes. The United States President's Emergency Plan for AIDS Relief is responding to promote continuity of HIV care, such as the implementation of multimonth dispensing of antiretroviral medicines, implementing new strategies, such as telemedicine, and allowing some programme flexibility in reporting requirements, staffing and funding re-allocation (4). The World Health Organization is compiling, exchanging and analysing information on HIV services that have been impacted and is liaising with manufacturers of antiretroviral medicines for emergency supply and with countries to switch to available quality alternative products and on possible mitigation measures (5). UNAIDS has been coordinating efforts to address the procurement and supply management challenges of antiretroviral therapy caused by the COVID-19 response.

What is the current situation from a production perspective?

Logistics support for imports and exports

Sea shipments have slowed down in many countries because of the following:

- Slow movement of goods in ports due to the lack of customs personnel.
- Shortage of workers for loading/unloading ships.
- Lack of road transport, which makes getting goods to the port a challenge.

Air freight processes have also become more complex:

- In three out of five countries, air freight is undergoing lengthy bureaucratic customs certification processes and delays.
- Only a few air cargo companies are operating in some of the key countries producing HIV medicines. This has resulted in a threefold increase in the cost of air cargo.
- Cargo movement through passenger planes contributes to a large proportion of overall air freight capacity. The cancellation of passenger flights has placed added pressure on available cargo space.

In-country logistics

The lockdowns have closed provincial and state borders in some countries. The result has been increased transport times for the raw materials and other essentials needed to run a pharmaceutical plant and for the finished products on their way to ports. Reduced availability of transport vehicles and labour has also resulted in increased costs for domestic transport.

Some countries are seeking special measures to mitigate logistics issues in order to ease the domestic transport of medicines.

Production sites

- Some of the key starting materials, which are precursors to active pharmaceutical ingredients, were in short supply due to extended factory closures in China during the first quarter of 2020.

While those factories resumed operations in April and May 2020, the effects can still be seen, as the transport of those materials is now an issue.

- Manufacturers normally keep two to three months of stock of all key starting materials and active pharmaceutical ingredients. However, the lead time for the delivery of imported active pharmaceutical ingredients is now between four and 12 weeks, which could delay the production of finished products.
- Stocks of ancillary products (such as packaging materials) are generally lower at production sites. Shortages of such materials are already being seen, and they may have an impact on the delivery of antiretroviral medicines.
- Lockdown restrictions in India are allowing manufacturing plants to operate at only approximately half the normal levels of human resources. Other constraints restricting the movement of people have further constrained the actual operational capacity.
- There is no more storage space for finished products in factories due to slower movement across the supply chain.
- There is a likely delay of at least three to five weeks in the production of finished products due to workforce shortages and shortages of materials.

The aggregate impact of these issues is likely to be seen in the coming weeks.

If coordinated action is taken by governments and suppliers to resolve these issues soon, there may be a minimal impact on supply chains and market prices. Inaction, however, may result in rising costs for some key antiretroviral regimens, and several countries may experience issues in their stock levels and a delayed supply and distribution pipeline of antiretroviral medicines.

COVID-19 and possible future volatility in market prices of antiretroviral medicines

Several cost drivers have affected manufacturers due to the current crisis (see Figure 1). If swift action is not taken by various stakeholders to mitigate the risks, those cost drivers may increase the final cost of some antiretroviral regimens by 10–25%. UNAIDS

estimates that exports of generic HIV medicines from India are worth between US\$ 850 million and US\$ 900 million per year. A 10–25% increase in costs may result in an annual increase in the final prices of exported antiretroviral medicines from India of between US\$ 100 million and US\$ 225 million.

At this stage, the implications for the cost of innovator medicines are unclear. Cost pressures may result in a reduction of the operating margins of manufacturers, adding to increased procurement costs for low- and middle-income countries.

Increases in cost may place an additional burden for HIV financing on low- and middle-income countries.

Some countries fear that manufacturers may favour larger buyers with higher margins and better prospects over smaller buyers. Diversion of production capacity for COVID-19-related medical products may also place additional constraints on the supply of antiretroviral medicines, leading to a possible increase in their costs.

Figure 1. Key cost drivers of antiretroviral medicines due to COVID-19

Overhead costs



Overheads, such as fixed costs for running a factory, account for 5–10% of increased costs due to the production capacity being reduced to 50% in several plants.

Alternative sourcing



Some of the key starting materials and active pharmaceutical ingredients for manufacturing are either in short supply or are being procured from different sources. This results in additional manufacturing costs of 10–25%.

Transport



Air freight charges from India have increased threefold due to the reduced number of carriers currently operating.

Active pharmaceutical ingredients



Information obtained from manufacturers indicate that active pharmaceutical ingredient prices have increased for tenofovir, efavirenz and ritonavir. There may be other regimens that experience similar issues if the situation does not resolve.

Currency fluctuations



An imminent economic crisis places additional risk on the volatility of currencies, which may affect the prices of antiretroviral medicines.

Product-specific issues

While there is no direct impact of product-specific delays that threatens the supply of any antiretroviral medicines so far, countries should be cognizant of the changes that have taken place over the past few months and the need for mitigation actions. As buyers, Kenya, South Africa and Thailand have taken measures to monitor delays from suppliers, forecast for the longer term and plan alternative procurement mechanisms to mitigate supply risk.

Similarly, manufacturers are implementing measures to ensure business continuity. Those measures include alternative sourcing of key starting materials and active pharmaceutical ingredients that are now in short supply, using air shipments instead of sea traffic and bearing the additional costs for workforce resources. It is important that the risk mitigation measures on alternate sourcing of raw materials by manufacturers should not result in lower-quality end products. Key active pharmaceutical ingredients that need to be managed are:

- Tenofovir.
- Efavirenz.
- Zidovudine.
- Lopinavir.
- Ritonavir.
- Abacavir.
- Darunavir.

These are important products used in existing antiretroviral therapy regimens. As of April 2020, manufacturers in India have been able to limit the delays in supply to one to three weeks. However, there are indications of widespread product delays in the next few months (June and July of 2020) if measures are not taken or if normality is not established within the next few weeks.

In addition, the small and fragmented paediatric antiretroviral medicine market has faced challenges around costs and supply stability for several years. Given that the number of manufacturers for each paediatric product is lower, it would be difficult for buyers to switch sources. Based on the UNAIDS analysis, further delays or increases in prices are anticipated for paediatric formulations since a higher priority for both manufacturing and procurement may be given to the high-volume adult first-line regimens.

Delay in the arrival of products and low stock levels reported by countries

The data from the five countries that responded to the survey indicate that some are experiencing low stock levels of active pharmaceutical ingredients, while others are in a better position to have stock for longer. When countries reported low levels of stock or delays in delivery from manufacturers, the following products were impacted:

- Tenofovir/lamivudine/efavirenz (TLE).
- Tenofovir/lamivudine/dolutegravir (TLD).
- Abacavir.
- Lopinavir/ritonavir (LPV/r), 100/25 mg.
- Zidovudine/lamivudine (AZT/3TC), fixed-dose combination (60/30 mg) tabs.
- Zidovudine solution, 10 mg/ml.
- Cotrimoxazole suspension.
- Ritonavir tablets, 100 mg.
- LPV/r pellets, 40/10 mg (paediatric formulation).
- Nevirapine suspension, 10 mg/ml (paediatric formulation).¹

Based on UNAIDS estimates and country-reported data, more than 80% of people on HIV treatment in low- and middle-income countries are either on TLD or TLE as a first-line regimen, with an ongoing shift from TLE to TLD. Since these products may face potential delays, it is key to identify the risk level for stock of all antiretroviral medicines in countries and to plan advance coordination to analyse supply chain pipelines.

¹ It has to be noted that the shortages of LPV/r may be due to the limited global capacity of production of this product and not necessarily due to COVID-19.

POLICY RECOMMENDATIONS

For countries

- **Improve forecasting accuracy.** There is a critical need for countries to improve predictability of the demand. Countries should forecast for a longer period (12 months or more) and initiate early procurement. Countries should also verify the forecasts in order to limit the stocks in-country and to avoid global shortages, while also reducing pressure on production.
- **Process innovation.** Develop innovative processes for regulatory actions to be undertaken in order to facilitate the export/import of health commodities and raw materials for production, especially at the entry and dispatch ports and at local borders. Countries should be more vigilant in the processes of monitoring the quality of medicines and should work with approved suppliers as counterfeiters may try to fill the gaps.
- **Custom waivers.** Consider tax waivers to mitigate potential increases in prices for health commodities.
- **Transparent communication.** Ensure transparent and timely communication between countries, buyers and suppliers for accuracy of the supply and distribution planning process for all stakeholders.
- **Ensure adequate in-country distribution and a supply chain to remote areas.**

For buyers of antiretroviral medicines

- **Enhance the demand verification process.** Funders should enhance the demand verification process to correct inflated demand.
- **Mitigate cargo movement risks.** Plan alternative mechanisms to move goods, involving special measures as necessary. In the interim, implement budget measures for increased procurement costs due to logistical challenges. Explore interventions as necessary, such as humanitarian flights or the formal collaboration established between the World Health Organization and the World Food Programme to facilitate the shipping of essential commodities.
- **Move to multimonth dispensing while managing the stock and supply line.** A move towards multimonth dispensing is necessary since it reduces the pressure on busy health facilities. Also, during the COVID-19 pandemic, it is important to keep people living with HIV away from health-care settings in order to avoid transmission of COVID-19. At the same time, there is a need to manage actual dispensing in the coming months depending on the stock and supply of medicines (6). Undertaking regular stockpile assessments is necessary. A supply for a shorter period may be warranted given the available stock and expected supply. Alternative distribution mechanisms may also be considered, such as community medicine delivery or alternative sites for dispensation other than health centres.

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