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Antimicrobial Resistance and Substandard and Falsified Medicines:The Case of HIV/AIDS

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To the Editor—

Wallis et al recently reviewed key determinants of human immunodeficiency virus (HIV) drug resistance in low- and middle-income countries (LMICs) [1]. In addition to the determinants that were reviewed, we believe the *quality* of antiretrovirals (ARVs) available in antiretroviral therapy regimens also merits attention.

The World Health Organization (WHO) recently released a report on the burden of substandard and falsified antimicrobials. Based on their global analysis, 11% of antimicrobials contained subtherapeutic concentrations of active pharmaceutical ingredients [2]. The proportion for ARVs was 4.2% [2]. People with HIV exposed to subtherapeutic ARVs are at increased risk of developing HIV drug resistance [3, 4]. Continued vigilance to ensure use of quality ARVs is critical for three reasons. First, in many countries procurement is transitioning to domestic mechanisms that may not have the same stringent requirements for quality as the President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund (GF). Second, there may not be enough supply from qualified manufacturers to supply all countries with newly recommended ARVs, such as dolutegravir-containing regimens, increasing the risk of a possible influx of nonquality-assured ARVs in some countries. Finally, in countries moving toward national and privatized health insurance schemes as part of universal health coverage, different pharmacies may procure ARVs through different manufacturers (some of which may not adhere to stringent quality standards).

Historically, PEPFAR and GF have played major roles in procurement of ARVs in LMIC. Both PEPFAR and GF require medicine manufacturers to meet stringent regulatory requirements to be eligible for procurement. Currently, countries are increasing their domestic allocations to the HIV/AIDS response [5]. This transition may include a change from external to national procurement mechanisms [6]. National ARV procurement mechanisms must establish and maintain stringent regulatory processes to prevent potential introduction of subtherapeutic ARVs. Funders have an important role to play in capacity

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development and assuring quality standards are maintained when procurement mechanisms shift to indigenous systems.

National pharmaceutical regulatory systems would ideally have the capacity to assess the quality of medicines procured through national systems. Unfortunately, regulatory systems are underdeveloped in many countries [7]. These countries often rely on other quality assurance mechanisms, such as WHO prequalification, to fill this void [8]. Although this is a promising approach, WHO prequalification may not have the capacity to validate all potential medicine manufacturers globally in a timely manner, given the time and resources required to assess individual manufacturers. Additionally, manufacturers may choose not to submit their products for such review. Regional medicine qualification, such as that recently used in the Association of Southeast Asian Nations and East Africa Community, is emerging as an important mechanism to reduce duplication and promote efficiency of medicine quality assurance in different regions of the world by allowing a regional regulatory authority to assess medicine quality for multiple countries [8]. The recent treaty of the African Union to establish an African Medicines Agency should support this effort in Sub-Saharan Africa [9].

One mechanism to ensure sustained availability of quality-assured medicines is through central procurement and distribution systems that have rigorous quality standards. This can reduce cost and improve availability of quality-assured medicines in the country, as it prevents smaller-volume pharmacies from issuing their own tenders and procuring medicines of unknown quality. Historically, pooled procurement has been the norm for ARV procurement by PEPFAR and GF [6].

To illustrate the potential implications of increased low-quality medicine use in countries, we take a hypothetical country example. Currently, the national first-line regimen is tenofovir, lamivudine, and efavirenz. In four scenarios we explore changes in procurement modality and/or national first-line regimen (Table 1). In this example, we assume that the change in procurement modality is from one that requires quality assurance to one that does not, while a change in regimen includes introduction of a new medicine class without any resistance. Although there may be differences in magnitude of effects with careful quantification, this exercise suggests that regimen and procurement changes have the potential to affect acquired drug resistance.

While pharmacovigilance is dedicated to monitoring adverse events of medicines, passive and active surveillance systems will also be useful in monitoring medicine availability, quality, and effectiveness during regimen and procurement changes [10]. Passive surveillance relies on providers to report suspected substandard and falsified medicines, perhaps because of lack of therapeutic effectiveness in patients, while active surveillance requires testing the therapeutic quality of medicines. Strengthening and implementing national surveillance systems may help ensure timely detection of substandard and falsified ARVs.

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References

1. Wallis CL, Godfrey C, Fitzgibbon JE, Mellors JW. Key factors influencing the emergence of human immunodeficiency virus drug resistance in low- and middle-income countries. J Infect Dis 2017; 216:851–6.
2. World Health Organization. A study on the public health and socioeconomic impact of substandard and falsified medical products, 2017 http://www.who.int/entity/medicines/regulation/ssffc/publications/Layout-SEstudy-WEB.pdf. Accessed 23 April 2018.
3. Zoufaly A, Jochum J, Hammerl R, et al. Determinants of HIV-1 drug resistance in treatment-naïve patients and its clinical implications in an antiretroviral treatment program in Cameroon. J Int AIDS Soc 2014; 17:19615. [PubMed: 25394119]
4. Ahoua L, Guenther G, Pinoges L, et al. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. BMC Infect Dis 2009; 9:81. [PubMed: 19493344]
5. Global Burden of Disease Health Financing Collaborator Network. Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995–2015. Lancet 2018; 391:1799–829. [PubMed: 29678342]
6. Ripin DJ, Jamieson D, Meyers A, Warty U, Dain M, Khamsi C. Antiretroviral procurement and supply chain management. Antivir Ther 2014; 19 (Suppl 3):79–89.
7. World Health Organization. Assessment of medicines regulatory systems in sub-Saharan African countries, 2010 http://www.who.int/healthsystems/Assessment26African_countries.pdf. Accessed 31 May 2018.
8. World Health Organization. Towards Access 2030: WHO Medicines and Health Products Programme Strategic Framework 2016–2030, 2017 http://www.who.int/medicines/publications/Towards_Access_2030_Final.pdf. Accessed 23 April 2018.
9. Zarocostas J Health ministers adopt African Medicines Agency treaty. Lancet 2018; 391:2310. [PubMed: 30047404]
10. World Health Organization. Global surveillance and monitoring system for substandard and falsified medical products, 2017 http://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report.pdf. Accessed 23 April 2018.

Table 1.

Potential Effects of National Antiretroviral Regimen and Changes Procurement Regulatory Requirements on Acquired Drug Resistance (ADR)

	Effect of Regimen on ADR	Effect of Procurement Modality on ADR	Cumulative Effect of ADR
Scenario 1: no changes	↔	↔	↔
Scenario 2: change in regimen and not procurement modality	↓	↔	↓
Scenario 3: no change in regimen and change in procurement modality	↔	↑	↑
Scenario 4: change in regimen and procurement modality	↓	↑	↔