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NEWS ON THE FIGHT TO END HIV/AIDS, VIRAL HEPATITIS, AND TUBERCULOSIS

Fair Pricing: Reclaiming Drugs for the Common Good

By Tim Horn

> *The way I see it, you can go down in history as the poster boy for greedy drug-company executives, or you can change the system—yeah, you.*
>
> —U.S. Representative Elijah E. Cummings (D-MD)

With these words, directed at execrated former Turing Pharmaceuticals CEO Martin Shkreli at a House Oversight and Government Reform Committee hearing on Capitol Hill this February, ranking member Elijah E. Cummings drew attention to a serious culpability problem that continues to dominate public discourse on the egregious pricing of prescription drugs in this country. The hearing was political theater at its most compelling, and Shkreli, smug, snide, and intransigent in his refusal to answer questions from committee members, was ideally cast in the role of villain. But to suggest that Shkreli and other pharmaceutical executives bear the sole responsibility for actually changing the system—a hodgepodge of laws, regulations, and loopholes underscoring health care as a commodity and unregulated profits as a free-market right of the prescription drug industry—misses the mark entirely.

We begin this issue of *TAGline* with "Greed and the Necessity for Regulation," in which Erica Lessem, Kenyon Farrow, and I review the need for increased statutory and regulatory oversight to mitigate what can only be described as an epidemic in domestic drug pricing. In the wake of unsubstantiated launch prices set for Gilead's hepatitis C treatments Sovaldi and Harvoni, Turing's 5,000 percent markup of the decades-old drug Daraprim for toxoplasmosis, and other recent egregious examples—all resulting in significant access barriers—a growing number of statutory and regulatory proposals have been put forth by federal and state elected officials and presidential candidates. Some strategies are revolutionary, others are more conservative, and all steer clear of the stringent price-control measures in place in other high-income countries.

In "PrEP Pricing Problems," James Krellenstein and Jeremiah Johnson explore several challenges associated with the high cost of Truvada as pre-exposure prophylaxis. These include known and anticipated access difficulties tied to high out-of-pocket costs and public-payer barriers, along with weaknesses in Gilead Sciences' assistance programs, not to mention the gall of maintaining a premium price for an FDA approval that was made possible only through a patchwork of federally funded clinical trials.

Finally, Tracy Swan interviews the University of Liverpool's Andrew Hill about his group's work exploring what it actually costs to profitably mass-produce generic drugs for HIV, viral hepatitis, and cancer. The resulting calculations have become a cornerstone of advocacy efforts in low-, middle-, and high-income countries, where there is now increasing pressure on the pharmaceutical industry to address the discrepancy between the price of drugs and what it costs to produce them.

Not touched upon in this *TAGline* is an issue directly related to efforts to control drug pricing and expenditures: the dire need for cost savings to be reinvested in the systems of HIV, hepatitis C, and TB prevention and care already stretched to the brink. Despite ambitious global strategies to end these epidemics, too little new money is being earmarked to improve diagnosis rates, engagement in care, and vital community infrastructure. Instead, the repurposing of existing funds for ambitious health initiatives—the National HIV/AIDS Strategy for 2020 notwithstanding—is often the financing tactic of choice. While advocates continue to push for expanded commitments from funders, we must also work to ensure that every dollar saved through drug cost containment efforts is earmarked for the betterment of public health.•

Greed and the Necessity for Regulation

The story of U.S. drug pricing run amok isn't just about corporate arrogance and avarice—it is also about government permissiveness and inaction

By Tim Horn, Erica Lessem, and Kenyon Farrow

On December 1, 2015, the U.S. Senate Finance Committee issued a scathing investigative report concluding that Gilead Sciences strategically priced its curative hepatitis C virus (HCV) treatments Sovaldi and Harvoni to yield an immediate financial windfall for the company, ignoring evidence and expert opinion that doing so would bust the budgets of public and private insurers and, consequently, prevent the medications from becoming available to all who need them. In February, Valeant Pharmaceuticals Limited and Turing Pharmaceuticals stood before members of the House Committee on Oversight and Government Reform, which conducted its own investigations into the sudden, inexplicable price increases for a number of lifesaving drugs. A month later, Turing executives were back on Capitol Hill, this time in front of irate members of the Senate Special Committee on Aging.

With the surge in narratives of scandalous corporate greed and villainy, the pharmaceutical industry's drug pricing practices are now firmly entrenched in American political discourse. The real scandal, however, is that monopolistic drug pricing is completely legal in the United States. Political condemnation of the pharmaceutical industry for its fleecing of consumers can feel vindicating, but it is also specious and hypocritical in the face of long-standing governmental encouragement of profit-driven private-sector practices, even when they have very real consequences for public health. CEOs like Martin Shkreli of Turing know this and, indeed, fully and unapologetically inhabit this system.

Unless the recent public cries of outrage are addressed by stricter government regulations and the possibility of bona fide price controls, exploitive drug pricing practices can be expected to continue.

According to a 2015 IMS Institute for Healthcare Informatics report, prescription drug expenditures in this country approached $374 billion in 2014. This represents a whopping 13.1% increase over 2013 spending that, according to the IMS report, can be at least partially blamed on one major factor: Sovaldi (sofosbuvir), Gilead's premiere HCV regimen component that debuted in December 2013 at a wholesale acquisition cost (WAC) price of $1,000 a tablet ($84,000 for a 12-week course). Sovaldi alone accounted for one-fifth of this increase—an additional $7.9 billion in 2014 spending by insurers, entitlement programs, and individual patients. Sovaldi and Harvoni (a combination of sofosbuvir and ledipasvir) have actually been among the most costly prescription drugs to Medicaid programs. In New York State alone, Medicaid paid more than $360 million for Sovaldi in 2014 to treat approximately 4,000 of its nearly 60,000 recipients living with HCV.

And it's not just HCV drugs that are straining budgets. WAC prices for antiretrovirals (ARVs) are also considerable. Genvoya (a combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), one of the recently approved single-tablet regimens for HIV manufactured by Gilead, debuted in November 2015 at $31,362 for a one-year course. It was welcomed as a bargain by groups like the Fair Pricing Coalition (FPC), if only because its launch price wasn't higher than the 2015 WAC price for its predecessor, Stribild. And with the WAC prices of virtually all ARVs increasing between 6 and 8 percent a year—more than twice the rate of inflation—older regimens have effectively doubled their price since launch (e.g., Atripla entered the U.S. market in 2006 at $13,800 per year; it now exceeds $26,000).

WACs for many common generic drugs—which account for 80 percent of U.S. prescriptions and have saved the U.S. health care system $1.2 trillion between 2003 and 2012—have also spiked in recent years for a number of reasons, including industry mergers and acquisitions (and, quite possibly, collusion), that have reversed free-market competition trends necessary to keep prices low.

Equally troubling are companies acquiring the rights to historically low-cost ("undervalued" in corporate parlance) medications without marketplace competition and then raising the prices astronomically. Among the most rank examples: Rodelis Therapeutics, which purchased the rights to the 60-year-old tuberculosis (TB) drug cycloserine in August 2015, increased the price from $500 for 30 capsules to more than $10,000, but ultimately agreed to return the drug to its former nonprofit manufacturer; and Turing, which purchased the 50-year-old Daraprim (pyrimethamine) for the life-threatening parasitic disease toxoplasmosis, raised its price per tablet from $13.50 to $750.

The adverse effects of skyrocketing drug prices are well established—and becoming increasingly glaring. Most egregiously, the high cost of HCV drugs has resulted in a clear inability of people living with the virus to get curative treatment. Numerous U.S. health plans, both public and private, have instituted treatment utilization polices and prior authorization processes based almost entirely on cost-containment concerns. Many Medicaid programs cover HCV treatment only for patients with advanced fibrosis and have policies that deny curative therapy to people who use drugs or alcohol, despite U.S. Food and Drug Administration (FDA) labeling, guidelines, and clinical evidence to the contrary.

The impact of high prices on patients for other drugs, including ARVs for HIV and medications for AIDS-related infections, is also considerable. Some private insurance plans, such as those offered by Ambetter Health in 12 states, have refused to cover the cost of several single-tablet regimens (in response to a joint advocacy campaign by the AIDS Foundation of Chicago and the AIDS Institute, Ambetter agreed in March to expand its list of covered options). Numerous private insurance plans also place ARVs in their highest-coverage tiers, which can mean steep co-payment and co-insurance amounts and cumbersome prior authorization requirements—not to mention higher premium costs eventually passed on to all policy holders.

Public payers such as Medicaid are also facing higher costs for newer stand-alone and co-formulated ARVs, resulting in efforts to give preferential coverage status to older regimen options (prior authorization requirements for all single-tablet regimens other than Atripla are now required by Illinois Medicaid). And when there's a massive spike in a drug's price, such as with pyrimethamine and cycloserine, payers balk, public resources are squandered investigating work-arounds and alternatives, and lifesaving therapy is delayed.

Exorbitant drug pricing, particularly when it impedes patient access, has long been a top issue for U.S. activists. In 1989, under intense pressure from ACT UP, Burroughs Wellcome reduced the price of the first approved HIV drug, AZT, by 20 percent, which, when combined with recommended dose reductions for safety reasons, resulted in a price drop from approximately $8,000 to $2,200 a year. A more recent example is the 57 percent domestic price drop for the TB drug rifapentine, which was finally announced by its manufacturer, Sanofi US, in December 2013 following a TAG-inclusive coalition effort demonstrating that its previous price, which vacillated wildly between $51 and $130 for a box of 32 tablets, was a barrier to treatment. Sanofi US lowered the price to $32 a box, $3 below the price requested by activists.

U.S. drug pricing and access activism continues in earnest. A central player since 1998 has been the FPC, of which TAG is a member. The FPC not only pushes back against HIV and HCV medication debut and annual (and sometimes twice-yearly) price increases that perpetually threaten financially constrained public-payer systems (e.g., Medicaid, Medicare, AIDS Drug Assistance Programs [ADAPs],

the VA health system), but also works to ensure adequate support strategies for uninsured and underinsured individuals, such as patient assistance programs (PAPs), and to mitigate steep out-of-pocket costs, such as co-pay assistance programs (CAPs).

Unfortunately, the Burroughs Wellcome and Sanofi US examples are exceptions, and the net outcome of domestic pricing advocacy is a mixed bag. Some manufacturers heed a few advocacy demands, notably the need for discounted pricing for ADAPs and robust PAPs and CAPs, while sidestepping more fundamental changes promoted by activists such as ends to premium pricing and annual price increases. Others have willfully overlooked activist guidance and pushback—Gilead's HCV treatments, for example, are still priced beyond what payers can reasonably bear without significant restrictions, along with PAP barriers for many people living with HCV unable to get curative treatment.

Regrettably, there is no evidence that the U.S. public's frustration with drug pricing has brought much more than a bit of political theater and some public relations headaches for pharmaceutical executives. Cases in point: despite an unprecedented level of media attention and vilification in late 2015, the WAC prices of Sovaldi, Harvoni, and Daraprim remain at their outrageous highs. Thus, is it time for the U.S. government to consider prescription drugs as public goods subject to government regulations and price controls?

One possible intervention involves allowing Medicare—which accounted for nearly a third of prescription drug expenditures in 2014—to negotiate prices. Congress prohibited this possibility when it added the Part D drug benefit in 2003, leaving it up to the individual Part D private insurance plans to negotiate directly with pharmaceutical companies. Though these individual plans can refuse to cover some drugs for many diseases as a price-negotiation tactic, they must cover at least two products in each drug class and must cover all drugs for certain conditions, including HIV and mental illness.

Giving Medicare itself the power to bargain—which presidential candidates Hillary Clinton, Bernie Sanders, and Donald Trump are advocating—has bipartisan voter support, according to a Kaiser Family Foundation poll. There are a number of possible approaches for the president and Congress to consider, with a proposal supporting the secretary of Health and Human Services to negotiate high-cost prescription drugs included in the Obama administration's FY 2017 budget. According to the Office of Management and Budget and the Congressional Budget Office, however, the potential cost savings associated with this proposal are likely negligible. What hasn't been calculated are the cost savings that may come from bona fide centralization of price negotiations, with all drugs subject to coverage denials if unsubstantiated costs remain beyond what the public can reasonably bear.

Another strategy includes forcing manufacturers to divulge their research and development (R&D) costs along with their sales and marketing costs. Having access to this information could prove critical to payers, policy leaders, and activists in negotiating lower WAC prices and deeper discounts to insurers. According to an analysis conducted by GlobalData, many major prescription drug manufacturers spend more on marketing than on research. Additionally, manufacturers frequently cite massive R&D expenditures to justify their prices. A 2014 study conducted by the pharmaceutical industry–supported Tufts Center for the Study of Drug Development indicated that it costs $2.56 billion to develop a new drug. However, according to a 2013 report by the Drugs for Neglected Disease initiative analyzing its own drug development practices, new drugs can be developed at a cost of less than $200 million—and that's after taking into account the inherent risk of pipeline failures (see "Decoupling R&D and Egregious Pricing," page 7).

Another option to increase bargaining power that would work especially well for drugs for conditions that are rare in the United States (like TB and toxoplasmosis) is centralized procurement. In the absence of a system that can centralize purchases

and negotiate volume-based pricing and discounts with manufacturers, medications in small markets are much more susceptible to price fluctuations and shortages and end up leaving capacity-stretched hospitals and regions to fend for themselves. Also challenging are strict confidentiality rules surrounding federal 340B drug discount determinations, which apply to many programs catering to low-income patients such as those living with HIV or TB, thereby preventing providers, payers, and community advocates from sharing information and ultimately working together to ensure that affordability thresholds aren't being crossed (see "Differential Pricing" sidebar, page 8).

Shifting toward a national system that pools demand, at least for certain conditions, would not only help consolidate purchasing power, but also create a more predictable and streamlined market with less administrative and outreach work for manufacturers or suppliers. The current initiative to create a national emergency stockpile of some key TB medicines under President Obama's National Action Plan for Combating Multidrug-Resistant Tuberculosis offers an entrée into creating a more stable, broader procurement system, which will be squandered without expansion of the mandate for centralized procurement of all TB drugs.

Also of considerable interest are "march-in" rights under the 1980 Bayh-Dole Act, whereby the National Institutes of Health (NIH) can break a drug's patent(s) if federally funded research is critical to its development and "action is necessary to alleviate health and safety needs which are not being reasonably satisfied [or] available to the public on reasonable terms." Lawmakers and activists have long argued that this readily applies to prohibitively priced drugs. Thirty-five years later, however, the NIH has never exercised its march-in rights, denying five petitions—including one earlier this decade challenging the intellectual property rights of the HIV protease inhibitor Norvir (ritonavir), the price of which was raised 400 percent in December 2003.

Other strategies that have been noted by candidates, elected officials, and advocates include:

- increasing federal involvement in state Medicaid program negotiations for supplemental rebates;
- reducing the Medicare Part B percentage-per-sales-price disbursement to providers for certain drugs and biologics administered in clinics or hospitals, thereby discouraging the use of high-cost products over cheaper, efficacious options;
- replacing industry-set monopolistic pricing with cash prizes for researchers and manufacturers developing new compounds with clear therapeutic value over existing agents, along with generic competition immediately after FDA approval;
- legalizing the importation of brand-name and generic drugs from countries with price controls—an option popular with the U.S. public—but facing considerable pushback from drug makers, the FDA, and insurers;
- speeding up FDA review and approval times for generic versions of essential off-patent drugs without competition;
- making it more difficult for manufacturers to block or delay generic drug competition (e.g., Turing's ploy of maintaining Daraprim in a tightly controlled distribution system to prevent generics manufacturers from acquiring the amount of drug necessary to conduct bioequivalence studies);
- and, of serious concern to TAG and consumer protection groups, deregulating FDA approval processes to encourage lower-cost products by reducing stringent registrational requirements.

Many of the arguably pro–free market system approaches described here have, however, been introduced by federal and state policy makers, only to fizzle out or be voted down. With the growing public frustration with drug pricing practices, particular in an election year, the time is ripe for government action. And if these moderate proposals don't work—that is, if they fail to reduce budget-busting expenditures while ensuring fair profits to drive ingenuity and R&D investments—bolder steps, with an eye toward price-control measures being employed to maximize affordability in other high-income countries (see figure below), will be necessary. •

Special thanks to Sean Dickson, JD, MPH, of the National Alliance of State & Territorial AIDS Directors (NASTAD) for his review of this article.

FIGURE: Price Controls in High-Income Countries

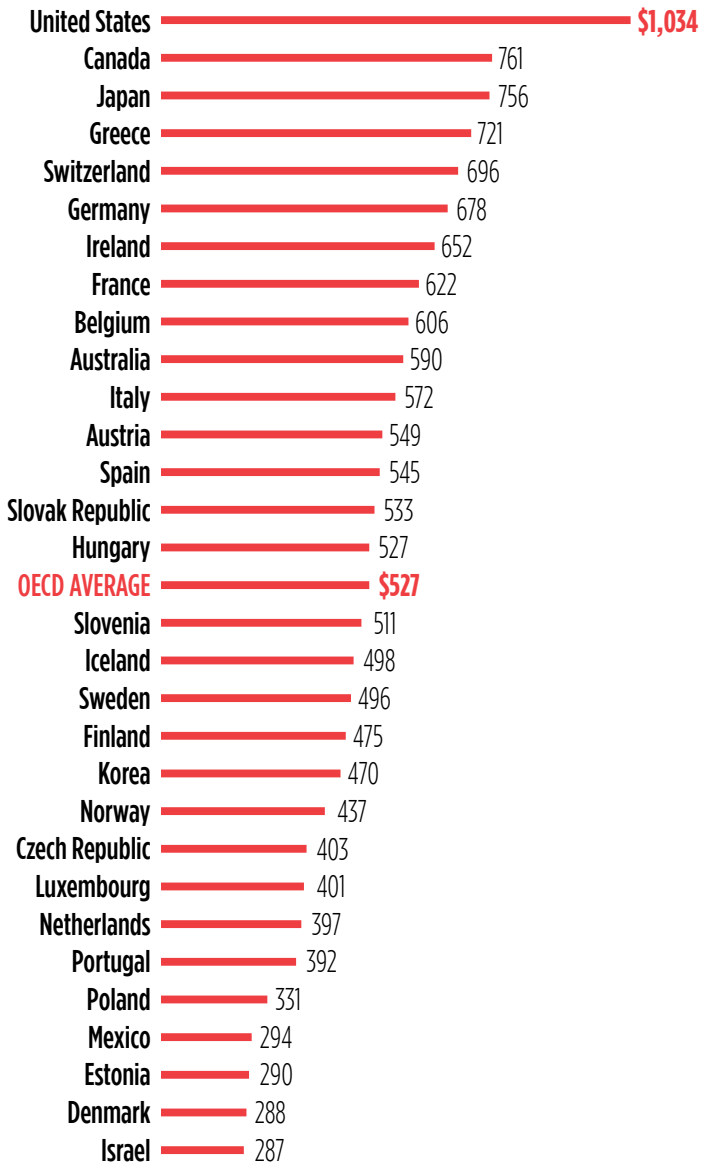
OECD member country expenditures on retail pharmaceuticals, per capita (US$), 2013 (or nearest year)

The disparity in drug prices between the United States and other high-income nations—listed in this bar graph of retail pharmaceutical expenditures are country members of the Organization for Economic Cooperation and Development (OECD)—certainly contributes to the growing public outrage at their prohibitive costs and the demand for more aggressive price controls. In fact, the United States is the only country in the OECD that does not impose price controls directly on the pharmaceutical industry.

Examples of price controls in other high-income countries include: maximum annual national budgets dedicated to drug expenditures; prescribing budgets and caps placed on health care providers and clinics; pharmaceutical company profit controls; price controls on specific drugs or within classes of drugs; setting prices based on comparisons with those in other countries; and economic evaluations.

The result? In the United States, the level of pharmaceutical spending was twice the 2013 OECD average and more than 25 percent higher than in Canada, the next highest spender. At the other end of the scale, Denmark spent less than half the OECD average.

Adapted from: OECD (2016), Pharmaceutical spending (indicator). doi: 10.1787/998febf6-en.



SIDEBAR: Decoupling R&D and Egregious Pricing—Does Innovation Suffer?

Protectors of the status quo defend exorbitant drug pricing by inciting fears that curbing the rising costs of pharmaceuticals will discourage innovation. But are affordable pricing and innovation really incompatible?

For many reasons, the answer is no. First, as estimates of research and development (R&D) costs are greatly inflated, the revenues needed to recoup R&D costs are much lower than commonly reported. Second, overpriced prescription drugs like Sovaldi and Harvoni have rapidly recouped far beyond even the highest estimated R&D costs. Older drugs like pyrimethamine and cycloserine have been on the market for decades—long enough to have recovered their costs many times over, with no additional research conducted in recent years to justify price increases. However, some opponents of drug cost controls argue that high prices allow for funding of future R&D, including the development of new products, rather than just recouping previous investments to bring existing products to market.

The pharmaceutical industry claims that its commitment to R&D of new and improved therapies is largely dependent on current sales of existing products; this is patently false. In the United States alone, the National Institutes of Health (NIH), the Department of Veterans Affairs (VA), the Department of Defense, the Food and Drug Administration, the Centers for Disease Control and Prevention, the Agency for International Development, and the Biomedical Advanced Research and Development Authority all contribute vast amounts of public resources to help subsidize R&D that will ultimately translate into substantial shareholder dividends. U.S. government funding alone accounted for over a third of all spending on R&D for tuberculosis in 2014. The discovery of Gilead's groundbreaking treatment for HCV, Sovaldi, was rooted in NIH- and VA-funded research, and its phase II clinical development was conducted, in part, by the NIH. And yet most people in this country who now need Sovaldi cannot benefit from it—due to its price, it remains largely out of reach.

But will efforts to curb rising drug costs deter innovation? Price controls, such as those in the Organization for Economic Cooperation and Development (OECD) high-income countries, have been very effective at lowering drug spending (see figure, page 6). But several critiques, including a 2008 report from RAND Health and a 2004 study from the U.S. Department of Commerce International Trade Administration, caution that those savings come at a steep cost to R&D.

The RAND report posited that price controls would create modest consumer savings but risk larger costs through decreased innovation in the long run, even leading to decreased life expectancy. Instead of price controls, it favors reducing co-pays and other out-of-pocket expenditures that affect consumers.

The U.S. Department of Commerce International Trade Administration estimated diminished revenues in the range of $18 billion to $27 billion annually due to price controls in OECD countries and concluded that, without price controls, more money would be available for R&D.

But these analyses have serious weaknesses. First, while it is logical to think that reduced revenues resulting from price controls leave less money available for pharmaceutical companies to invest in R&D, it is unclear whether windfall profits from uncontrolled drug pricing are proportionally invested back into R&D. Second, both studies extrapolate data from a small set of OECD countries—just six in the case of the Department of Commerce report—to various markets including the United States, without considering the various factors that can influence prescription drug consumption and profit. In fact, the Department of Commerce report states that its analysis is based on two very flawed assumptions: that financial resources would be available to cover higher drug prices and that increased expenditures would not

affect sales volumes. From the rationing seen with hepatitis C drugs, we already know this is not true. And the RAND analysis misses the point that if drugs are not affordable to public payers and private insurers, cost mitigation strategies for consumers, such as co-pay assistance programs, are insufficient to create adequate access.

To be sure, though, drug sales do indeed support investments in R&D, even if those are lower than what is often reported due to public support and exaggerated estimates of R&D expenditures. Also, importantly, anticipated drug sales play a large role in determining which products developers pursue, leaving out diseases that affect small numbers of people in this country.

Uncoupling the cost of R&D from sales would help with fair pricing. It would also encourage R&D regardless of how large or profitable a disease market may be. Several ideas for how to do this exist. For example, Médecins Sans Frontières and others have introduced the 3P Proposal to overhaul funding for TB R&D: Push funding to finance R&D activities up front (through grants); pull funding to encourage R&D activities through the promise of financial rewards such as "milestone prizes" on the achievement of certain R&D objectives; and pool data and intellectual property to ensure open collaborative research and fair licensing for competitive versions of the final products. As the United States continues to explore new options for curbing rising drug prices, it too should fully evaluate alternative systems for funding R&D.

With alternative research financing, more innovation could occur, without driving up prices. But even under the current R&D financing paradigm, the U.S. government can—indeed must—do considerably more to ensure fair drug pricing and access, without sacrificing innovation. •

SIDEBAR: Differential Pricing of Outpatient Prescription Drugs in the United States

Pharmaceutical industry representatives frequently argue that wholesale acquisition cost (WAC) prices do not adequately represent the actual prices paid by private or public payers for their drug products. This is true: different payers, because of price adjustments made possible through negotiations, volume-based purchasing, prompt payments, and discounts and rebates required by law, typically end up paying different amounts for prescription drugs, and pharmaceutical companies bring in revenues based on a net price below the WAC.

But how much below the WAC, exactly? And how can we work to ensure that these pricing adjustments aren't simply heralded as market-regulated price controls, but actually translate into affordable pricing for public payers, private insurers, and consumers? So many of the details pertaining to the costs of drugs—costs we cover in cash at the pharmacy, as taxpayers, and in the form of increasing private insurance plan deductibles—are shrouded in layers of secrecy. This makes it incredibly difficult for advocates to meaningfully engage with both manufacturers and payers—not to mention the array of health care and pharmacy systems shouldering some responsibility for the high costs of prescription drugs—to benchmark prices and ensure that cost does not stand in the way of access.

Average wholesale price (AWP)	The wholesaler's catalog or list price; approximately 120% of the WAC price. *Public price*
Wholesale acquisition cost (WAC)	The manufacturer's negotiable list price to wholesalers. *Public price*
Average manufacturing price (AMP)	The average price paid to manufacturers by wholesalers for drugs sold to pharmacies. *Confidential price* reported to the U.S. Centers for Medicare & Medicaid Services (CMS) by manufacturers
Best price (BP)	The lowest price paid by private payers to manufacturers for brand-name drugs, taking into account rebates, discounts, and other price adjustments. *Confidential price* calculated by CMS
Medicaid rebate	Federal unit rebate amount (URA) calculations are used to determine the rebates that must be offered to state Medicaid programs by manufacturers. URAs for brand-name drugs are either a minimum of 23.1% of the AMP or the difference between the AMP and the BP (whichever is larger), *plus* additional rebates if the AMP increases since the drug's launch price exceeds the consumer price index-all urban consumers (CPI-U) marker of inflation. The URA for generic drugs is 13% of the AMP, without other mandatory adjustments. In addition to URAs, many state Medicaid programs negotiate supplemental rebates with manufacturers. *Confidential price*
340B price	The 340B drug rebate program extends URAs to eligible health care organizations and covered entities, such as federally qualified health centers, Ryan White HIV/AIDS Program grantees, AIDS Drug Assistance Programs, and TB clinics in order to set a maximum, or "ceiling," price for outpatient drugs. Participating organizations and entities are free to negotiate additional rebates that exceed the URA; they are also allowed to bill private payers at rates closer to the public list prices, with the difference between the acquisition cost and reimbursement amount to be reinvested in patient care and services. *Confidential price*
"Big Four" prices	The Department of Veterans Affairs (VA), the Department of Defense, Public Health Service/Indian Health Service, and the Coast Guard—the "Big Four"—receive special pricing discounts on prescription drugs. These drug prices are capped at no more than 76% of the non–federal average manufacturer price (non-FAMP)—a 24% discount from the net prices wholesalers pay to manufacturers for covered drugs. This is the federal ceiling price (non-FAMP x 0.76). The VA average price may be lower than the price available to the other Big Four because the VA negotiates further price reductions using its preferred formulary. Big Four prices may be 40% to 50% of the AWP and are made public: http://www.va.gov/nac/index.cfm?template=Search_Pharmaceutical_Catalog

PrEP Pricing Problems

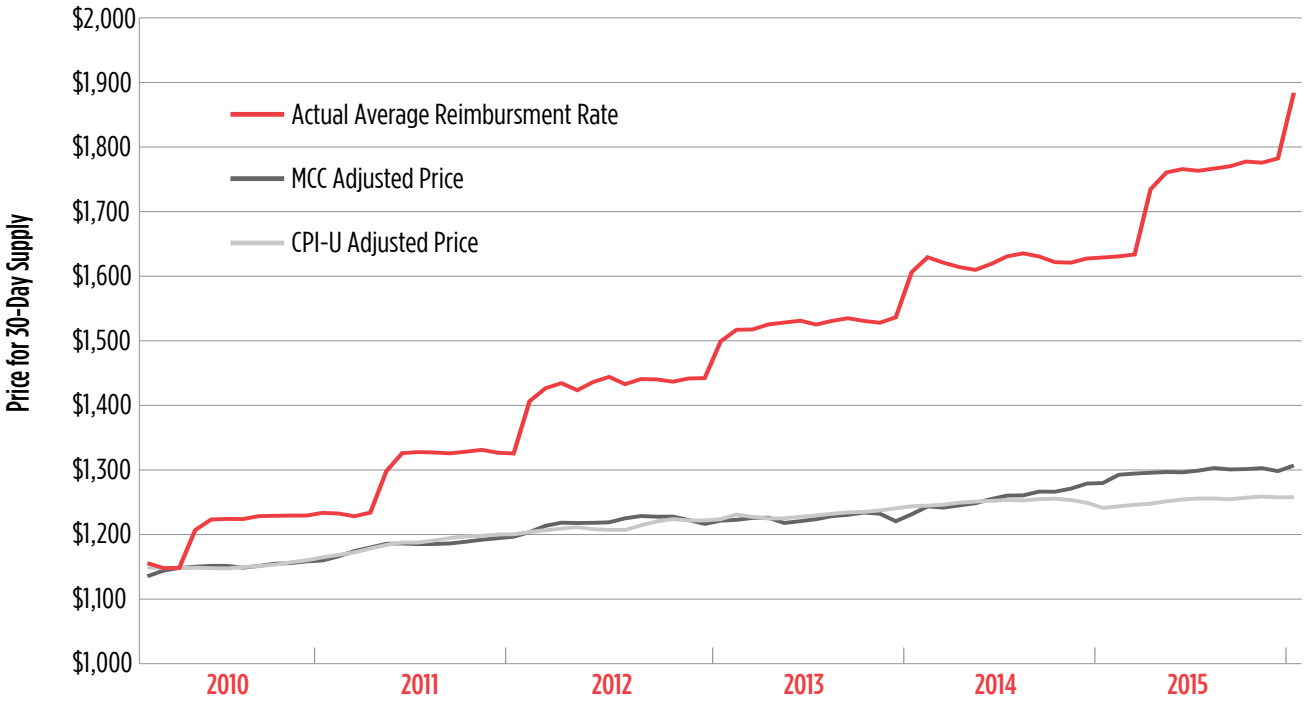
A number of barriers to pre-exposure prophylaxis (PrEP) uptake, use, and adherence have been identified—cost shouldn't be one of them

By James Krellenstein and Jeremiah Johnson

On July 16, 2012, the U.S. Food and Drug Administration (FDA) approved Gilead Sciences' Truvada (co-formulated tenofovir disoproxil fumarate and emtricitabine) for HIV pre-exposure prophylaxis (PrEP). The approval of Truvada is a historic advance for HIV prevention efforts. Results of multiple randomized controlled trials indicate that PrEP is highly effective in preventing HIV infection; the risk of sexual HIV acquisition can be reduced by more than 99 percent in individuals who take the drug consistently. Despite the overwhelming success of PrEP in preventing HIV infection in trials and postapproval demonstration projects, uptake in the real world has been painfully slow. In February of this year—nearly four years after FDA approval—Gilead estimated that only 40,000 U.S. residents were on Truvada for PrEP, less than four percent of the 1.2 million for whom the Centers for Disease Control and Prevention (CDC) estimates PrEP is indicated.

One barrier to the adoption of Truvada as PrEP that has received surprisingly little attention from activists is its price. Truvada, despite costing very little to produce, is an incredibly expensive drug to purchase, with an average retail reimbursement price of over $1,700 per 30-day supply in 2015.

FIGURE: Actual Truvada Reimbursment Cost vs. CPI-U and MCC Adjusted Prices



The average retail reimbursement price for Truvada grew six times faster than overall inflation (consumer price index for all urban consumers [CPI-U] inflation) and four times faster than inflation for drugs and other medical commodities (medical care commodities [MCC] inflation).

U.S. Bureau of Labor Statistics, Consumer Price Index for All Urban Consumers: Medical Care Commodities [CUUR0000SAM1] [Internet]. Saint Louis (MO): Federal Reserve Economic Data, Federal Reserve Bank of Saint Louis (cited 2016 March 1). Available from: https://research.stlouisfed.org/fred2/series/CUUR0000SAM1.

U.S. Bureau of Labor Statistics, Consumer Price Index for All Urban Consumers: All Items [CPIAUCSL] [Internet]. Saint Louis (MO): Federal Reserve Economic Data, Federal Reserve Bank of Saint Louis (cited 2016 March 1). Available from: https://research.stlouisfed.org/fred2/series/CPIAUCSL.

Bloomberg Intelligence Biotech Drug Explorer [Bloomberg Terminal]. New York (NY): Bloomberg L.P. [cited 28 February 2016]. Available (on Bloomberg Terminal) from: BI PHRMX <GO> "Drug Explorer."

Truvada was first approved in 2004 to treat HIV in combination with other antiretrovirals, but researchers were also interested in its potential to be used as PrEP, ultimately leading the National Institutes of Health to fund the key studies that established its value for HIV prevention. Although Gilead Sciences now profits handsomely from the use of Truvada for PrEP, it funded none of the research that led to the drug's approval for this indication. Despite this, the company has refused to ensure affordable access to Truvada and, since 2010, has been increasing its price at a rate six times that of inflation—more than doubling the price since 2004.

The exorbitant price of drugs that treat HIV has long been a concern of AIDS activists. Indeed, the first drug approved for the treatment of HIV—zidovudine, commonly known as AZT—was, at the time of its introduction, the most expensive drug in history despite costing almost nothing to produce and being discovered through taxpayer-funded research. Ironically, just to ensure that people with AIDS were able to get AZT, Congress was forced to appropriate even more taxpayer money to create the Health Resources and Services Administration's AZT Drug Reimbursement Program in 1987—which would lay the groundwork for the AIDS Drug Assistance Program (ADAP)—to subsidize the high price of the drug as well as give people without health insurance access to it. In 1990, as more antiretrovirals were approved, Congress incorporated ADAP into the Ryan White HIV/AIDS Program, which to this day ensures that uninsured and underinsured people living with HIV can get antiretroviral drugs.

Although the Ryan White program has been highly effective in ensuring near-universal access for HIV-positive individuals in the United States, no such programs exist for those who are HIV-negative. In lieu of this, people taking PrEP who lack health coverage are forced to rely on Gilead's medication assistance program (MAP) to obtain this incredibly expensive therapy. In addition to being without any form of health insurance, individuals must have an income less than 500 percent of the federal poverty level ($55,990) to be eligible for the program. The MAP, however, is not broadly used because it does not cover required PrEP-related medical costs such as quarterly blood work.

People who have some form of health care coverage, however, must use their insurance to pay for Truvada and, in the case of private insurance plans, use Gilead's co-pay assistance program (CAP) to pay for the often-exorbitant out-of-pocket expenses (e.g., deductible spend downs, copayments, and coinsurance amounts). For people with high-quality coverage, such as through "platinum" health insurance plans purchased in the health insurance marketplaces (exchanges) mandated by the Affordable Care Act (ACA), this poses almost no challenge as their out-of-pocket prescription expenses are likely below Gilead's CAP allowance of $3,600 a year. Unfortunately, for many health care plans, the expected out-of-pocket costs for a person on Truvada would far exceed $3,600 a year. Health insurance plans are allowed by statute to charge up to $6,850 a year in out-of-pocket expenses for covered services, including pharmacy benefits.

The discrepancy between the maximum out-of-pocket expenses and Gilead's CAP is particularly problematic for individuals who have "bronze" and "silver" plans purchased through the exchanges. More than 90 percent of health insurance plans purchased on the exchanges have been bronze and silver. On almost all health insurance plans, individuals have to pay a certain amount—known as the deductible—before receiving any benefits from the health insurance plans (and before co-payments or co-insurance requirements begin). Eighty-seven percent and 21 percent of bronze and silver plans, respectively, have combined medical-drug benefit deductibles in excess of $4,000 per year, with 38 percent of bronze plans having a deductible above $6,000.

For many individuals covered by bronze or silver plans, the out-of-pocket expenditures for a year of Truvada can exceed $3,000—even assuming a full use of the Gilead CAP—posing a significant barrier to many individuals who need PrEP. Indeed, even a much smaller out-of-pocket cost can become a deterrent. According to data reported in February at the Conference on Retroviruses and Opportunistic Infections by a Northern California Kaiser Permanente program, individuals with a co-pay of over $50 were significantly more likely to discontinue PrEP—31 percent of those with the higher co-pay dropped PrEP, compared with 21 percent for those with co-pays less than $50.

The Patient Advocate Foundation, funded in part by Gilead, does have a program to reimburse out-of-pocket costs in excess of the CAP allowances for those meeting certain criteria (income less than 400% of the federal poverty level, with adjustments for cost of living), although it appears that few people actually know about this program. Each layer of complexity that is added to covering out-of-pocket costs needlessly obstructs access to this incredibly important HIV prevention tool, particularly when support services like prevention case management are rarely available.

An obvious solution to this problem would be for Gilead to simply increase the CAP maximum to the statutory maximum of out-of-pocket expenses. A near doubling of its CAP contribution might seem like a large financial contribution, but it is important to remember that by matching the ACA maximum out-of-pocket cost, Gilead would almost certainly be increasing its sales volume. Additionally, given that Gilead's present market cap—the total dollar market value of the company's outstanding shares—is over $125 billion (as of early March 2016), the company is likely capable of weathering an even more substantial cut in profit.

Unfortunately, it can be challenging to determine the impact on Gilead of any such changes given the longstanding tradition of cloak-and-dagger secrecy when it comes to pharmaceutical companies' full budgets, particularly their research and development costs. Instead, we are always led to believe that the pharmaceutical industry is toiling in climates of scarcity due to sky-high research and development costs that we are assured exist even though no one is allowed to see proof.

If increasing access for communities that have seen the AIDS epidemic rage on for over three decades really is the main priority, advocacy pushing to improve and expand both the Gilead MAP and CAP are just two objectives. Advocacy is also needed to ensure that insurers and government are doing their parts to end the ongoing HIV epidemic; that includes expanding Medicaid

in all 50 states so that low-income people vulnerable to HIV infection have access not only to PrEP, but also to the care needed to support its safe and effective use.

Even if the ACA were to be fully implemented in all states, however, the high price of Truvada makes it challenging to effectively engage public and private payers regarding the need for unencumbered access to PrEP and related prevention services. Facing such enormous costs means that both private and public insurers are hard pressed and, arguably, more justified in implementing cumbersome and time-consuming prior authorization requirements, increasing cost-sharing responsibilities, mandating specialty pharmacy ordering, and enacting other deterrents that frequently discourage uptake. The high price, even after taking into account discounts and rebates that are applied to drugs being covered by federal or state spending, is also likely to serve as a deterrent to state and local governments' exploring the development of other public programs, such as the Washington State PrEP Drug Assistance Program, to expand access. One of the best examples of how potential systemwide costs can set the stage for battles over coverage comes from the United Kingdom, where the National Health Service is likely dragging its feet on approving PrEP largely due to the potential cost.

Gilead's reluctance to prioritize access to PrEP is ethically troubling on two fronts. First, Gilead is only grudgingly engaging in measures to improve access to a medication in which they themselves have invested little. The initial studies that ultimately led to approval of Truvada as PrEP were funded solely through taxpayer money via the U.S. National Institutes for Health. Gilead did donate free drug to these studies, but considering how cheap it is to make Truvada (in 2005, Gilead stated that the cost of manufacturing and distributing a month's supply was less than $30), its contribution is unquestionably negligible compared with what the American public invested. This fact has not deterred Gilead from maintaining the already exorbitant price of Truvada and even disproportionately increasing its cost relative to the rate of inflation.

Second, Gilead is profiting from its PrEP monopoly while strategically allowing HIV infections to continue. Gilead currently possesses five of the six top HHS recommendations for HIV treatment, meaning that its best business model for maximizing profit most likely does not involve a full scale-up of PrEP and a good faith effort to end the epidemic. Gilead would profit most by providing PrEP to populations at lower risk of getting HIV to avoid cutting too far into its HIV treatment market.

Given that communities with lower incomes tend to disproportionately bear the burden of HIV, the fact that PrEP continues to be far more accessible to individuals with greater resources could be seen as good news for Gilead's shareholders.

It may seem cynical and unfair to accuse Gilead of perpetuating an epidemic for financial gain, but this is not the first time that Gilead has privileged profit far above access, equity, and public health (see "Greed and the Necessity for Regulation," page 2).

While Gilead has participated in state- and city-level efforts to increase access to PrEP, including the opening of a PrEP clinic in Atlanta and guaranteeing additional discounts for Medicaid as part of the New York State plan to end the AIDS epidemic, these efforts are merely a drop in the bucket compared with what will be required to provide access to comprehensive HIV prevention for all key populations. At a minimum, Gilead must increase its CAP contribution to match the current maximum out-of-pocket cost for ACA coverage plans, which for 2016 is $6,850 per year for individual plans (and $13,700 for a family plan—an important consideration for young people, who are especially vulnerable to HIV infection, still on their parents' policies). Gilead must also widely and aggressively promote its MAP and CAP and reduce paperwork burdens for individuals to apply. If Gilead were truly invested in ending the epidemic, it would lower the price to a level that wouldn't burden overstretched public programs; minimize the need for prior authorization and prohibitive cost-sharing requirements; and otherwise demonstrate a commitment to an evidence-based public health strategy through tremendous public investments.

Without a doubt, it is in everyone's interests for the pharmaceutical industry to continue making profits; we must always weigh activist demands for price reductions with the true costs of developing innovative treatments and the costs of providing access to nations in the developing world. However, when the pursuit of profit so clearly detracts from access and ensures huge disparities in care between the rich and poor in America, particularly when Gilead refuses to disclose research and development budgets to justify such high profits from PrEP and its HIV and hepatitis C medications, it is time for activists to apply whatever pressure is necessary to create meaningful change.•

The Low Cost of Universal Access

Generic treatments for HIV, viral hepatitis, and cancer can be affordably—and profitably—mass-produced for broad, unobstructed availability

By Tracy Swan

TAG talks with Andrew Hill, senior visiting research fellow in the University of Liverpool's Department of Pharmacology, about his group's work exploring what it actually costs to profitably mass-produce generic drugs for HIV, viral hepatitis, and cancer. These estimates are based on the molecular structure, complexity, dose, and duration of treatment with each drug.

Achieving these prices—between $200 and $400 for a course of sofosbuvir and daclatasvir for hepatitis C virus (HCV), for example—is necessary to facilitate the mass scale-up of HCV treatment programs in low-, middle-, and high-income countries.

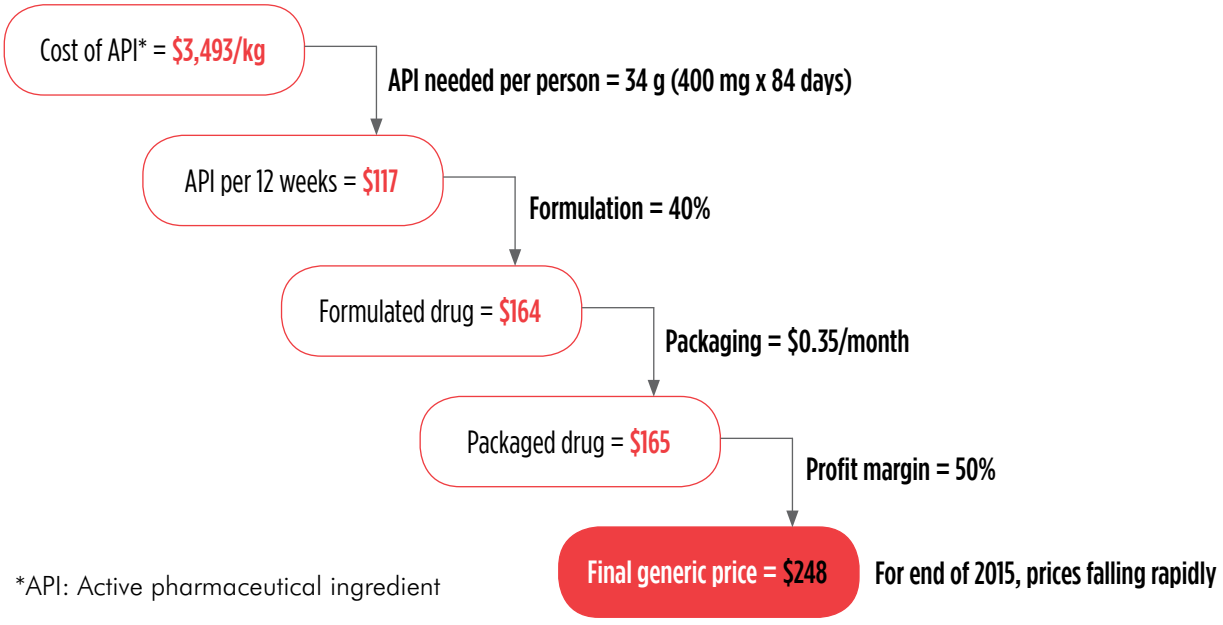
TS: What inspired you to look at production costs for hepatitis C treatment?

AH: By 2000, our group—and others—found out that HIV could be treated for about $500 per year. As soon as people realized that HIV treatment could be made for a dollar a day, universal access could be achieved. Now, over 15 million people are on treatment.

We decided to do the same thing for hepatitis. We looked at the doses and structures of the drugs and found that they were actually very similar to those used for HIV—often by the same research teams at the same companies. That was the inspiration.

The feedback I've had from doctors in almost every country is that prices for HCV drugs are too high everywhere; they have to come down in Brazil, in Thailand, in the U.K. We've got this opportunity to eliminate the HCV epidemic, and we are not doing it because the drugs are too expensive.

FIGURE: Current Costs of Production: Sofosbuvir



*API: Active pharmaceutical ingredient

Source: Hill A, et al. Significant reductions in costs of generic production of sofosbuvir and daclatasvir for hepatitis C treatment in low- and middle-income countries (Abstract PE13/43). 15th European AIDS Conference; 2015 October 21–24; Barcelona, Spain.

TS: The initial U.S. launch price for sofosbuvir [Sovaldi, a drug that is the backbone of many HCV regimens] was $1,000 per pill. Thanks to work from you and your colleagues, we know that it can be profitably mass-produced for a little more than $1 per pill. It's been really helpful for people doing hepatitis C treatment access advocacy to have this solid, credible information about production costs. We can now discuss the discrepancy between the price of a drug and what it costs to produce it.

AH: I agree, it gives people a term of reference to then say to a company, "If your drug is extremely cheap to make, and you haven't done that much spending on research and development, how can you justify the prices that you are charging for your medicine?"

In the U.K., we probably have enough money—with the price that Gilead charges —to treat about 8,000 people a year. Now, there are 200,000 people with hepatitis C in the U.K. It would take 25 years to treat all of those people at the current prices.

TS: What about access to HCV treatment—and other drugs—in low- and middle-income countries?

AH: Companies will say, "we have authorized the use of our drug in 90 or 100 countries," but if you look, some are tiny little islands in the Pacific or the Caribbean that hardly have any people living there at all. If you look at the number of countries where a company has actually filed and registered their drug—and where they have made sure that there is a generic producer—it might be only a small fraction of the original number of countries in their access programs. For example, Gilead claims that 101 countries have access to sofosbuvir. We've looked at the countries where sofosbuvir is actually registered and available through a voluntary license; this covers only a quarter of the hepatitis C epidemic—it is not universal coverage by any means.

I can see a time coming in the next 12 months where treatment with sofosbuvir and daclatasvir [Bristol-Myers Squibb's drug, branded as Daklinza] will cost no more than $300 or $400 per person—we are nearly there. The prices are only going to come down over time and make it more affordable to treat people.

TS: You are looking into drugs for other conditions….

AH: After we did the analysis of hepatitis C drugs, we looked at entecavir, a drug used to treat hepatitis B. It was incredibly cheap to make—it almost cost more money to put the drug into a bottle and package it than the drug itself. Entecavir could cost $24 per person per year because the dose is only half a milligram per day; it's like a grain of salt per person, per day.

Tyrosine kinase inhibitors [used to treat breast cancer, lung cancer, liver cancer, and leukemia] are amazingly cheap, in a way that I had never anticipated. These lung cancer and breast cancer treatments are sold in the U.S. for well over $100,000 per person per year. They can be made for $100 or $200 per person per year.

Showing that cancer can be treated cheaply, as we found for HIV and viral hepatitis, could cause a real backlash. People cannot access the treatments that could save their lives because of the high profits that a company is demanding.

TS: Have you looked at production costs for tuberculosis drugs?

AH: Treatment of multidrug-resistant tuberculosis [MDR-TB] is complicated. There's a real complexity to TB treatment at the moment, which means that drugs are going to remain expensive. It involves a wide variety

of drugs, produced in quite small quantities, to treat a selected group of people. You are not talking about treating millions of people for HIV with mass-produced drugs that are all the same.

With MDR-TB, the challenge now is to make treatment as uniform as possible so we have single combination treatments that then could be made cheaply and mass-produced in a more standardized way. We are not going to be stuck with this problem for that long—when we look at the cost of the newest drugs, like delamanid or bedaquiline, we believe that, fundamentally, they should be cheap drugs to make. This depends on producing large qualities of drugs, to treat large numbers of people. We haven't had negotiations with the right governments yet to ensure the orders of a large enough supply to get prices down.

TS: What about tenofovir and TAF for HIV treatment and prevention?

AH: If you go to South Africa to buy a year's supply of tenofovir, it will cost about $60—just above $1 per week. It is going to go off patent soon; by the end of 2017 or early 2018, you should be able to buy generic tenofovir very cheaply.

Now, Gilead is trying to sell a version of tenofovir called TAF [tenofovir alafenamide], by claiming that it has a better safety profile in terms of bone loss and kidney function. If you look at the difference in bone loss between normal tenofovir and TAF, it occurs within the first six months of treatment. In the START study, that difference had no clinical significance at all.

With any drug, you have to find out the safety profile in the long term. There are a lot of things that we don't know about TAF. Other drugs can lower its concentration and might lower its efficacy. It's quite a fragile drug in terms of drug-drug interactions, unlike normal tenofovir. TAF might have some problems down the line, when it is used in real-life studies and outside of phase III clinical trials.

We know a great deal about normal tenofovir. If someone takes normal tenofovir, in the first few months of treatment they will get a slight reduction in bone density and a slight change in kidney function—which may worsen over time. It is not clear whether TAF will have less kidney toxicity than normal tenofovir over time.

TS: How would you like to see some of your work used by activists and other people who are deeply concerned about drug pricing?

AH: In the United Kingdom, we now have people buying drugs through buyer's clubs, for PrEP [HIV pre-exposure prophylaxis] or to be cured of hepatitis C. It is a last resort and unfortunate that we have to do this. But if it is a choice between buying a drug from a recognized generic supplier in India—which supplies drugs all over the world—or having nothing, the benefit of generic drugs is going to outweigh the risks for many people. We have to be careful to make sure that any drugs coming in are from authorized suppliers and that they have been approved by a regulatory authority.

People need to buy these drugs through established channels, to look for particular websites—we are working with a group called fixhepC.com. They have already treated over 1,000 people and cured almost all of them with drugs that they have secured themselves. If you work with established networks and you know that the drugs being distributed through those networks are curing people, you've got a bit more assurance that you are going to get a supply of good-quality drugs. Just buying them randomly on the Internet is not a good idea, because you don't know where the drugs are coming from.

TS: We often hear that these profits are essential for innovation.

AH: Gilead spent 11 or 12 billion dollars on sofosbuvir and a maximum of $500 million on the clinical trials program. So there you have about $12.5 billion. By the end of 2015, Gilead had already sold $31.5 billion of Harvoni and Sovaldi. So they have a profit of just under $20 billion—for drugs with another 15 years of patent life.

The average pharmaceutical company will spend 70 to 80 percent of profits on marketing, advertising, and lobbying governments—and put the intellectual property of a drug in Ireland to avoid paying taxes.

I'd love it if pharmaceutical companies genuinely spent the majority of their profits on research and development and then produced new drugs. Then I wouldn't be protesting. •

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ABOUT TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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