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From advocacy to austerity: The new role of the U.S. public sector in HIV drug development and access

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Abstract

Whereas advocacy was once the driving force for U.S. public support for HIV drug development and access, the nation's response to the global epidemic is now shaped by austerity. Extending past scholarship about the role of advocates and governments in support of drug development and access around the world, in this article I identify key shifts in U.S. public sector support over the past 40 years. During the early years of the AIDS epidemic, the U.S. government and civil society expedited drug development for antiretroviral therapy (ART). After the turn of the century, a new wave of advocacy expanded access for ART, including to low- and middle-income countries through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). On the heels of these accomplishments, advocates and governments set an ambitious agenda to 'End AIDS' by 2030. However, progress toward this goal has been limited by a new era of austerity, as demonstrated by U.S. government spending on HIV.

Keywords

HIV; drug development; access to medicines; history of pharmaceutical markets; medical anthropology

Introduction

After more than 40 years since the beginning of the HIV epidemic, there are approximately 38 million people living with the virus, but just over half (21.7 million, 59%) are on antiretroviral therapy (ART) (UNAIDS, 2019). With funding from the U.S. government, primarily through the President's Emergency Plan for AIDS Relief (PEPFAR), global ART coverage and HIV-related health outcomes have improved significantly since the turn of the century. However, the epidemiological burden remains highest in low- and middle-income countries. And since the PEPFAR budget has plateaued for the past decade (PEPFAR, 2016) progress in improving outcomes has been severely limited. Meanwhile, the number of FDA-approved drugs for HIV treatment has skyrocketed.

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How did we get here? When did domestic drug development for HIV therapy begin to outpace the world's largest bilateral initiative to advance global access to ART? Beginning in the late 1980s, U.S. government agencies responded to the call of advocates to save the lives of people who had acquired the virus by deregulating domestic drug development. Through the next decade, the rate of pharmaceutical production gained momentum, as several pharmaceutical firms rushed into the market. After the turn of the century, and in response to a new wave of advocacy for global access to ART, the U.S. government launched PEPFAR, and thereby greatly expanded access in low- and middle-income countries. Meanwhile, the U.S. also increased NIH funding for clinical research to support domestic development (Fleming, Greene, Li, Marx, & Yao, 2019). Building on these accomplishments in recent years advocates and governments developed a new vision: to 'End AIDS' by 2030.

To realise this vision will require additional public support to scale up HIV testing and treatment programmes, including by committing more resources to end the epidemic. Unfortunately, the U.S. government has not risen to the challenge. While the U.S. has played a leading role in the global response to the epidemic, after the onset of the 2008 financial crisis a new era of austerity emerged and the PEPFAR budget plateaued. Ten years later, planned spending is only slightly higher than pre-crisis levels, and recently the current administration proposed a 25% cut to all foreign aid for global health. Meanwhile, annual NIH-wide funding for HIV has also flatlined, averaging $3 billion per year since 2008 (U.S. National Institutes of Health [NIH], 2019). Yet, we have witnessed an unprecedented trend in new drug approvals: between 2008 and 2018, the FDA approved 20 HIV therapies for commercial use; over the previous three decades, the agency had only approved 29 (U.S. Food and Drug Administration [FDA], 2019). Of course, this increase in the number of new drug approvals does not necessarily translate to greater therapeutic benefit. But it does represent a new strategy among pharmaceutical firms to recombine existing drugs and commercialise new products.

Scholarship in the social sciences of medicine provides important perspectives about the development of the HIV treatment market, and contemporary issues in ART access. Scholars in this field have examined several ways access to ART has been shaped by political and economic issues around the world, and have mapped disparities in access, especially in low- and middle-income countries (Crane, 2013; Farmer, 2001; Nguyen, 2010). These scholars have also demonstrated how international political dynamics have influenced the global response to the epidemic, including by highlighting the role of states and activists in extending the right to treatment for all (Biehl, 2004, 2007; Epstein, 1995, 1996) and showing how bilateral aid limited the development of the public sector (Pfeiffer, 2013). Recently, scholars have also charted a path for inquiry about contemporary trends in the global response to the HIV epidemic, including by examining the emergent discourse about the 'end of AIDS' (Kenworthy, Thomann, & Parker, 2018). Meanwhile, related scholarship has examined the relationship between public and private actors in other pharmaceutical markets, including by showing how drug development stitches together the interests of public and private actors yet the financial interests of pharmaceutical firms tend to overdetermine the clinical research enterprise (Hayden, 2003; Petryna, 2009; Rajan, 2006).

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Adding to this rich body of literature, in this article I trace the changing role of the U.S. public sector across the history of the market for HIV treatment. First, I review two periods in the history of the HIV epidemic when drug development was expedited and access to ART was expanded. Next, I review U.S. planned spanned on foreign aid for HIV during a period of rapid domestic drug development. In each section, I highlight how public actors, including civil society, government agencies, and research universities have created opportunities for private pharmaceutical firms to commercialise new drug products, such as by opening more efficient pathways for drug development. I also highlight how pharmaceutical firms have shifted their business strategies in response to public advocacy. For example, following advocacy to expand ART access to low- and middle-income countries, brand name firms outsourced the work of manufacturing and distribution to generic firms, and began to re-commercialise existing products into fixed-dose combination tablets. Lastly, I ask what the cap on U.S. foreign spending for HIV means for the ongoing management of the global epidemic, including the future role of the private sector.

In sum, my analysis focuses on the historical and contemporary role of the U.S. public sector in the ongoing response to the epidemic, spanning the history of the market from its inception to the present day. No comparable history of the HIV treatment market has been represented in the literature of the social sciences of medicine to date. Thus, I intend to contribute to existing scholarship by offering this historically-informed inquiry, and hope to push future scholarship to represent similar histories of pharmaceutical markets in order to more adequately explore the social lives of medicines (Whyte, Geest, & Hardon, 2002) and the ways they are shaped by the public sector through processes of co-production (Jasanoff, 2004).

Materials and methods

The findings presented in this article draw from document analysis involving diverse resources, including pharmaceutical market reports, public health research articles, and documents from governmental and non-governmental agencies, spanning a period from the early 1980s to the present day. Reports about pharmaceutical markets including mergers and acquisitions (M&A) were found through queries on BMI Research (bmo.bmiresearch.com) and Crunchbase (crunchbase.com). Public health and clinical research articles were sourced from Internet-based resources hosted by the U.S. National Institutes of Health and National Library of Medicine (pubmed.gov; clinical-trials.gov). Information about the commercial availability of specific antiretroviral drugs was sourced from public data made available by the U.S. Food and Drug Administration (FDA) and the European Medicines Association (EMA). While the regulatory approval dates of the FDA were used in the analysis, information provided by the EMA about the pharmaceutical manufacturer and relevant clinical studies expedited the research.

While the data presented was sourced materials accessed from university libraries and online resources, the analysis has also been informed by ongoing ethnographic research about HIV drug development and access, including interviews and participant observation with clinical research investigators, public health providers, and patients in high-, middle-, and low-income countries. Conducted over the past eight years, this research has examined several

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issues in clinical research for drug development, and traced contemporary challenges related to new health care policies, including the Affordable Care Act and Universal Health Coverage. Furthermore, the analysis has been informed by a series of applied research studies about best practices for ensuring access to medicines and continuity of care, which the author has conducted in collaboration with public health departments in the United States.

Saving lives: How public interests created commercial opportunities

In the early years of the AIDS epidemic the actions of patient advocates, health organisations, and regulatory agencies created opportunities for pharmaceutical firms to more efficiently commercialise new drug products. This began in the process of developing Retrovir, the very first HIV therapy. While the development of Retrovir (or 'AZT' as it would become known more commonly) was made possible in part by Burroughs Wellcome, which had dedicated resources to research about the drug, it was also shaped by the actions of U.S. government agencies, patient advocates, and people living with HIV. Through contestation and collaboration, this group of stakeholders propelled the drug through the research and development (R&D) pipeline.

Indeed, Burroughs Wellcome had devoted significant resources to research about retroviruses, which positioned the firm to bring the first drug to market for HIV treatment. Whereas many large pharmaceutical firms had filled their R&D pipelines with candidates to address more lucrative medical needs, Burroughs dedicated resources to research for rare conditions. In the five years before the commercialisation of Retrovir, Burroughs Wellcome and its parent company spent $726 million on R&D in related therapeutics, including to develop the pharmaceutical compound, azidothymidine ('AZT') as a cancer therapy (O'Reilly, 1990). While that attempt was not successful, the firm was left with a viable drug candidate for HIV therapy, and the capacity to bring a new drug to market.

This time, Burroughs Wellcome was able to move Retrovir through the development pipeline across early phases of research, however, the development of the therapy was also significantly supported by U.S. governmental agencies concerned by the growing public health emergency. For example, even though a phase-II study evaluating the safety of the drugs found it had significant side effects, including severe intestinal problems, damage to the immune system, nausea, vomiting and headaches, regulators deemed it safe enough to treat the deadly illness it was meant to address. Since people without treatment were quickly dying, regulators allowed an exception to standard protocol, and elected to move AZT into a phase-III clinical trial, where investigators would evaluate the efficacy of the experimental medication. At this stage of development, a group of stakeholders convened to support the successful design and completion of the trial. These stakeholders consisted of representatives of industry, regulatory agencies, and scientific teams, as well as activists and people living with the virus themselves, who had fought for their right to sit at the decision-making table, and cultivated a kind of 'lay expertise' (Epstein, 1995).

Collectively, this group of stakeholders determined the trial would enrol nearly 300 participants; one half of the group of participants would receive Retrovir, the experimental

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medication, and hence, comprise the ‘experimental’ arm, while the other half of participants would receive a placebo, comprising the ‘control’ arm. In the first few months of the study, one participant taking Retrovir died. Meanwhile, over this same timeline a total of 19 participants in the placebo arm died. When investigators observed this clear difference, the study was quickly unblinded. Those still alive in the placebo arm were given Retrovir. In 1988, the FDA approved the treatment for commercial use. Thus, the development of Retrovir was supported not only by the pharmaceutical firm, but also governmental agencies and a group of public stakeholders, which propelled the drug through clinical research, across the desks of regulators, and onto the market.

With the commercialisation of Retrovir, it became clear that civil society and the public sector had strengthened a commercial opportunity. In fact, as Retrovir remained the only commercial product available for HIV treatment for the next three years, it generated significant revenue for Burroughs Wellcome. Sales of Retrovir reached $113 million in 1988, its first year in the US market (Pink Sheet, 1988). This number grew to $134 million in 1989 and $170 million in 1990. However, AIDS activists soon argued for fair pricing. Burroughs Wellcome justified the $6,300 annual (wholesale) price of the new product based on the high costs of R&D, production, and related expenses. Advocates contended Burroughs Wellcome had used government resources and regulatory approval mechanisms to repackage a failed drug candidate for cancer into the product they marketed as Retrovir (Emmons & Nimgade, 1991). After two years of ongoing debate over the price of the drug, the firm cited the ability to lower operational costs for ongoing production and distribution, and lowered the price by 20%. Sales plateaued, and Burroughs recorded only a $7 million gain in sales for fiscal year 1991. At this nexus of public advocacy and commercial opportunity, the HIV treatment market began to take shape.

In the early 1990s, the processes of drug development and conditions of access in this new market would continue to form, as advocates urged regulators to expedite drug development to commercialise new HIV therapies. Specifically, activists argued that people living with HIV could not wait for lengthy clinical trials to be completed to gain access to new HIV therapies. In response, regulators changed the usual requirements for efficacy studies. Instead of requiring the use of longitudinal health outcomes as clinical endpoints for the trials, for the first time in the history of the HIV market they allowed ‘surrogate endpoints’ to be used, including end points defined by levels of detectable virus (HIV viral load) and T-cells in the blood of participants (Murray, Elashoff, Iacono-Connors, Cvetkovich, & Struble, 1999). Using these new measures of pharmaceutical efficacy streamlined the path to commercialise new drugs. Whereas it might have taken eight to ten years to bring a drug from phase one to the commercial market under the standard clinical research model, the new research model reduced the timeline to as few as two years.

In effect, activists facilitated the deregulation of drug development, which free-market economists had been striving toward for decades. Whereas previous reform efforts led by free-marketers had been dismissed, when people affected by the virus themselves critiqued the government’s practices as overly paternalistic practices, they achieved reform (Gere, 2017). And by making drug development faster, regulators and activists offered pharmaceutical firms more attractive opportunities to enter the market. Though few firms

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had active R&D programmes for antiviral therapeutics in-house, those that did could now move their drug candidates through the development pipeline more quickly, and those that were considering entering the market could more clearly predict the returns on investment.

And invest they did. At this time, firms began pursuing mergers and acquisitions (M&A). By merging with and acquiring smaller biotechnology companies that had promising drug candidates in the development pipeline, pharmaceutical firms could enter the HIV treatment market more efficiently than through in-house R&D. The first major merger to affect the HIV treatment market was completed in 1989, as Bristol-Myers merged with Squibb, creating the world's second-largest pharmaceutical company (Crunchbase, 2019). In less than two years operating as Bristol-Myers Squibb (BMS), the firm received FDA approval for Videx (didanosine, dideoxyinosine, ddI), which became just the second HIV treatment on the market. This rapid development was made possible for the newly merged company because Bristol-Myers had secured an exclusive license to produce and test dideoxyadenosine (DDA) and dideoxyinosine (DDI) two years before the merger completed. For Squibb, the merger represented an opportunity to capitalise on the licensing acquisition and R&D programme Bristol-Myers had established. And since activists had reduced the necessary investment of time and resources to bring a new drug to market the firm had an efficient path forward for commercialising drug candidates in its newly-merged development pipeline.

Of course, investing in a HIV treatment product during this time was still a significant risk because the market was young and relatively untested. In fact, in an independent report about the newly restructured company, Videx was referred to as 'the biggest wild card in the Bristol Myers Squibb pipeline' (Bernstein Research, 1989). Compared to Retrovir, Videx seemed to offer higher efficacy, lower toxicity, and fewer side effects. However, the product still posed risk for the company because pricing would likely be affected by political pressure, and market growth was predicted to be relatively slow, since 'fear, social stigma, and concerns about insurance coverage' would likely limit screening and diagnosis, 'particularly in high-risk, asymptomatic populations' (Bernstein Research, 1989).

Nevertheless, Videx had significant potential. By 1993, pharmaceutical market reports projected that Videx would generate annual revenues between $250 and $300 million. These projections relied on a few key assumptions. The first assumption was that the total number of new diagnoses would increase each year. That is, as infections increased, the market potential of the drug would as well. The second assumption was that people on treatment would begin living longer. By sustaining life, the product would also extend its own commercial potential (Bernstein Research, 1989, p. 147, Table 53). Indeed, the market projections were partially correct. While the number of new infections declined after 1990, the total number of people living with HIV only increased.

And when the epidemic grew, so did the market. Through the combination of an accelerated regulatory pathway and an efficient commercial strategy, several more firms also brought new HIV treatment products to market at this time. For example, beginning in 1995 and continuing through the end of the decade, GlaxoWellcome completed a series of M&A deals through which the firm acquired six HIV therapies. In the final deal of this M&A series, the

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firm merged with SmithKlineBeecham, and emerged as a leader in the market under a new name: GlaxoSmithKline (GSK). By the end of this series of M&A deals, GSK held six HIV therapies in its commercial portfolio, including Retrovir, Epivir, Combivir, Ziagen, Agenerase, and Trizivir. The firm also held marketing licenses for more promising drug candidates that would be commercialised in the years to come.

Thus, the early HIV treatment market was shaped by public actors aiming to save the lives of people who had acquired HIV. Through contestation and collaboration, patients, advocates and regulators changed the conditions of clinical research and thus shaped an efficient pathway for firms to bring new products to market. This sparked competition in an emerging market. Firms commercialised HIV therapies as quickly as they could through intensive M&A activity. At the same time, the potential value of HIV therapies began to expand because they were extending the lives of those who had acquired the virus and the number of people living with HIV was growing. In fact, amid this frenzied period of market activity, the safety and efficacy of medications used to treat HIV advanced through the advent of highly active antiretroviral therapy (HAART), which effectively suppressed viral replication and significantly improved patient outcomes (for details, see Lange & Ananworanich, 2014). However, access to these new antiretroviral drugs (ARVs) remained limited for several years because pharmaceutical firms were focused on marketing the drugs in high-income markets, where they could recover the costs of the capital-intensive M&A activities of the past decade.

Expanding access: When public-private relations were rearranged

Moving into the twenty-first century the mechanics of the market were reconfigured. Whereas public support had expedited drug development and advanced therapeutic efficacy over the previous decade for people living in high-income countries, at the turn of the century a new wave of activism emerged, which focused on expanding access around the globe. Soon after domestic policies including the Ryan White Act expanded access across high-income countries, global advocacy expanded access in low- and middle-income countries, where HIV incidence and prevalence were highest. This wave of activism once again involved alliances among people living with HIV, advocates and governments. However, this time activism took aim at licenses, and broke open intellectual property (IP) regimes. While successfully expanding access, the actions of civil society and governments also influenced pharmaceutical firms to pursue other commercial strategies, which supported drug development and access, but not through M&A or R&D. Instead firms offered voluntary licenses to generic firms and developed combination therapies, thereby working within the confines of new regulatory mechanisms by leveraging existing assets.

The era of expanding access began to emerge in the late 1990s through controversies over patent rights for antiretrovirals, including in Brazil (Biehl, 2004, 2007; Nunn, 2009) and perhaps most infamously, with the case of ‘Big Pharma vs. Nelson Mandela’ in South Africa (e.g. Fisher & Rigamonti, 2005). Following these disputes, the new era for expanding access gained momentum in 2000 when the UNAIDS Secretariat introduced the Accelerated Access Initiative (AAI) through which pharmaceutical firms would offer ARVs at reduced prices to a range of low- and middle-income countries (WHO and UNAIDS, 2002). In

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addition to establishing the first differential pricing scheme for ARVs, this new Initiative provided evidence that ARVs could be safely and effectively used in low-resource settings, where some had presumed there would be low adherence, which would lead to drug resistance and thus, exacerbate the impact of the epidemic (Crane, 2013). While the AAI was supported by the pharmaceutical industry, the terms of the agreement were extremely limited in reach and did not include sufficient price reductions (‘t Hoen, Berger, Calmy, & Moon, 2011).

However in 2001 the mission of expanding access across the globe gained momentum, including as member nations of the World Trade Organization (WTO) established the Doha Declaration, which affirmed patent rules should be interpreted and implemented to protect public health, including by promoting access to medicines for all (‘t Hoen et al., 2011). This was made possible largely because the WTO agreement on Trade-Related aspects of Intellectual Property Rights (TRIPS) had been previously established in 1995, requiring WTO member nations to maintain standards of IP protection and procedures for dispute settlement, which could be used to secure existing licenses, or break open property regimes in the interest of public health. Before TRIPS pharmaceutical patent policies and practices varied greatly, and many national governments and bilateral trade agreements, did not consider patents on pharmaceuticals to be in the public interest (‘t Hoen et al., 2011). The Doha Declaration built on this framework, affirming patent rules should be interpreted and implemented for the protection of public health including by promoting access to medicines for all. Backed by the WTO and Doha, governments began to override patents, such as by issuing compulsory licenses, maintaining ‘high standards for patentability to ensure only innovative products are rewarded with patent monopolies’ and upholding oppositions to patent applications (MSF Access Campaign, 2012). In effect, with the support of the WTO, countries forced the hand of the pharmaceutical industry and increased access around the globe.

The mission of expanding access was soon subsidised by governments, including through the support of PEPFAR and multilateral organisations, such as the Global Fund to Fight AIDS, Malaria and Tuberculosis. While PEPFAR was a bilateral initiative led by the United States and became a primary source of support for HIV funding in several countries around the world, including throughout subSaharan Africa, the Global Fund represented a new approach to financing the international response to the epidemic through partnerships with governments, civil society, technical agencies, the private sector, and people living with HIV. And in combination with compulsory licensing agreements for generic drugs, this swell of foreign aid for HIV greatly increased access to ARVs in low- and middle-income countries. However, it did not guarantee significant returns on future investment for brand name pharmaceutical firms, which derive most of their revenue from sales in high-income countries, such as the United States.

In response to these collective actions to expand ART access around the globe, firms shifted their commercial strategies. Specifically, brand name firms formed strategic partnerships with generic firms that would manufacture and distribute generic medicines in low- and middle-income markets. Through these strategic alliances, brand name firms essentially outsourced the work of expanding access, including by granting voluntary licenses to

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generic firms, and collecting a percentage of revenue from sales of their products. Several firms also turned their attention to other therapeutic markets, and stopped commercialising new HIV therapies at this time. Meanwhile, firms that continued to commercialise products for HIV treatment co-formulated active pharmaceutical ingredients (APIs), many of which were already used in single-drug tablets (or 'monotherapies') and marketed them as fixed-dose combination tablets (or 'combination therapies') under new brand names.

The value of combination therapy was supported by clinical research findings that demonstrated a combination tablet was non-inferior to the single drug tablets (LaMarca et al., 2006) and would assist adherence because a single pill would be easier for a patient to take than two separate tablets (Maitland et al., 2008). The single tablet would also be protected by a new patent, and sold at a higher price. Combination therapy accelerated the rate of drug production in the new century, as firms combined several existing APIs to commercialise new drug products. In fact, between the years 2000 and 2008, firms not only commercialised nine new monotherapies, but also brought five new combination therapies to market. By the end of 2008, there were 29 FDA-approved HIV therapies available for commercial use in the United States, and many of these therapies were also available for use around the world.

In these key ways, initiatives to expand access rearranged relations between public institutions and the pharmaceutical industry. Whereas the activist demand to save lives had opened the door for the deregulation of drug development and invited firms to commercialise new products quickly through mergers and acquisitions, initiatives to expand access limited the potential revenue for brand name firms in some markets, but also opened opportunities for these firms to leverage their assets, including through generic contracts and by combining existing products.

Ending AIDS: Public and private commitments today

Extending support for drug development and access, in recent years advocates, governments, and health organisations have rallied around a new vision: ending AIDS by 2030. Led by the Joint United Nations Programme on HIV/AIDS (UNAIDS), this new vision aims to align the interests of donor governments, civil society, and private industry toward achieving three key metrics: 90% of people living with HIV will know their HIV status; 90% of people who know their HIV status will be on ART; and 90% of people on ART will have suppressed HIV viral loads (Cohen, 2018). According to the midterm report from UNAIDS, this collective effort has contributed to significant progress in the global management of the virus. In 2016, 'more than two-thirds of all people living with HIV globally knew their HIV status' and 'among those who knew their HIV status, 77% [57– >89%] were accessing antiretroviral therapy' meanwhile '82% [60– >89%] of people on treatment had suppressed viral loads' (UNAIDS, 2017). Unfortunately, the pace of progress has been uneven around the globe. Across several countries and regions of the Caribbean, Asia and the Pacific, these metrics are not being met, meanwhile 'key populations' including gay men and other men who have sex with men, sex workers, transgender people, people who inject drugs, prisoners and other incarcerated people and migrants and their sexual partners are being 'left behind' (UNAIDS, 2017).

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The reason the goals are not being met and select nations and populations are being left behind is directly linked to the flatlining of foreign aid among donor governments in an ongoing era of austerity (Basu, Carney, & Kenworthy, 2017). In fact, following the global financial crisis, the source of most HIV funding shifted from foreign aid to domestic resources (UNAIDS, 2019). In many countries, this meant that decisions to care for key populations were left to governments that also criminalise them, including through laws penalising sex work, sex between men, and injection drug use (Davis, Goedel, Emerson, & Guven, 2017).

While the decline of foreign aid among donor governments is a global problem, in the case of foreign aid for HIV the issue has been most clearly illustrated by trends in U.S. public sector support, as demonstrated by the PEPFAR budget. Shortly after the 2008 financial crisis, the PEPFAR budget plateaued. Whereas the budget had grown quickly from $2.3 billion in 2004 to more than $6.7 billion annually by 2009, after the financial crisis set in, all programme spending stagnated. In fact, today the annual budget is virtually the same as it was before the crisis. PEPFAR is now also operating under a new strategic initiative, which has narrowed the organisation's focus from 35 countries and regions across the globe to 12 countries in sub-Saharan Africa in addition to Haiti (Office of the Spokesperson, 2017). The stated aim of the strategy is to increase the impact of the programme's funding where it has proven successful. However even in focus countries that have met key epidemiological targets, the current administration has proposed substantial budget cuts, including a 44% decrease in funding for Kenya (compared to the 2017 budget) (Green, 2019). While the U.S. remains the biggest donor for the management of the ongoing epidemic in low- and middle-income countries (LMICs), these cuts are indicative of the new era of austerity, and suggest U.S. foreign aid for HIV may continue to decline in the near future.

During this era of austerity, U.S. domestic funding for HIV has also plateaued, as evident in organisation-wide NIH funding for HIV, which has hovered around $3 billion annually. With little public support to continue to develop novel therapies, pharmaceutical firms have continued to extend the value of their assets by co-formulating existing drugs and novel compounds into combination therapies. Whereas the previous generation of combination therapies co-formulated two APIs into fixed-dose combinations, the new generation combines three or four APIs from multiple drug classes into a single tablet. By developing these 'multi-class combinations' pharmaceutical firms have been able to commercialise many new products. Whereas in 2008 there had been 29 HIV therapies on the U.S. market, by the end of 2018 there were 20 additional FDA-approved therapies to treat HIV (FDA, 2019). Thus, despite ongoing austerity measures, pharmaceutical firms have benefited from the most rapid period of pharmaceutical production this market has ever seen. At the same time, antiretroviral products that were originally commercialised for HIV treatment have been recommercialised for biomedical HIV prevention (through a method known as HIV pre-exposure prophylaxis, or 'PrEP' for short), thus limiting cost for drug discovery, and expanding the market size for ARVs.

To truly improve HIV-related health outcomes and move closer to the end of the epidemic, this trend will need to change. Programmes for expanding access need to keep pace with the rate of pharmaceutical commercialisation. Unfortunately, despite steep economic growth in

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recent years, the U.S. government has proposed a 25% reduction in all global health funding by 2020 (Rose & Janeen Madan, 2019), so it seems assistance will need to come from different sources, including domestic governments, philanthropies, and multilateral organisations. Fortunately, there is some reason for hope. For one, multilateral organisations are scaling up investments. In its 6th replenishment, the Global Fund realised its goal of raising $14 billion to support the ongoing response to the overlapping epidemics of HIV, tuberculosis and malaria, including through record-high support from the Gates Foundation (Chadwick, 2019). However, significantly more support will be needed to move beyond the rhetoric of ‘ending AIDS’ (Kenworthy et al., 2018), and achieve the goal. UNAIDS estimates $26.2 billion will be required by 2020 in order to effectively control the epidemic, unfortunately current funding commitments fall short of this goal. By the end of 2018, $19 billion was available for the AIDS response in LMICs, and over half (56%) of total resources in these countries were derived from domestic sources (UNAIDS, 2019).

Several questions remain unanswered about who will bridge the funding gap to support the ongoing response to the epidemic, and moreover, how relationships between public and private actors will be rearranged. One pressing question concerns the ways public actors will work with private industry to reach the common goal of controlling the epidemic. Another question concerns the future role of the pharmaceutical industry: In the wake of several new drug approvals, as firms continue to benefit from federal funding and the recycling of old products with new compounds, what role will they play in expanding access around the globe? The history of HIV clearly demonstrates that relationships between public actors and private industry have shaped our collective response from the development of the very first HIV therapy to the present-day push to expand access around the globe. As new public-private partnerships are forged, how will civil society and governments work effectively with private industry? In the past, answers to these questions saved millions of lives. Today, we need new answers to these old questions if we are to end AIDS in this lifetime.

Conclusion

In review of the past 40 years of the HIV epidemic, this article examined the shifting role of the public sector in drug development and access, including by tracing trends associated with U.S. advocates and governmental agencies. Whereas in past years the U.S. government and civil society expedited drug development and a network of advocates, donor governments and multilateral agencies, in recent years progress has been limited by austerity, as demonstrated by caps in U.S. government spending to promote global ART access. The article also offered an over-arching perspective about the ways a therapeutic market has been stitched together at the uneasy intersection between public and private institutions. If advocates and public agencies first created opportunities for private pharmaceutical firms to commercialise products in an emerging market, international advocacy later broke open intellectual property regimes and thus limited market potential. However, more recently, ongoing public sector support for private drug development has allowed pharmaceutical firms to craft new solutions to remain profitable, including by recombining existing drug products and marketing them under new brand names. And in the decade following the financial crisis, as firms have commercialised an unprecedented number of new products in high-income countries, support for access in low- and middle-

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income countries has stagnated. Ultimately, 'biomedical innovation' including the repackaging of existing compounds into multiclass combination therapies has outpaced foreign aid for ART. And thus, over a four decade- long history in which civil society, government, and industry have jointly facilitated HIV drug development and access, the article traced the shifting role of the U.S. public sector – whereas it was once associated with advocacy, following the global financial crisis U.S. public support has been shaped by austerity.

It is my hope future research in the social sciences of medicine will continue this form of analysis, which looks across the logics and practices of pharmaceutical firms, governmental agencies, public health departments, and advocacy organisations to deepen contemporary inquiries about our collective health. Since all histories are partial, I fully expect other scholars will write additional histories of HIV, and I sincerely hope that our combined inquiries will productively inform the ongoing management of the HIV epidemic and several further issues influencing and the uneven distribution of the global burden of disease today. If this history has shown nothing else, it certainly shows that a commitment to collective action is required to make a lasting impact on the epidemic and improve health equity.

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