COVID-19 antivirals must not affect HIV drug supply

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On Nov 16, 2021, Pfizer announced submission of an application to the US Food and Drug Administration (FDA) for Emergency Use Authorization for its investigational oral drug combination for COVID-19, ritonavir-boosted PF-07321332. Results from the phase 2/3 interim analysis are promising, but are yet to be peer reviewed.

Speculation from Pfizer's announcement could affect markets for ritonavir (and the materials used for its manufacture) within weeks. The case of ritonavir-boosted lopinavir early in the pandemic serves as a cautionary tale: despite tenuous evidence suggesting clinical effectiveness in treating COVID-19, ritonavir-boosted lopinavir had an eight-fold increase in hospital use between March and April, 2020.[1] Mirroring this increase, there was a sharp rise in higher priced shipments of ritonavir's active pharmaceutical ingredient exported from India (appendix). The market for the active pharmaceutical ingredient of ritonavir largely settled by October, 2020, but the expectation that ritonavir-boosted lopinavir would be effective in treating COVID-19 probably had downstream effects on supply and availability. These mere expectations produced the observed market disruptions (appendix). Convincing data or an Emergency Use Authorization could increase market uncertainty, volatility, and prices.

In November, 2021, Pfizer announced an agreement with the Medicines Patent Pool that allowed particular manufacturers to supply ritonavir-boosted PF-07321332 to 95 countries (53% of the global population).[2] Although this is an important step to the scaling up of manufacturing, restrictions such as the exclusion of large countries such as Brazil and China discriminate and will segment and disrupt the market.

When demand exceeds supply, medicines generally go to the highest bidder, regardless of the greatest clinical need. Throughout the COVID-19 pandemic, high-income countries have purchased experimental vaccines and treatments well in advance of comprehensive clinical evidence. By contrast, low-income and middle-income countries (LMICs) cannot usually afford to divert health system resources towards speculative purchases. The business practice wherein companies renege on earlier contracts with LMICs to redirect sales at increased prices to high-income countries is well documented. Speculative purchasing and stockpiling affect patients: in 2020, thousands of people living with lupus were unable to access hydroxychloroquine because of COVID-19-related stockpiling.[3] Without a course correction, the pattern will probably continue with ritonavir-boosted PF-07321332, as Pfizer and prospective licensees or competitors might purchase current ritonavir stock and reserve existing manufacturing capacity to scale-up production as part of the new COVID-19 antiviral combination. Countries excluded from the license that do not have domestic ritonavir manufacturing will be particularly affected.

There have been chronic shortages of ritonavir-boosted lopinavir,[4-6] and global production has decreased with the introduction of dolutegravir. Increased demand could exacerbate affordability challenges. Ritonavir has a long history of access challenges, as evidenced by the numerous times governments issued compulsory licenses to overcome patent monopolies (eg, Tajikistan, 2005; China, 2007; Thailand, 2007; and Indonesia, 2012).[7] In March, 2020, Israel issued a compulsory license for ritonavir-boosted lopinavir for the treatment of COVID-19 because AbbVie and its authorised importer were unable to supply requested quantities.[8]

See Online for appendix

The volume of ritonavir that could be diverted to the COVID-19 market is large. Pfizer has claimed that they can supply 80 million treatment courses of ritonavir-boosted PF-07321332 by the end of 2022. Ritonavir is used for HIV treatment by over 1 million adults and 500000 children in LMICs and has wider effects by preventing transmission.[9] Thus, access to ritonavir-boosted PF-07321332 for the treatment of COVID-19 must be pursued alongside maintaining the care for people living with HIV. To ensure anticipation of and planning for potential shortages, we propose the following five actions.

First, WHO, the US President's Emergency Plan for AIDS Relief, The Global Fund to Fight AIDS, Tuberculosis and Malaria, and national procurement agencies should coordinate to anticipate shortages and reallocate stock as needed. Particular focus must be given to paediatric antiretroviral markets, which are likely to be disproportionately affected by capacity and price shocks because they account for smaller volumes than adult markets. Existing forums such as the Antiretroviral

Procurement Working Group could be an efficient convening mechanism. The unusual supply visibility, centralisation, and predictability of the antiretroviral market should be leveraged to ensure continuity in deliveries. For example, procurers with high volumes of security stock could amend delivery dates on contracts so that manufacturers can service orders to those with more immediate need first.

Second, Pfizer should make information on procurement mechanisms, supply capacity, price, and global registration status publicly available.

Third, Pfizer should ensure that there is sufficient global capacity to manufacture ritonavir, including investing in new or repurposed manufacturing lines where needed.

Fourth, Pfizer should not enforce patents for the duration of the COVID-19 pandemic in LMICs. This would increase global supply of a potentially important COVID-19 treatment and stabilise ritonavir markets by increasing the number of manufacturers. At a minimum, Pfizer should expand the current Medicines Patent Pool license to include more countries, especially those with high COVID-19 and HIV burdens. Pfizer forecasts US$82 billion in revenue in 2021 (double Pfizer's 2020 revenue),[10] affording the company these opportunities as a gesture of global goodwill.

Finally, high-income countries purchasing ritonavir-boosted PF-07321332 should immediately increase funding available to national HIV treatment programmes and The Global Fund to offset antiretroviral price increases.

The expansion of HIV treatment coverage is a remarkable public health success, but the inequitable distribution of COVID-19 vaccines and therapeutics has been a profound failure of solidarity. Immediate action is needed to ensure that potential disruptions to ritonavir markets do not unravel years of progress in HIV treatment and prevention.

We declare no competing interests.

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1 IQVIA. Shifts in healthcare demand, delivery, and care during the COVID-19 era tracking the impact in the United States. April 29, 2020. https://www.iqvia.com/insights/the-iqvia-institute/covid-19/shifts-in-healthcare-demand-delivery-and-care-during-the-covid-19-era (accessed Nov 11, 2021).

2 Pfizer. Pfizer and the medicines patent pool (MPP) sign licensing agreement for covid-19 oral antiviral treatment candidate to expand access in low- and middle-income countries. Nov 16, 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-medicines-patent-pool-mpp-sign-licensing (accessed Nov 18, 2021).

3 Ziadé N, El Kibbi L, Hmamouchi I, et al. Impact of the COVID-19 pandemic on patients with chronic rheumatic diseases: a study in 15 Arab countries. *Int J Rheum Dis* 2020; **23:** 1550–57.

4 University of Capetown Medicines Information Centre. Lopinavir/ritonavir shortage. Sept 3, 2015. http://www.mic.uct.ac.za/MIC/News/Sep15/LPVr (accessed Nov 11, 2021).

5 Bhuyan A. A year since stock-outs, India continues slow roll-out of child-friendly HIV drugs. Sept 17, 2018. https://thewire.in/health/india-child-friendly-hiv-drug-slow-roll-out (accessed Nov 11, 2021).

6 WHO. WHA65.29: addressing the global shortages of medicines and vaccines: case study, progress and activities. June 2017. https://www.who.int/medicines/areas/policy/Information_sessionIPCshortagesJune2017.pdf (accessed Nov 11, 2021).

7 Medicines Law & Policy. The TRIPS flexibilities database. http://tripsflexibilities.medicineslawandpolicy.org/ (accessed Nov 11, 2021).

8 Knowledge Ecology International. Israel issues compulsory license to allow the government to import generic versions of Kaletra. March 23, 2020. https://www.keionline.org/32503 (accessed Nov 11, 2021).

9 Clinton Health Access Initiative. 2021 HIV market report. October 2021. https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2021/10/2021-CHAI-HIV-Market-Report.pdf (accessed Nov 11 2021).

10 Pfizer. Quarterly reports. 2021. https://investors.pfizer.com/financials/quarterly-reports/default.aspx (accessed Nov 23, 2021).