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VIEWPOINT

# Promoting Global Cardiovascular Health

## Ensuring Access to Essential Cardiovascular Medicines in Low- and Middle-Income Countries

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**On May 13, 2010, a resolution passed at the United Nations for a high-level meeting with heads of state on noncommunicable chronic diseases (NCDs), catapulting NCDs atop the political and health agendas. This meeting on NCDs, slated for September 2011, provides the rare political moment to commit to scaling up international, regional, and national efforts to prevent and treat NCDs, giving the issue the priority it deserves. An analogous high-profile meeting transpired in 2001 on human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), effectively serving as the nucleating event for a vigorous global and political movement towards universal prevention and treatment. As was the case at the HIV/AIDS meeting, a key priority area in the new NCD movement remains ensuring universal access to reliable, affordable essential medicines to prevent and treat NCDs. The upcoming meeting, therefore, provides the perfect opportunity to capitalize on the increased political and social awareness of NCDs and to apply the lessons learned from the HIV/antiretroviral experience in order to improve access to essential medicines for NCDs. Social mobilization and political advocacy, used in tandem with technical solutions, is an important lesson from the HIV experience, and will likely be important to ensure access to essential medicines for NCDs, including cardiovascular disease. Here, we use cardiovascular disease as a specific case study to examine the issue, outlining early solutions while drawing parallels and analogies to the HIV experience. (J Am Coll Cardiol 2011;57:1980–7) © 2011 by the American College of Cardiology Foundation**

On May 13, 2010, a resolution passed at the United Nations for a high-level meeting on noncommunicable chronic diseases (NCDs), catapulting NCDs atop the political and health agendas. This meeting on NCDs, slated for September 2011, provides the rare political moment to commit to scaling up international, regional, and national efforts to prevent and treat cardiovascular disease (CVD) and other NCDs. Currently, there is insufficient political incentive to control global CVD, reflected in the severe underfunding of global CVD and related NCDs (1). Given that CVD is the leading cause of death worldwide, and that age-standardized CVD mortality is higher in low- and middle-income countries (LMICs) (2,3), the global cardiovascular community should take advantage of this opportunity to marshal the resources required to control global CVD.

An analogous high-profile meeting transpired in 2001 on human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), effectively serving as the nucleating event for a vigorous global and political movement toward universal prevention and treatment. Similar to the HIV/AIDS experience, a key priority area in the new global CVD movement remains ensuring universal access to reliable, affordable essential medicines to prevent and treat CVD.

Currently, essential CVD medicines have poor availability in the public sector in LMICs (4,5). Although there is better availability of these medicines in the private sector, the end-user cost makes many medicines unaffordable to the majority of LMIC populations. In addition, the pharmaceutical component of CVD prevention requires daily, long-term medication treatment, rather than short-course or 1-time therapy, which increases the lifetime financial burden. Moreover, given that the vast majority of medicines are currently purchased through individual out-of-pocket payments in LMICs (6), the household-level financial burden is heavy. Differences in local epidemiological CVD burden, and differences in local practice patterns, can lead to geographically distinct problems with access to cardiovascular medicines (7). For instance, a 1-month course of combined therapy for secondary prevention (aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, and statin) for patients with established CVD could cost as much

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as 18 days' wages in Malawi (4). In India, an adult male with CVD is 20% more likely to have catastrophic spending (when health care costs capture 40% of a household's capacity to pay) and is at 8% greater risk of impoverishment compared with age-adjusted controls (8). Therefore, it is imperative to ensure a guaranteed supply of affordable CVD medicines via the public sector to the majority of LMIC populations at little or no cost (3).

The path traveled by the HIV/AIDS pioneers over the past decade to broker increased access to essential life-saving medicines can serve as a model to do this (9), and given the current political momentum, should be levered to mobilize increased global access to drugs for CVD. In 2001, HIV medications in LMICs rivaled and sometimes exceeded Manhattan prices. After a decade of activism and coordinated efforts by various stakeholders, including political advocacy and social mobilization by civil society, HIV medications are increasingly accessible in LMICs, and HIV is increasingly becoming a chronic disease in parts of the world where it used to mean an unquestionable and acute death sentence (9). Social mobilization and political advocacy, used with technical solutions, is an important lesson from the HIV experience, and will be critical to ensure access to essential CVD medicines in LMICs.

## A Starting Point: Social Mobilization and Political Advocacy

The "axis of access" to CVD medicines consists of entities including multilateral agencies, pharmaceutical companies, procurement bodies, local financing and regulatory factors, and end users, operating within a social and political environment (Fig. 1). Each component of this axis interacts with the other components and with the surrounding environment, thus providing multiple points of intervention and impact. By engaging in political advocacy and social mobilization, and thereby modifying the social and political environment, the axis can be reoriented toward increasing access to essential CVD medicines in LMICs.

A key lesson from the HIV movement is that access to medicines will not become a priority for particular diseases unless they move up on the political, as well as the health, agendas. The Treatment Action Campaign (TAC), a South African group that effectively argued and amplified the demand for HIV medicines, is a powerful example of social mobilization leading to political prioritization of a disease entity. TAC first framed its argument as a human rights issue, making access to medicines a fundamental issue of social justice (10). Social mobilization was animated by thousands of patients and citizens draped in "HIV POSITIVE" t-shirts, lively protests, and widespread civil disobedience campaigns. TAC's engagement of civil society helped lead to a comprehensive South African national HIV/AIDS prevention and treatment plan, including access to antiretroviral (ARV) medicines in the public sector (11). In light of this experience, reframing global CVD in the context of health

**Abbreviations and Acronyms**

**AIDS** = autoimmune deficiency syndrome
**ARV** = antiretroviral
**CL** = compulsory license
**CVD** = cardiovascular disease
**EML** = Essential Medicines List
**FDC** = fixed-dose combination
**HIV** = human immunodeficiency virus
**LMIC** = low- and middle-income country
**NCD** = noncommunicable chronic disease
**NEML** = national Essential Medicines List
**NGO** = nongovernmental organization
**TRIPS** = trade-related aspects of intellectual property rights
**WHO** = World Health Organization
**WTO** = World Trade Organization

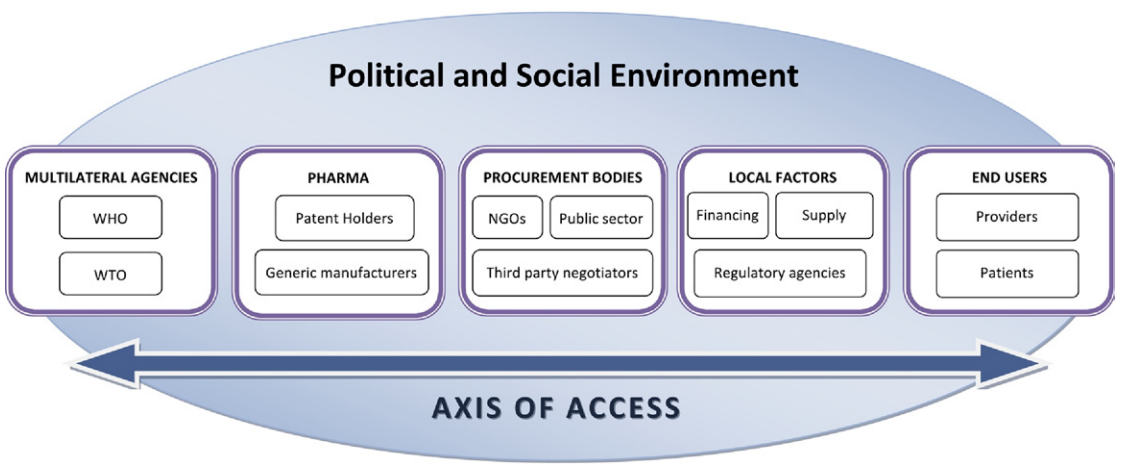


**Figure 1** Axis of Access to Cardiovascular Disease Medicines

The "axis of access" to cardiovascular disease medicines consists of entities including multilateral agencies, pharmaceutical companies, procurement bodies, local financing and regulatory factors, and end-users, operating within a social and political environment. NGO = nongovernmental organization; WHO = World Health Organization; WTO = World Trade Organization.

equity and social justice is an important step to inspire and energize social mobilization and political advocacy, with the ultimate goal of improving access to CVD medicines.

## WHO Essential Medicines for CVD

Essential medicines are defined by the WHO as medicines that satisfy the priority health care needs of the population and are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness (12) . The medicines that are considered to be of highest priority are included on the WHO Model List of Essential Medicines, or Essential Medicines List (EML). The EML, first published in 1977 and revised every 2 years by an expert committee, catalogs critical medicines, and guides purchasing decisions of governments and many organizations (12–14). Individual nations align the WHO EML with the epidemiologic profile and health priorities of their population, yielding a national essential medicines list (NEML). Medicines on the NEML are subsidized by the public sector (15); this has helped to reduce the price of antihypertensive medication in sub-Saharan Africa by over 70% (16). In addition, medicines on the NEML are the highest priority for coverage by voluntary or national health insurance programs. In the national *Mutuelle* insurance system in Rwanda, for example, members are eligible to receive NEML drugs for outpatient treatment with a 10% copayment (17).

In addition, drugs purchased by major nongovernmental organizations and the United Nations agencies for donation are generally limited to those on the EML (12). The EML can also serve as an advocacy tool. Pressure by HIV treatment and patient communities, for instance, prompted a special expert committee meeting that led to the inclusion of the first ARVs to the EML in 2002 (9). Critically, anyone in the public can petition the WHO to add or delete a medicine from the EML.

The first EML included nitrates, lidocaine, hydrochlorothiazide, aspirin, and dopamine (Fig. 2). In 1988, epinephrine and sodium nitroprusside were added, followed by verapamil, digoxin, methyldopa, and streptokinase in the 1990s. In 1997, atenolol was added. Amlodipine, enalapril, and furosemide were added to the EML in 2003 to 2005 (18). Simvastatin was added in 2007 and amiodarone in 2009. Notably, as of the EML published in 2009, there was no beta-blocker listed for the heart failure indication. This fact underscores the need to accelerate EML listing of new CVD medicines to ensure equitable access to evidence-based medicines.

## Beyond the Model List: Ensuring Access to Essential Medicines

Although addition to EML is an important step to drawing attention to drug selection and use by nations, a host of structural and financial factors still create barriers for LMIC populations to access essential CVD medicines. Several approaches, based on the lessons of the HIV experience, and all currently endorsed by the WHO (13), can help (Fig. 3): 1) enhancing capacity for generic substitution; 2) expediting generic availability by overcoming legal barriers related to patents and licenses; 3) optimizing local procurement practices in the public sector; 4) broadening global procurement via third-party price negotiations; 5) engaging the private sector to differentially price CVD medicines in LMICs; 6) regulating retail markups in the supply chain; 7) eliminating tariffs on medicines; and 8) developing a fixed-dose combination (FDC) for CVD (the "Polypill").

**Enhancing capacity for generic substitution.** Generics are more affordable in LMICs, ranging from 3 to 12 times less expensive than brand-name medicines in the Americas and the Western Pacific, respectively (5). Thus, substitution of generic drugs over branded ones is a sensible strategy to close the treatment gap. But to increase acceptance and use of low-priced generics, quality must be assured. The WHO prequalification project completes due diligence on product manufacturing standards, cataloguing global manufacturers with safe, reliable, and predominantly generic products for rapid drug import and use. Manufacturers submit product dossiers to a WHO committee, that undergo both clinical and quality assessments, followed by on-site inspection of the manufacturing plants. The pre-qualification program has been credited with increasing market penetration by generic firms and reducing the price of ARVs since 2001 (9). The pre-qualification listing, however, has been limited to 275 HIV/AIDS, 27 tuberculosis, 17 malaria, and 7 influenza products. The inclusion of CVD products would immediately strengthen the uptake, procurement, and patient access to quality generic essential CVD medicines (19).

At the local level, it is critical to promote the uptake of generics by health professionals and patients alike. Providing practical incentives, such as fast-tracking regulatory status approval at the local medicines regulatory authority for quality generics, can promote dispensing generic CVD medicines. In addition, cardiology societies in high-income countries, such as the American College of Cardiology and the American Heart Association, can work together with the WHO and regional cardiology societies from LMICs to jointly develop evidence-based guidelines that encourage the appropriate use of generic medicines. These guidelines can guide locally specific and relevant treatment goals and monitoring outcome measures for simple interventions such as, for example, use of beta blockers and statins after myocardial infarction.

**Expediting generic availability by overcoming legal barriers related to patents and licenses.** Legal barriers to access, including patents enforced in LMICs and exclusive licenses, can thwart generic competition. Countering these legal barriers can yield substantial reduction in the costs of essential medicines; generic competition for ARVs reduced costs from more than $15,000 per patient-year in 2001 to $87 in 2008 (20). Article 31 of WTO Trade-Related Aspects Intellectual Property Rights (TRIPS) legislation features a clause permitting compulsory licenses (CLs), which allow for local generic production or

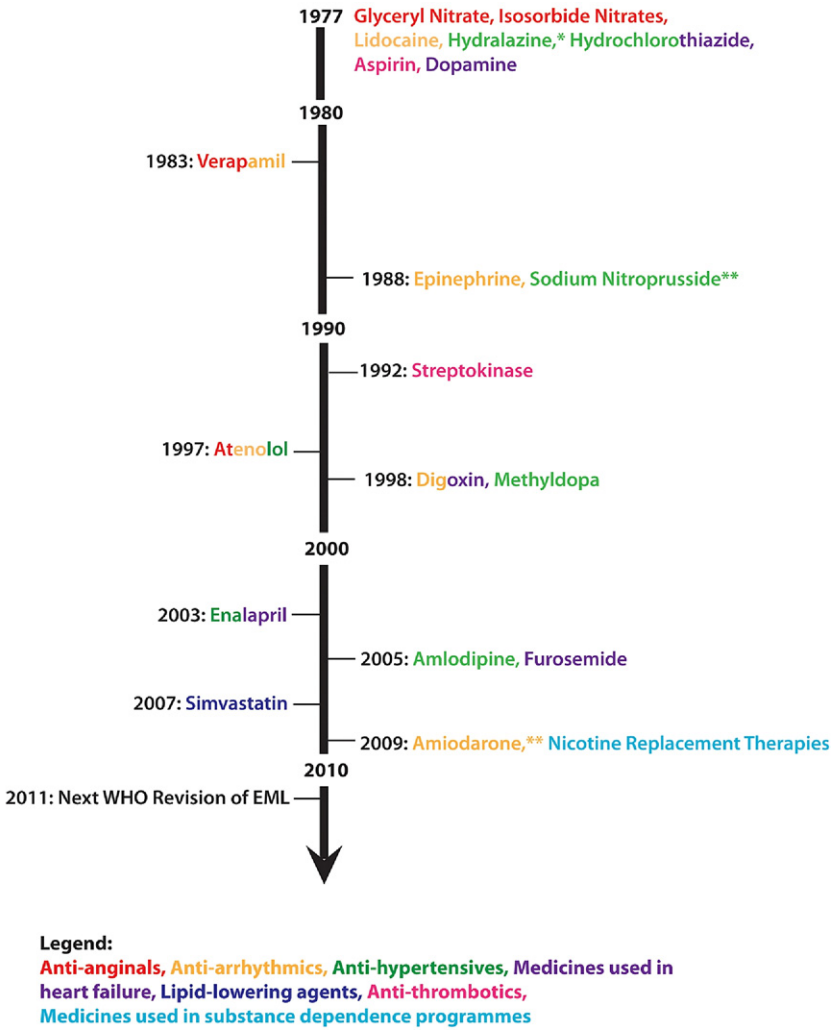


**Figure 2** WHO Essential Medicines for Cardiovascular Disease

A timeline of when essential cardiovascular medicines were added to the World Health Organization (WHO) Essential Medicines List (EML) (starting in 1977) and relevant indications for the medicines (in color) (18). *For pregnancy-induced hypertension only. **On the Complementary List, for which specialist care is required.

drug importation of patented products by non patent holders (21,22). The interest in CLs for CVD drugs remains relatively meager in contrast to HIV; to date, the only CVD drug to receive a CL was clopidogrel in Thailand, where prices dropped by a reported 90% for generic versions of the drug (23,24). Other patented cardiovascular drugs with greater efficacy than generics in the same class may be good candidates for CLs; however, achieving this will require more social and political pressure, as was seen for HIV.

**Optimizing local procurement practices in the public sector.** Inefficient procurement practices and management have yielded regular stock-outs of medicines, particularly for CVD medicines in the public sector (4,5,16). In Uganda, where essential medicines are provided free of charge in the public sector, availability of atenolol was only 10%, and captopril only 20%, and the average length of stock-outs is nearly 6 months (25). In India, availability of generic atenolol was 4% and 15% in the states of Karnataka and West Bengal, respectively (26).

Human resource and geographical constraints, insufficient funding for training, and poor performance incentives for supply managers are partly to blame for inefficient supply chain management. In sub-Saharan Africa, the key lesson from the HIV experience has been to improve the training and capacity for supply chain management and maintenance of buffer stocks of medicines. Currently, the "Stop Stock-Outs" program has been initiated in which local health personnel and community volunteers report the availability of a list of primary care drugs, including atenolol, captopril, and simvastatin, to the Ministry of Health via Short Message Service (SMS) text (27). Underperforming dis-

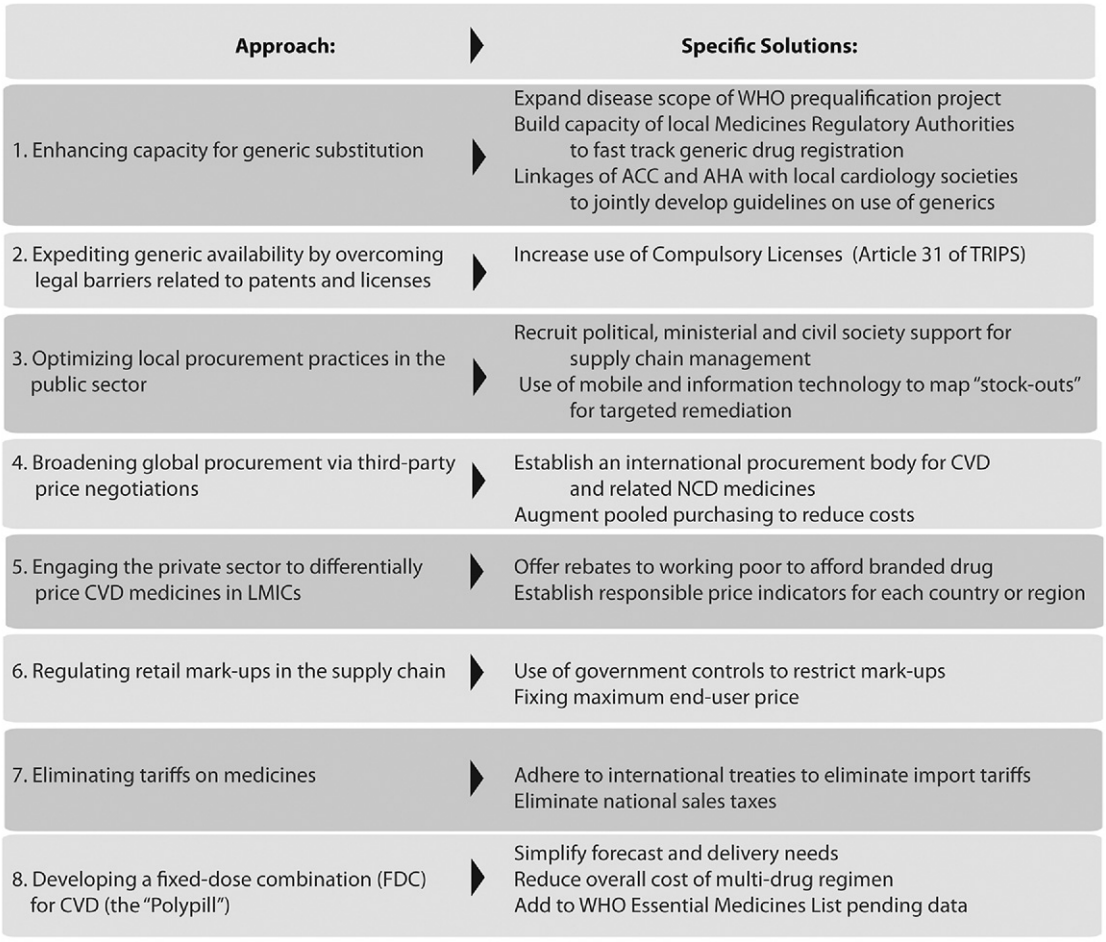


**Figure 3** **Summary of Approaches and Specific Solutions to Increase Access to Essential Cardiovascular Medicines**

The 8 key approaches and the specific solutions to increase access to essential cardiovascular medicines are displayed. Please see text for full descriptions of each. ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; LMIC = low- and middle-income countries; TRIPS = trade-related aspects of intellectual property rights; WHO = World Health Organization.

tricts are supported with supply chain management support by ministerial and WHO staff. Although promising, no rigorous data to measure effectiveness of this program are available yet.

**Broadening global procurement via third-party price negotiations.** Third-party price negotiations involve guaranteeing increased demand by wholesale purchasers for medications supplied at lower cost by pharmaceutical companies. These agreements are generally brokered by third parties (not the consumer or the supplier), such as the Clinton Foundation (28). As a result, pharmaceutical companies that make generic HIV medications, such as India's Cipla, have benefited from greater market information on drug forecasts, leading to optimal management of production risks and more sustainable profits. At the same time, a consortium of low-income countries is able to access cheaper medicines for HIV/AIDS patients. The WHO recently reported that third-party price negotiations via the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) generated the greatest cost-savings over both differential pricing and pooled purchasing schemes (28). Partly owing to sweeping civil society advocacy, the last decade has seen unprecedented investment by large donors and procurement agencies, including: the GFATM, the Global Alliance for Vaccines and Immunizations, the Global Alliance for Improved Nutrition, and the U.S. President's Emergency Plan for AIDS Relief. These agencies can exert significant buying power and negotiate price discounts for disease priorities based on large order volumes and economies of scale.

Given the benefits demonstrated by third-party price negotiations for HIV medicines, analogous efforts should be initiated for CVD medicines. A coordinated, high-profile procurement arm to fight for pooled purchasing for CVD and related drugs is now needed. Such a central body could protect patients' financial and health interests while simul-

taneously forecasting regional needs for essential CVD medicines and coordinating global supply with selected generic manufacturers. This can only exist with political prioritization—as was seen for HIV/AIDS.

**Engaging the private sector to differentially price CVD medicines in LMICs.** Differential, or tiered pricing, where drugs are sold at lower prices in LMICs, has historically been a slow and expensive solution for improving global access (29). Manufacturers prefer not to offer brand-name drugs in LMICs at reduced prices for fear of price referencing or parallel re-importation into high-income countries. Furthermore, when differential pricing has been employed for HIV medicines, brand-name medicines still cost more than generics (28). For CVD, branded atenolol in Uganda is 14 times more expensive and 35% less available than generic counterparts (25).

However, pharmaceutical firms are now aggressively looking to LMICs, and their exploding middle class populations, as potential sources for revenue (30,31). Pfizer (New York, New York) recently launched atorvastatin (Lipitor) in Venezuela, offering the branded drug at 30% less cost than the U.S. price with additional 10% to 20% rebates for the working poor, yielding a patient cost of $70 to $180 per year for 40-mg Lipitor (32). In comparison, the global procurement prices on 40-mg generic simvastatin currently ranges from $25 to $40 per year (33). Although 80% of all medication expenditures are out of pocket in Venezuela, Pfizer's Lipitor has seen success, now accounting for $44 million in sales, up 44% from 2007 (30). These recent developments will have important implications for access to medicines in the private sector, where branded drugs are most often used. Establishing responsible price indicators for each country or region will be essential for success, particularly as there is wide variation in per capita incomes worldwide. The effect on the public sector, where low-cost generics are most often used, remains to be rigorously evaluated.

**Regulating retail markups in the supply chain.** Wholesale and retail markups in the private sector also substantially increase the cost of medicines for individuals in LMICs, which is particularly problematic given the low availability of CVD medicines in the public sector (4). In Uganda, retail markups increase the price by over 40% for medicines in general (25). It is estimated that branded atenolol purchased in the Ugandan private sector would impoverish an additional 20% of the population versus just 1% for the lowest-priced generic equivalent (34).

To address the issue of price markups, the government of Mali effectively fixed maximum end-user prices for wholesale and retail purchases in the private sector for over 100 medicines from the NEML. Survey analyses 3 years later revealed that overall, retail prices had decreased by 22%, and prices for CVD-specific medicines, such as aspirin and captopril, had decreased by 11% and 54%, respectively (35). Critically, the decree did not alter the availability of the medicines. In Syria, the government has fixed the fees for the price components of the medicines (i.e., 20% markup as profit for manufacturer, 8% markup for marketing, and 8% wholesale markup; the final dispensing pharmacist's markup is applied regressively) (36). On balance, the Syrian solution yields total retail markups substantially lower than other comparator regions (e.g., ~68% in Lebanon) (37).

**Eliminating tariffs on medicines.** For CVD medicines, the cumulative post-manufacture pharmaceutical tariffs on freight, storage, and distribution of medicines can be as high as 55% (in India) (38) and are widely known to represent a regressive form of taxation that unfairly targets the sick. The tariffs could be eliminated without adverse revenue or industrial policy impacts (38). Pharmaceutical tariffs generate <0.1% of gross domestic product in 92% of countries. Moreover, it has been demonstrated that the economic losses from tariff reductions can be recovered via economic gains from a healthier population with greater access to treatments (15,39). International consensus favors tariff elimination efforts via the General Agreement on Tariffs and Trade (40), the Pharmaceutical Tariff Elimination Agreement (41), and the Doha Declaration (22). Similarly, the removal of national sales taxes on medicines would counter the regressive, impoverishing effects of taxation. Advocacy pressure helped lead to the removal of a standard 10% tax by the East African Community (Kenya, Tanzania, and Uganda) in March 2005 on any imported pre-packaged medicines (42). Eliminating tariffs and national sales taxes for CVD medicines would improve access in LMICs.

**Developing a fixed-dose combination for CVD.** Multidrug regimens, which are a mainstay for the control of major communicable diseases such as tuberculosis, HIV/AIDS, and malaria (43), present problems that intensify as the number of pills increases: decreased patient adherence, prescribing and dispensing errors, and increasing cost (44). The FDC arose as a solution—a proposal to chemically incorporate and package a multidrug regimen into single pill. For communicable diseases in LMICs, FDC has clearly been shown to increase patient adherence, minimizing prescribing errors and missed doses by patients while reducing costs (by as much as 50% in the specific case of the tuberculosis FDC) (44). FDC use simplifies supply chain management while reducing the administrative and logistical burden on procurement officers: forecasting a single pill rather than several is easier (43). Finally, use of the FDC is a positive force for patient education and counseling (43,44), minimizing patient confusion and simplifying treatment.

The successful experience with FDC for communicable diseases portends well for the recent international movement to implement an FDC for CVD prevention (the "Polypill") using subtherapeutic doses of key drugs (aspirin, statin, antihypertensive medication) (45). It has been shown that multidrug regimens for primary and secondary prevention of CVD are cost-effective in all global regions except sub-Saharan Africa (46). Thus, interest in the Polypill has increased in recent years, and there are

now several different formulations and combinations in the process of development and testing (47). If shown to be effective for primary and secondary prevention of CVD, the Polypill could become a major public health action item for the global CVD community (e.g., inclusion on the WHO EML).

## Concluding Thoughts: Highlighting the CVD Treatment Gap

Although one of the Millennium Development Goal targets is to "provide access to affordable essential drugs in developing countries" (48,49) and the WHO Secretariat is committed to "provide support to countries in enhancing access to essential medicines and affordable medical technology"(50), the current situation is far from the goal. The fact that CVD is global in scope but patients face stock-outs or exorbitant price hikes for basic essential CVD medicines is fundamentally inequitable.

The upcoming high-level meeting on NCDs can help move us forward, but requires careful attention to the importance of social mobilization and political advocacy. In this article, we have outlined some of the strategies that can be adopted in order to optimize the axis of access for essential CVD medicines by learning from the experiences of HIV/AIDS treatment advocates for ARVs. The success of robust, patient-centered, human rights–based advocacy for HIV/AIDS medicines animates the vital role of civil society in ensuring that all patients are able to access and afford basic, life-saving essential medicines.

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