Agenda item 7

UNAIDS/PCB (43)/18.27

UPDATE ON THE ACCESS COMPONENTS OF THE UNAIDS 2016-2021 STRATEGY: REMOVING ACCESS BARRIERS TO HEALTH TECHNOLOGIES FOR HIV AND ITS CO-INFECTIONS AND CO-MORBIDITIES IN LOW- AND MIDDLE-INCOME COUNTRIES

11-13 December 2018 | Geneva, Switzerland
UNAIDS Programme Coordinating Board
Issue date: 19 November 2018

Additional documents for this item: *None*

Action required at this meeting—the Programme Coordinating Board is invited to:

1. Recall the commitments at previous Programme Coordinating Board meetings and relevant paragraphs from Resolution 70/266 of the UN General Assembly – Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030, June 2016: which recognized that access to safe, effective and affordable medicines and commodities for all, without discrimination, in the context of epidemics such as AIDS is fundamental to the full realization of the right of everyone to enjoy the highest attainable standard of physical and mental health.

2. *Take note* of the findings in the report.

3. *Request* UNAIDS to:

    a. *Develop* a programme of work, through 2021, for the implementation and monitoring of the relevant recommendations in this report and to fully maximize existing and new financial and human resources that can promote access to affordable technologies for all, and ensuring sufficient technical and financial resources to implement such programme of work;
    b. *Engage* in advocacy and support, where relevant, to countries, multilateral organizations, the private sector and civil society to collectively ensure innovation and continued access to medicines that meet the needs of all people living with HIV and to prevent transmission of HIV;
    c. *Provide* support to low- and middle-income countries to take all necessary steps to address current and future challenges to ensure quality-assured, safe and affordable HIV-related medicines and other health technologies;
    d. *Convene* on a regular basis, key actors and stakeholders across the HIV response to discuss and address critical challenges and opportunities related to ensuring innovation and access to medicines and other health technologies for HIV;
    e. *Report* the progress in the implementation of these decision points to the Programme Coordinating Board no later than the December 2021 Board Meeting.

Cost implications: None

ACRONYMS

AIDS	acquired immune deficiency syndrome
ARV	antiretroviral
ART	antiretroviral therapy
FTC	emtricitabine
Global Fund	Global Fund to fight AIDS, Tuberculosis and Malaria
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IP	intellectual property
MDG	Millennium Development Goal
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
NGO	nongovernmental organization
PAHO	Pan American Health Organization
PCB	Programme Coordinating Board
PEPFAR	President's Emergency Plan for AIDS Relief
PrEP	pre-exposure prophylaxis
R&D	research and development
SDG	Sustainable Development Goal
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TRIPS	trade-related aspects of intellectual property rights Agreement
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UN	United Nations
US	United States (of America)
WHO	World Health Organization

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. **Improving access to affordable and effective antiretroviral treatment and reducing AIDS-related deaths has been at the heart of UNAIDS' mandate.** UNAIDS has played a critical leadership role advocating for universal access to HIV treatment, including registration of key antiretroviral medicines (ARVs), development of paediatric formulations, and the full use of safeguards and flexibilities included in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).

2. **UNAIDS should intensify efforts to promote access to affordable medicines across low- and middle-income countries, in accordance with its mandate.** UNAIDS can:
   - utilize its convening authority to maintain an open and positive dialogue between diverse stakeholders on issues related to innovation and access to medicines;
   - promote capacity building for national governments to address threats and opportunities or to itself engage in advocacy where needed;
   - act as a strong voice on the particular opportunities, best practices, concerns and challenges related to access to paediatric and adult ARVs and other HIV-related health technologies; and
   - maintain expertise on new developments and provide such information to its partners, government counterparts and civil society.

3. **While data and analysis of HIV-related technologies are superior compared to other therapeutic areas, there are multiple gaps.** They include:
   - pricing data for upper-middle-income countries;
   - registration data across low- and middle-income countries;
   - information on the availability and suppliers of ARVs;
   - comprehensive data on medicines to treat opportunistic infections, paediatric HIV, coinfections and comorbidities, and diagnostics;
   - patent analyses for low- and middle-income countries; and
   - real-time market data that can provide rapid information on uptake and use of priority products.

   UNAIDS has an important role in collecting data, convening stakeholders for joint analysis and encouraging collaboration to improve data collection.

4. **Advocacy and mobilization are essential for overcoming barriers to affordable and appropriate health technologies**. Advocacy can ensure that political barriers, a lack of political will or countervailing commercial considerations are overcome.

5. **Nongovernmental organizations (NGOs) and treatment advocates are losing resources, capacity and space to advocate for access to affordable health technologies.** NGOs, advocates and activists are central to many of the advances that have improved access to medicines. However, the resources, technical capacity building and opportunities that enable them to promote the most effective responses to AIDS are diminishing. Without the leadership of civil society and treatment advocates, it will not be possible to meet the needs of populations who are denied access to treatment due to political, institutional or economic considerations.

6. **Local production of medicines is increasing in countries outside of India.** An estimated 80% of all ARVs used to treat people living with HIV are manufactured in India. Additionally, new producers of ARVs and other medicines are emerging elsewhere, including in Algeria, Bangladesh, Brazil, China, Egypt, Morocco, the Russian

Federation and Uganda. Some of the companies produce medicines in partnership with originators.

7. **There is enhanced protection of intellectual property (IP) in low- and middle-income countries, in particular through free trade agreements.** Such rules can create barriers that prevent the introduction of low-cost generic ARVs and appropriate formulations or that undermine the development of fixed-dose combinations for treating HIV and coinfections and comorbidities.

8. **WHO-led programmes and the efforts of the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund), the United States President's Emergency Plan for AIDS Relief (PEPFAR) and UNITAID have improved the timely and efficient registration of ARVs and other key products. However, many delays and challenges remain.** Registration continues to lag for many products, particularly in countries that are low-income, that have introduced new forms of market exclusivity that delay registration, or that have insufficient resources or complex approval processes.

9. **Upper-middle-income countries face significant challenges to address high prices of new health technologies.** These challenges may deepen as upper-middle-income countries transition from Global Fund-supported programmes, are excluded from industry-driven access initiatives and face growing demands to introduce stricter IP rules, which hinder generic competition.

10. **Neglected populations, especially children living with HIV and tuberculosis (TB) patients, struggle to get access to affordable and appropriate technologies to address HIV and related coinfections and comorbidities.** Several factors undermine access, including insufficient research and development (R&D) to achieve appropriate formulations of existing or new drugs, and a lack of appropriate pricing, licensing, use of TRIPS flexibilities and rapid registration of existing medicines.

11. **TRIPS flexibilities have been important for expanding access to HIV treatment**. Governments have applied strict patentability criteria and employed compulsory licensing, and civil society has used patent oppositions and advocated for compulsory licensing to prevent or overcome patent barriers.

12. **Multiple secondary patents delay generic competition**, create supply shortages or impede the development of appropriate combinations or formulations. Applying strict patentability criteria and enabling oppositions and third-party observations can ensure that only merited patents are granted.

13. **Voluntary licensing plays an important role in expanding access to HIV treatment.** The Medicines Patent Pool (MPP) has been successful in widening access for low- and low-middle income countries, but many upper-middle-income countries are excluded from those licensing agreements. Some originator companies still do not sign agreements with the MPP, which affects affordability and availability of ARVs. The MPP publishes details of all its license agreements and has improved some key terms and conditions. License agreements not negotiated through the MPP are often not published and may include more restrictive terms and conditions. Due to greater collaboration between originator and generics companies via voluntary licensing, generics firms are less interested in challenging patents filed by originator companies in low- and middle-income countries.

14. **Competition remains the most effective tool to reduce prices of medicines, improve the availability of health technologies, alleviate or address product**

shortages and encourage the development of appropriate formulations or fixed-dose combinations. In the absence of competition, negotiations, including pooled procurement, can help reduce prices of new medicines. Some companies employ tiered pricing to commercialize their products in low- and middle-income countries.

15. **Some companies continue to employ donation programmes in low- and middle-income countries.** WHO guidelines discourage donation programmes, except in limited circumstances.

16. **Shortages and stock-outs, while episodic, are serious threats to affordable medicines and could occur more frequently in the future.** While each instance of a shortage and/or stock-out is due to unique circumstances, these events can occur regularly and may result in frequent treatment interruptions or suboptimal treatment and prevention strategies. Legitimate efforts to address environmental pollution could further stress the supply of active pharmaceutical ingredients and raw materials and exacerbate shortages and stock-outs.

17. **The HIV pipeline features new compounds, new technologies for the dosing and delivery of medicines, long-acting formulations and biologics, all of which may present novel access challenges.** New health technologies protected by IP could reduce access in low- and middle-income countries, especially when competition is limited or when originator companies do not sign licensing agreements. New long-acting formulations will involve product development, health systems and access challenges. Biological drug development could generate effective HIV therapies, but there are concerns that biologics will not be affordable for use in low- and middle-income countries unless significant policy interventions are made.

18. **New approaches to Research & Development (R&D), especially R&D incentives that separate the cost of R&D from the final product price, could present opportunities to address the particular needs of children living with HIV and people with TB. It could also remove trade-offs between innovation and access.** Some product development partnerships have already implemented and successfully used delinked models of R&D. Such new models of R&D could provide a sustainable incentive framework for developing new medicines in areas with insufficient market incentives, including medicines that meet the needs of children living with HIV and people with TB.

19. **Efforts to combat antimicrobial resistance could boost resources and encourage innovative approaches to R&D, but they could also lead to gaps.** Member States have agreed to encourage new R&D models that do not rely on high prices or large volumes, as well as encourage the development of and increased access to diagnostics that improve treatment accuracy. The response should also include strategies to promote access to new and existing health technologies.

20. **There is a need for the Joint Programme to engage with concerned stakeholders to elaborate a consistent policy framework to address coinfections and comorbidities.** Some coinfections, such as TB, are leading causes of morbidity and mortality in people living with HIV. Other public health challenges, such as noncommunicable diseases, are increasingly a cause of death and disability as people with HIV live longer lives. In the context of declining donor funding for AIDS responses, the access challenges (and costs) of other diseases present a challenge both to government budgets and to people living with HIV.

INTRODUCTION

21. Access to medicines is recognized as a core aspect of the human right to health. In July 2016, the UN Human Rights Council adopted a resolution on access to medicines. The resolution reaffirms the importance of using TRIPS flexibilities to advance public health outcomes in the areas of research, development and access to medicines and other health technologies.[1] The Council issued a new road map on human rights and HIV in 2018, including measures to promote access to affordable medicines.[2]

22. At the 35th Programme Coordination Board (PCB) meeting, the NGO delegation submitted a report titled *When rights cause wrongs: addressing intellectual property (IP) barriers to ensure access to treatment for all people living with HIV*.[3] In response, the PCB approved a resolution directing the Joint Programme to "produce a synthesis report of existing research and literature on IP-related and other factors impacting the availability, affordability, and accessibility of treatment and diagnostics for HIV and coinfections in lower-middle-income countries."[4]

23. In 2016, a report was submitted for discussion.[5] The PCB agreed to prepare a subsequent report on progress in implementing the UNAIDS Strategy 2016–2021 with respect to overcoming IP-related barriers and other factors affecting access to medicines, and to identify gaps, challenges and best practices to better support countries.[6]

24. The current report covers the period from 1999 to the present, with a particular focus on developments in the past decade related to access to medicines for HIV, its coinfections and comorbidities. Ensuring access to medicines requires a range of actions and activities across UN agencies, governments, industry, product development partnerships, foundations and civil society. This report surveys their collective policies and actions.

25. In order to fulfill the scope and requirements of the PCB's request, the current report drew on three sources of information:
    - a comprehensive literature review examining a range of primary and secondary source materials over the last two decades;
    - key-informant interviews with 25 stakeholders across government, intergovernmental organizations, industry, civil society and academia; and
    - case studies focused on multiple products to prevent and treat HIV and related coinfections, with an additional, in-depth review of pipeline technologies.

26. The report findings are presented below and are divided into the following sections:
    - **Overview of the access** components of the UNAIDS 2016–2021 Strategy and an update on progress and key challenges to fulfill the strategy;
    - **Overview of the data** related to HIV-products and the remaining data gaps;
    - **Case studies of products to treat or prevent HIV, HCV and TB**; and
    - **The role of UNAIDS** in promoting access to health technologies.

INITIATIVES, LEGAL AND POLICY TOOLS AND BEST PRACTICES TO OVERCOME ACCESS BARRIERS

27. The international community has scaled up numerous initiatives and best practices, as well as harnessed legal and policy tools to overcome access barriers to affordable medicines.

28. One critical component of affordable ART has been the availability of donor funding to pay for ART, which also facilitates price reductions and increased availability even after the onset of strengthened competition. Donors contributed more than US$ 8 billion towards the HIV response in 2017, although increased future donor funding is not expected. Respondents noted that inadequate funding could drive up ARV prices in the future.

29. Prior PCB UNAIDS reports on this topic, in 2014[7] and 2016,[8] provided full descriptions of the relevant initiatives, legal and policy tools and best practices to prevent or overcome access barriers. They included:
    - the relevant flexibilities available under the TRIPS Agreement;
    - voluntary licensing and particularly licensing through the Medicines Patent Pool;
    - the WHO, WIPO, WTO Trilateral Cooperation on Public Health, IP and Trade;
    - collaborative efforts to expand and accelerate registration (including the WHO Prequalification Program, the US Food and Drug Administration's “tentative approval" (fast-track) process, the Collaborative Registration Procedure managed by WHO, and the African Medicines Regulatory Harmonization Initiative;
    - competition law and policy;
    - pooled procurement and price negotiations;
    - local production of medicines; and
    - product development partnerships.

30. The UN Secretary-General convened a High-Level Panel on Access to Medicines to “review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies”. Released in September 2016,[9] the High-Level Panel’s report included several recommendations for improving policy coherence and governance regarding innovation of and access to health technologies. The Panel noted that lack of access to medicines, vaccines, diagnostics and other medical commodities, as well as a lack of new tools for tackling health problems such as antimicrobial resistance, was a problem for all countries.

31. At the 68th World Health Assembly in 2015, Member States extended the time frame of the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property until 2022.[10] At the 71st World Health Assembly in 2018, Member States requested WHO to develop a road map to outline the programming of WHO’s work on access to medicines and vaccines, including activities, actions and deliverables, for the period 2019–2023.[11]

ACCESS TO MEDICINES IN THE 2016–2021 UNAIDS STRATEGY: OVERVIEW, PROGRESS AND CHALLENGES

32. In addition to the explicit HIV-related targets, the Sustainable Development Goals (SDGs) is relevant to the AIDS response in numerous respects. For example, SDG3 addresses access to affordable medicines as well as increased R&D for medicines and vaccines in accordance with the flexibilities included in the TRIPS Agreement and Doha Declaration.

33. The international community, led by UNAIDS, has also committed to the 90–90–90 targets for 2020 and to ending the AIDS epidemic as a public health threat by 2030. Those targets require speed, equity and efficiency, including for achieving improved paediatric treatment options, affordable prices, uninterrupted availability of ARVs and timely access to new HIV-related technologies. The 2016–2021 UNAIDS Strategy includes specific commitments related to ensuring access to HIV-related products.[12]

34. HIV prevention, diagnosis and treatment have evolved. Improved first- and second-line treatment regimens, salvage therapies and pre-exposure prophylaxis (PrEP) have each presented access-related challenges, including IP-related challenges.

35. Diagnosis is the first step towards accessing treatment or preventive care. The first of the 90–90–90 targets requires having at least 90% of people living with HIV know their HIV status. Diagnostics are critical to achieve that target. There are multiple barriers to the effective use of diagnostics, which UNAIDS is tackling through multiple interventions, including the Diagnostics Access Initiative. Barriers to the scale-up and use of diagnostics and treatment monitoring tools, such as viral load and CD4 tests, are not discussed in this report, but merit attention.

36. Gender inequalities, gender-based discrimination and human rights violations create barriers to access. UN Women's *Key barriers to women's access to HIV treatment* report examines the key issues women face in accessing treatment, including:
    - a scarcity of data on women's experiences with HIV treatment;
    - violence against women and the fear of such violence;
    - difficulty traveling to access care;
    - unpaid care work responsibilities, including for family members affected by HIV; and
    - stigma and discrimination from health-care workers.[13]

Assessment of UNAIDS Secretariat contribution to the implementation of UNAIDS Strategy

37. The UNAIDS Secretariat has a significant track record working with Cosponsors, governments, civil society and private sector to expand access to affordable treatment. One key area of work has been UNAIDS' advocacy to promote local production of ARVs in sub-Saharan Africa with WHO, UNIDO, UNCTAD, under the leadership of the African Union. The Secretariat has also convened critical discussions on access to medicines, including a joint meeting with the government of Brazil, WHO, UNITAID and the MPP in Brasilia in 2013 on access to medicines challenges in middle-income countries, and a regional discussion on access to TB treatment, convened with the government of Belarus, the Global Fund and the Stop TB partnership in 2016. The Secretariat is leading the implementation of the West and Central Africa catch-up plan, with a dedicated focus on paediatrics, to support countries from this region to bridge the treatment gaps, considering that this region presents the lowest levels of treatment coverage rates worldwide.

38. UNAIDS, PEPFAR and partners have launched the Start Free, Stay Free, AIDS Free Initiative, which by 2020 aims to end the AIDS epidemic among children, adolescents and young women.

39. Many respondents noted that the UNAIDS Secretariat would need to restore its technical expertise on access-related issues in order to improve its ability to share its institutional perspectives with other agencies. However, respondents did also praise the efforts of Secretariat staff members to fill those gaps. Several concerns were expressed.

40. Firstly, respondents noted that UNAIDS Secretariat participation has always been welcomed and that the Secretariat added an important voice to the discussions on access to medicines and health. The UNAIDS Secretariat should strengthen its role in particular coordinating and governance mechanisms that are critical for assuring innovation and access to medicines. This includes active participation with relevant technical expertise during board meetings and technical sessions hosted by UNITAID, at the TRIPS Council at the World Trade Organization and at other UN bodies, including WHO.

41. Secondly, the UNAIDS Secretariat should make full use of its "convening authority" to maintain an open dialogue between diverse stakeholders on issues related to innovation and access to health technologies. Efforts by the Secretariat to hold consultations to examine access to medicines challenges were widely appreciated. The lack of additional consultations supported by the UNAIDS Secretariat was deemed a "lost opportunity".

42. Thirdly, the UNAIDS Secretariat should mobilize capacity building of national governments to address access threats, and continue to advocate for opportunities to improve the affordability and accessibility of medicines. This is particularly relevant at a time of significant changes in the global ARV and HIV-related health technologies markets and when many countries are "transitioning" from established multilateral initiatives, notably the Global Fund.

43. Fourthly, the UNAIDS Secretariat should be a stronger voice on key concerns surrounding access to ARVs. While other agencies and nongovernmental entities also focus on access challenges related to ARVs, they are also engaged in a variety of other access challenges related to coinfections and comorbidities or drugs and diseases not related to HIV.

44. Fifthly, the UNAIDS Secretariat should focus upon emerging access barriers to ARVs and other health technologies and, in collaboration with Cosponsors, share such information with governments, civil society and other partners.

45. In summary, the UNAIDS Secretariat's contribution to efforts to expand access to treatment and prevention technologies should be reinforced. There is broad consensus that the unique voice and the advocacy and coordination role of the UNAIDS Secretariat on access to health technologies needs to be strengthened.

DATA TO MEASURE, EVALUATE AND ACT UPON ACCESS-RELATED BARRIERS

46. All respondents agreed that data describing access to affordable HIV-technologies (in particular for ARVs) were significantly more sophisticated, in-depth, accurate, up-to-date, and translated for public use, compared to any other therapeutic area.

47. Since 2001, Médecins Sans Frontières (MSF) has regularly published reports on ARV price trends, presenting data on the lowest prices from originator and generic manufacturers and on the IP status of selected medicines. The reports have also documented efforts of governments and civil society to overcome IP barriers to generic competition for ARVs.[14]

48. The Clinton Health Access Initiative has provided significant data, including pricing data for medicines and diagnostics.

49. Pooled procurement mechanisms, including those managed by the Global Fund, the Pan American Health Organization (PAHO) and PEPFAR, have also generated improved data and information on HIV technologies. The Global Fund's Price and Quality Reporting System is a publicly accessible online database that collects and displays data on procurement transactions made by Global Fund-supported programmes. PAHO, which established the Strategic Fund in 2004, regularly publishes ARV prices.

50. In 2002, WHO established the Global Price Reporting Mechanism, which records international transactions of HIV, TB and malaria commodities purchased by national programmes in low- and middle-income countries via multiple data sources.

51. As patent filings for ARVs increased, efforts to publish patent barriers to medicines emerged. These included efforts by MSF, WHO, MPP, UNITAID and civil society to publish patent information for key ARVs, as well as for HCV and TB medicines. The MPP's MedsPal database provides patent and patent application status and licensing information for all key ARVs (and other medicines) from more than 110 low- and middle-income countries as well as the data exclusivity status for 15 countries.

52. In 2018, the World Intellectual Property Organization and the International Federal for Pharmaceutical Manufacturers Association launched the Patent Information Initiative for Medicines.[15] It provides information on patents for small-molecule products, which is voluntarily submitted by companies that are active in various therapeutic areas, including HIV. While such efforts at transparency are welcome, several respondents noted a need for improvements. Not all drug companies have contributed data and the patent data do not include biologics.[16] The database also does not include pending patent applications. The database includes secondary patents or patents that are variations on the same medicine and which may not be relevant for procurement agencies.

53. Academic research, some of it conducted at the behest of WHO, has generated estimated manufacturing costs for a range of HIV, TB and HCV medicines. These estimates establish the lowest possible price through generic competition.

Identified data gaps

54. While acknowledging the ever-improving generation and publication of data related to HIV technologies, interviewees identified the following data gaps:
    - **Registration status**. Registration status or the number of registered products in low- and middle-income countries is largely unknown. This makes it difficult to identify barriers to competition;

- **Prices paid in upper-middle-income countries**. There is insufficient information for ARV prices in upper-middle-income countries, especially countries outside the PAHO region or countries that have already transitioned from Global Fund support;
- **Updated information on availability of ARVs**. Manufacturing shortages of ARVs could become more frequent as the numbers of people initiated on HIV treatment keep increasing. South Africa experienced a shortage of lamivudine and abacavir in the second half of 2018, while Brazil previously had a near-shortage of paediatric acabavir. Both shortages almost led to national stock-outs of those ARVs. Regional or international databases that provide updated information on existing stocks of ARVs or of manufacturers capable of meeting short-term demand would reduce search times (including determining whether the stock meets domestic regulatory requirements);
- **Accurate pricing data, including post-rebate and discount prices**. Accurate pricing information is needed, including actual prices paid for originator or generics products following discounts or rebates. One industry interviewee noted that actual pricing terms and conditions, including the volumes, delivery time and packaging (product presentation) were needed alongside the price point;
- **Data for medicines to treat opportunistic infections, paediatric HIV, comorbidities and coinfections**. Even though data (e.g. registration, pricing and patenting) for these medicines are improving, especially for HCV, more data across low- and middle-income countries are needed;
- **Diagnostic data**. Although some organizations are generating data on the diagnostics market, one industry interviewee noted that there are few systematic data on HIV diagnostics to inform the HIV response;
- **Full list of manufacturers of products**. While stressing that all products must meet relevant standards of quality, safety and efficacy, respondents stated that new producers in low- and middle-income countries, capable of eventually meeting international standards, are not known. Agencies could publish information about such producers, while clearly indicating which of them have met quality assurance standards set by WHO or other stringent regulatory authorities.
- **"Freedom to operate" analysis in low- and middle-income countries**. "Freedom to operate" refers to the existence of legal opinion as to whether current patents or patent applications may lead to infringement if a competitor were to introduce a particular medicine. Additional data on "freedom to operate" could clarify where generics access is possible and could help determine the likely delay until a generic can enter a particular market;
- **Real-time market data**. Data concerning market uptake, sales and prices for low- and middle-income countries for HIV products (and in general) are often out-of-date and slow to arrive.

55. Respondents also noted a need for convening agencies and stakeholders to jointly discuss and analyse data trends for HIV related products. UNAIDS could assume such a role in partnership with other agencies.

CASE STUDIES OF KEY MEDICINES AND OVERVIEW OF OTHER HIV-RELATED TECHNOLOGIES

56. This section examines access-related interventions, challenges and gaps related to four medicines: dolutegravir, sofosbuvir, bedaquiline and the combination of tenofovir and emtricitabine (which is used for PrEP). These case studies identify some of the key product-related barriers that can delay access to treatment in low- and middle-income countries, and the particular measures employed by governments, industry, international organizations, and civil society to address these barriers.

57. This section also looks at the particular gaps, challenges and opportunities related to paediatric HIV treatment and the HIV pipeline.

Dolutegravir

58. Dolutegravir is an alternative first-line ARV and salvage treatment that was approved in August 2013 by the US Food and Drug Administration. It has improved tolerability and reduced side effects compared to efavirenz as well as a higher barrier to drug resistance. Low dosing requirements are opportunities for low cost of production and coformulation into one pill.

59. Key findings include the following:
- Five patent applications provide the originator with the possibility of patent protection until 2031, including in numerous low- and middle-income countries;[17]
- Pre-grant oppositions were filed on key patent applications for dolutegravir by NGOs and patient groups in Brazil and India, where all patent applications are still pending. No patent oppositions were filed by generics companies in low- and middle-income income countries;[18]
- A voluntary license between the MPP and the originator permits generic competition in 130 low- and middle-income countries. In royalty-bearing territories of the voluntary license (including India), licensees are not permitted to sell low-cost generics in the private market;[19]
- Civil society advocacy and mobilization helped expand the scope of the license agreement to include countries such as Morocco, Tunisia and Ukraine;
- Some countries in which the patent has been granted are not included in the license agreement, including Algeria, Belarus, China, Colombia, Malaysia, Mexico and the Russian Federation;[20]
- In September 2017, global health agencies and two licensees announced the introduction of a once-a-day generic fixed-dose combination of tenofovir disproxil fumarate, lamivudine and dolutegravir (TLD) for no more than US$ 75 per patient per year;[21]
- In Brazil, where a patent application is pending, the government has negotiated successive price reductions. The price of dolutegravir is US$ 1.00 per pill (the lowest price for dolutegravir worldwide is US$ 0.167 per pill). The fixed-dose combination of TLD is not available;[22]
- Dolutegravir is not yet registered in Algeria, which is the sole country on the African continent not included in the voluntary license;[23]
- The originator has pursued manufacturing agreements in China[24] and the Russia Federation.[25] The terms and conditions of the agreements and final product price are not published. The licensed version of product has not been launched in either of those countries;
- Registration of generic fixed-dose combinations has been facilitated through the US Food and Drug Administration's tentative approval programme. Regulatory

requirements in India required companies to apply for a waiver of a required domestic clinical trial for the fixed-dose combination when filing for registration;[26]

- Development, uptake and registration of paediatric dolutegravir lags, despite it being a priority ARV. As of October 2018, the originator had obtained registration for pediatric formulations of dolutegravir in the upper-middle-income countries Albania, Azerbaijan, Brazil and Peru, and in one lower-middle income country, Georgia. The originator has not obtained registration of paediatric formulations in any low-income countries, though it has filed for registration in 22 additional low- and middle-income countries.[27]
- In May 2018, WHO announced a potential safety issue related to neural tube defects in infants born to women taking DTG at the time of conception. Agencies now recommend use of alternative first-line regimens for women initiating ART at child bearing age, including pregnant women;[28]
- In July 2018, UNITAID and the Clinton Health Access Initiative announced the launch of a partnership with the originator to speed up the development and introduction of optimized paediatric formulations with two generics companies.[29]

Sofosbuvir

60. New direct-acting antivirals to treat hepatitis C (HCV) were introduced in 2013. They offer treatment success rates above 90%. While the great majority of low- and lower-middle-income countries can now procure affordable generic or originator treatments, prices remain high in many upper-middle-income countries and high-income countries. Those high prices and a lack of sufficient financing have meant that so far only 3 million people of an estimated 70 million people with HCV globally have received treatment with new direct-acting antivirals.[30]

61. Sofosbuvir is a once-daily nucleoside polymerase inhibitor that is the backbone for most HCV treatment regimens. It is pan-genotypic, has a high genetic barrier to resistance, has few drug-drug interactions, and is safe and well tolerated. The drug was acquired by the current originator from Pharmasset for US$ 11.2 billion in 2012[31] and was approved by the US Food and Drug Administration in December 2013.

62. Key findings include the following:
    - In 2018, generic sofosbuvir was widely available in all low-income and many middle-income countries;[32]
    - The originator has filed up to 45 patent applications in high-income countries[33] and multiple patent applications in low- and middle-income countries;[34]
    - Patent oppositions, observations or invalidations by NGOs were filed in Argentina, Brazil, China, India, the Russian Federation, Ukraine and the US, and at the European Patent Office;
    - Sales of sofosbuvir were initially launched in the US at US$ 1,000 per pill, for a total cost of US$ 84 000 per treatment course. The originator pursued high prices in other high-income countries, as well.[35] The lowest global price was US$ 900.
    - An academic study published in 2014 found that the cost of production for sofosbuvir for a 12-week course was between US$ 68 and US$ 136;[36]
    - In September 2014, after the introduction of sofosbuvir in Europe and the US, the originator signed bilateral voluntary licensing agreements with 7 Indian generics companies. The initial territory included 91 low- and middle-income countries.[37] The MPP did not obtain a mandate to negotiate HCV licensing agreements until November 2015. The originator expanded the bilateral voluntary license agreement to 105 low- and middle-income countries by 2017;

- In Egypt some of the main patents were not filed and other applications were refused by the Egyptian patent office. HCV treatment in Egypt is available at US$ 84 per patient per treatment course;[38]
- Brazil is not included in the originator's voluntary licensing agreement. In 2018, the price of sofosbuvir was reported at US$ 4,200 per treatment course.[39] All key patent applications were opposed by NGOs and local manufacturers developed domestic versions of sofosbuvir. One patent application was rejected. The other key patent application was accepted and is now under additional review;[40]
- There are no blocking patents on sofosbuvir in Ukraine. A generic version was initially registered. However, it was subsequently deregistered because the Government of Ukraine had introduced data exclusivity, which prevents registration of generic products for some years after the registration of the originator product. The originator later included Ukraine in the voluntary license agreement;
- In Malaysia, the originator had a patent until 2028 on sofosbuvir, did not include the country in the voluntary license and offered a price of US$ 11 200 for a full treatment course.[41] In 2017, the Government issued a government use license to allow generic versions of the product into the market;[42]
- China is not included in the voluntary license agreement. The originator announced a price of US$ 8,937 per treatment course.[43] Patent oppositions and an invalidation filed by NGOs were successful which in principle should enable generic competition subject to registration;[44]
- WHO's prequalification programme and the Global Fund Expert Review Panel have helped encourage and facilitate the use of quality-assured generics manufacturers;
- DNDi has launched an HCV treatment R&D programme combining sofosbuvir with a new compound, ravidasvir, which could provide another affordable treatment alternative, once approved;[45]
- Prices for sofosbuvir continue to decrease worldwide. In India, a full treatment course for sofosbuvir is available at US$ 48.[46]

Bedaquiline

63. TB is the leading cause of death from a single infectious agent worldwide, with nearly 1.8 million people dying each year. Only two new TB medicines, bedaquiline and delaminid, have been developed in the past 50 years, and both drugs present significant challenges related to affordability and availability for populations in need.[47]

64. Bedaquiline is used to treat active TB. It was approved at the end of 2012 based on phase II trials by the US Food and Drug Administration.

65. Key findings include the following:
    - A priority since the preliminary regulatory approval of bedaquiline has been to evaluate regimens that incorporate bedaquiline with existing and new TB drugs. Since approval, multiple Phase II and III clinical trials have been launched to test the drug in novel treatment regimens;[48]
    - The originator, which is one of the few companies still active in TB research, filed five patent applications, the last of which expires in 2027. The base compound patent application was widely granted, including in India;[49]
    - No patent oppositions were filed by civil society on the key blocking patents. No patent oppositions were filed by generics companies on the key blocking patents;[50]
    - The originator initially established a tiered pricing approach: US$ 30 000 in high-income countries, US$ 3,000 in middle-income countries, and US$ 900 in low-income countries.[51] Existing TB regimens cost between US$ 1,670 and US$ 5,000. Civil society organizations have warned that a new regimen with bedaquiline would be unaffordable;[52]

- A 2017 study estimated the cost of production of bedaquiline at US$ 8–17 per one-month supply;[53]
- The originator introduced a four-year donation programme in December 2014 that included 30 000 courses. Countries eligible for Global Fund grants are also eligible countries for this programme.[54] It was introduced in China in 2018;[55]
- The originator has not yet negotiated an MPP voluntary license;
- The originator entered into an unpublished bilateral voluntary licensing agreement with a Russian pharmaceutical company to register, manufacture and market the drug in the Commonwealth of Independent States, Georgia, Turkmenistan and Ukraine.[56] The current known price in the Russian Federation is US$ 1,980;[57]
- The donation agreement has been extended to March 2019 for eligible patients;[58]
- South African Government-led negotiations reduced the price to US$ 745 (in South Africa) and subsequently to US$ 400 for a six-month treatment course. The price of US$ 400 is available to countries that purchase through the Global Drug Facility.[59] The price has been considered unaffordable by some members of civil society , particularly since TB treatment often extends beyond six months;
- Bedaquiline is registered in at least 17 countries and the European Union, with registrations pending in at least 9 other countries; it is not registered in 18 high-burden countries;[60]
- A paediatric version of bedaquiline is expected, though data have not been released. The process of expanding use of the drug in children aged six years and older has been slow.[61]

Pre-exposure prophylaxis

66. Oral pre-exposure prophylaxis (PrEP) combines tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC). TDF was first approved in 2001 and FTC was approved in 2003, and both are patented by the same originator. Currently, alternative generic combinations of PrEP (TDF and 3TC) are available in some countries as well as a different generic formulation of TDF and FTC.[62]

67. Key findings include the following:
    - The originator filed two secondary patents on TDF in 1997 and 1998. The patent applications were not filed in low- and middle-income countries, though there were some exceptions, including India where NGOs and a generics company filed successful oppositions;[63]
    - The originator signed a bilateral voluntary license for TDF in 2006 with multiple Indian companies and one South African producer. One Indian company did not agree to the voluntary license and pursued patent oppositions. The license, which was eventually published, included 95 countries and thus did not include many middle-income countries;[64]
    - The originator signed a license agreement for TDF with the MPP in 2011 for 112 countries, which was ultimately expanded to 116 countries in 2017. The originator included a "covenant not to sue" for FTC in the agreement for the same territory;[65]
    - The originator filed a patent application on the combination of TDF and FTC in 2004 (this will expire in 2024). Oppositions filed in Argentina and Brazil by NGOs led to rejection of the combination patent, but the patent has been approved elsewhere;[66]
    - Indonesia approved the combination patent but subsequently issued a government use license for patents on 7 ARVs in 2012, including the combination patent for TDF and FTC.[67] South Africa and Ukraine approved the combination patent, but were included in the voluntary license;
    - Other countries (including Azerbaijan, China and Mexico) were not included in the voluntary license and have granted the combination patent;[68]

- In the United Kingdom, the government used the Bolar provision to provide access to a generic version of TDF and FTC during a clinical trial;[69]
- Patent term extensions on the branded version of TDF and FTC in high-income countries in Europe have been rejected, with the rejections affirmed by the Court of Justice of the European Union.[70] Generic versions can enter many European markets;
- The US is the largest expected market for PrEP. Patents block competition until 2021. The branded version of TDF and FTC costs an estimated US$ 2,000 per month in the US.[71]

ADDITIONAL INFORMATION CONCERNING TECHNOLOGIES TO ADDRESS HIV, OPPORTUNISTIC INFECTIONS AND COINFECTIONS

HIV medicines for children

68. Only 52% of children with HIV were receiving paediatric treatment in 2017.[72] Current treatment options for HIV-positive children are inadequate. There is too little investment to ensure the safety and efficacy of ARVs for children or to develop child-appropriate formulations.[73]

69. Efforts to prevent mother-to-child transmission of HIV reduced the annual number of new HIV infections in children by 50% between 2010 and 2015.[74] This has caused the paediatric market to decline in size.

70. The market for paediatric ARVs is fragmented and neglected. Nearly 90% of children living with HIV are in sub-Saharan Africa. Their needs are not being met and some of the ARVs recommended by WHO do not exist in optimal formulations or presentations.[75] Paediatric ARVs, even when developed in optimal formulations and presentations, are often not registered quickly where they are needed most.

71. Even where paediatric ARVs are registered, supply shortages can undermine treatment. In 2017, shortages of paediatric lopinavir/ritonavir (LPV/r) occurred in India. Stock-outs led to emergency orders from another Indian generics company and a notification from the National AIDS Control Organization advising parents to subdivide tablets.[76]

72. Elsewhere, an interviewee noted that shortages of paediatric abacavir required emergency measures to import the product from another country, yet there was little to no information readily available to locate additional stock internationally.

73. There are multiple initiatives to address challenges surrounding paediatric HIV, including the Pediatric HIV Treatment Initiative.[77]

74. The Vatican, in collaboration with the UNAIDS Secretariat, PEPFAR, WHO and various NGOs, convened a discussion in 2017 to accelerate the introduction of child-friendly diagnostics and medicines. While some industry representatives claimed that the project was delivering results, key interviewees from civil society expressed disappointment that the process was not doing so quickly enough.

75. Multiple respondents noted that there were still no incentives or solutions to overcome the limitations of the paediatric market, which is fragmented and concentrated around the most vulnerable and neglected patients in the AIDS response. One industry interviewee

welcomed the introduction of new incentives, such as prizes, to encourage the development of appropriate paediatric formulations.

76. Even where IP is shared and funding is available, the development of adapted paediatric formulations is occurring too slowly. As one respondent noted, nobody will say "no" to taking on a paediatric HIV project, but the required urgency is lacking.

Vaccines

77. Efforts to develop a HIV vaccine began over three decades ago. A recent study funded by the Gates Foundation identified 41 candidate HIV vaccines, but noted that an additional 125 candidates are required at the preclinical stage.[78]

78. Other vaccines play an important role in reducing morbidity and mortality for people living with HIV. Cervical cancer is a leading cause of death of people in low- and middle-income countries, especially women living with HIV. Two HPV vaccines, patented by two originator companies, have been on the market for five years. The lowest price on offer is US$ 4.50 per dose, a price that is available only to countries receiving funding from Gavi, the Vaccine Alliance.[79] One study estimated the per-dose cost of production of the HPV vaccine at no more than US$ 0.60.[80]

79. Prices are higher in countries not supported by Gavi. While the PAHO Revolving Fund has negotiated a per-dose price of US$ 8.50 and US$ 9.50,[81] other middle-income countries may pay significantly higher prices than PAHO.[82] The South African Government paid approximately US$ 13 per dose in 2016.[83]

80. An MSF report found multiple classes of patents are applied to vaccines. It found at least 93 patent applications or issued patents for the HPV vaccine, many of which introduce significant challenges to either the production or use of a follow-on vaccine.[84]

HIV pipeline products

81. At least 13 new diagnostic devices and 10 new chemical entities to address HIV may emerge in the next 5 years.[85] A total of 99 products are in development.[86]

Small-molecule products

82. Small-molecule ARVs that could be approved include cabotegravir, fostemsavir and GS 9131. The originators for these ARVs already have voluntary licensing schemes and have indicated that their current licensing strategies would continue.

83. Doravirine and MK-8591 are expected to emerge from an originator company which has not employed voluntary licensing with the MPP for adult formulations of ARVs.

Nanomedicine

84. Nanomedicines could reduce dosing and overall manufacturing costs. An initial estimate of a nanoformulation of efavirenz and LPV/r indicates dosing could be reduced by 50%, with annual cost savings of US$ 200 million.[87]

85. In December 2015, the MPP signed a collaborative IP agreement with the University of Liverpool for its "solid drug nanoparticle technology" to accelerate the development of WHO-recommended ARVs as nanomedicines.[88] The territory of the agreement is broad and includes all 135 low- and middle-income countries, as well as two high-income

countries. It allows licensees to make, use and distribute ARVs that incorporate the technology.[89]

Long-acting technologies

86. Long-acting and extended release formulations are already used for the delivery of antipsychotics and hormonal contraception and for improving adherence and health outcomes.

87. New long-acting pipeline technologies for HIV include injectables, patches, implants and nanotechnology.[90] UNITAID convened a global technical consultation in November 2018 to consider the science and market landscape for these technologies.

88. Use of a single instramuscular injection of cabotegravir every eight weeks is undergoing Phase III trials for PrEP. A long-acting injectable formulation treatment combining cabotegravir and rilpivirine has established proof of concept,[91] and it should be possible to develop long-acting injectables with dolutegravir, efavirenz, emtricitibine, raltegravir, rilpivirine and tenofovir.[92]

89. Key challenges with long-acting formulations relate to product development, health systems and access (IP, regulatory and pricing).
    - Product development challenges include optimizing dosing, managing drug interactions and managing dosing for children, adolescents and during pregnancy;[93]
    - Health systems challenges are capacity related and include transitioning health-care workers to deliver long-acting products, introducing additional health-care infrastructure (including appropriate storage and disposal) and increased duration for each patient visit;
    - Access challenges include difficulties in establishing an effective regulatory pathway (including at the US Food and Drug Administration and the European Medicines Authority), with additional challenges at national medicines regulatory authorities. IP barriers pose further challenges. Three types of IP are involved in these formulations. They include IP on the underlying compounds used in long-acting formulations; IP on the relevant technology or process involved in formulation; and a third layer of IP that is related to the particular delivery device.[94]

Biologics

90. Respondents noted that biologics will eventually play an important role in HIV treatment. One biologic (*ibalizumab*) has been approved for HIV treatment. The monoclonal antibody, which was developed by a Chinese pharmaceutical firm, was approved by the US Food and Drug Administration in March 2018.[95] It is intended as a salvage therapy for people living with HIV-1 and experiencing multiclass drug resistance. It is priced at US$ 118 000 in the US and it requires significant infrastructure to be delivered to patients (a twice-monthly intravenous infusion).[96]

91. There at least three biologics for HIV in development.[97] While these products may not be approved or used widely, it is hoped that biological drug discovery could yield promising treatments and prevention technologies—along with concerns regarding access challenges for such products.

92. A critical challenge is the legal and regulatory barriers that impede competition (through a category of products known as "biosimilars"). Concerns include nonexistent, ineffective or inefficient regulatory pathways to approve biosimilars. Data or market exclusivity has been introduced in high-income countries and increasingly also in middle-income countries. Data exclusivity can prevent early biosimilar entry and competition.[98]

93. Pharmaceutical companies file a range of patents on biological products. Patenting on biologics has increased considerably: in 2009, 60% of all pharmaceutical patents filed by the top 10 pharmaceutical companies were for biologics.[99]

94. Some interviewees already believe that the high prices of biologics would make their uptake and use in low- and middle-income countries difficult. Biosimilar competition has led to price reductions of 40–75% in Europe.[100] Without competition, biologics can negatively affect health-care budgets. In Brazil, biologics represent only 4% of the volume of drugs distributed through the public health-care system, but those medicines absorb more than half the Government's public expenditure on drugs.[101]

95. A working group of key multilateral organizations, HIV funders and market-shaping entities are discussing the introduction of new HIV technologies in low- and middle-income countries and the challenges to be overcome. NGOs and treatment advocates historically responsible for the evolution of HIV treatment have been missing from these discussions. Without their participation, the debates and decisions shaping the future of HIV treatment will suffer.

KEY LESSONS LEARNED FROM CASE STUDIES, INTERVIEWS AND DESK REVIEW

96. Advocacy and community mobilization continue to play major roles in widening access to affordable medicines. Yet NGOs and treatment advocates increasingly lack the resources and access to decision-making they need to make an impact.

97. Originator and generics companies collaborate extensively around some health technologies, especially through voluntary licenses. This can expand access. However, generics firms appear to be less interested in challenging patents filed by originator companies in low- and middle-income countries.

98. Local production of medicines in low- and middle-income countries is growing. New producers of ARVs and other medicines are emerging in countries such as Algeria, Bangladesh, China, Egypt, Morocco, the Russian Federation and Uganda. These local production efforts are based upon different strategies: some focus on firms signing limited agreements with originator companies, while other firms, particularly in Brazil and Egypt, have not pursued licensing agreements with originators.

99. Originator companies engage in the practice of filing multiple secondary patents, which many interpret as an effort to extend the duration of patent protection beyond the twenty-year term as provided within the TRIPS agreement (strategy known as "ever-greening"), thereby delaying generic market entry. A recent study found that even in India, which has anti-"ever-greening" provisions and robust opposition procedures, up to 72% of 1,654 approved secondary pharmaceutical patents could have been found to not satisfy India's criteria for patentability.[102]

100. Efforts to overcome patent barriers in low- and middle-income countries are increasingly driven by NGOs (oppositions and advocacy) and governments (price negotiations, pooled procurement and the use or potential use of TRIPS flexibilities).

101. Upper-middle-income countries face significant challenges. Many pay higher prices for new medicines until generic versions can enter the market. Delayed generic competition is caused by several factors, including the introduction of TRIPS-plus rules, such as data exclusivity. There is also a growing assumption in some circles that upper-middle-income

countries should pay higher prices for new medicines and that treatment gaps are due to a lack of political will and insufficient domestic resource mobilization.

102. Upper-middle-income countries that have or will transition from Global Fund support may face additional pressure to pay higher prices for new medicines. Development assistance helps justify access to low-cost generics and price reductions since affordability enables "value for money", a key objective of most donor countries and agencies.

103. Neglected patients, particularly children living with HIV and people with TB, face a range of innovation and access-related challenges. One critical challenge for children living with HIV is the lack of appropriate formulations. For people with TB, treatments exist but the drugs lead to suboptimal outcomes and can cause painful side effects. According to MSF, two new TB drugs, bedaquiline and delaminid, were only accessible to 10% of the people eligible to receive them in 2017.[103] Neither of these neglected populations is seen to present an attractive commercial opportunity. Overall, respondents identified improved diagnostics and paediatric ARVs as key unmet needs.

104. Originator or generics companies seldom register existing paediatric HIV drugs and TB products in a timely fashion. Companies often do not prioritize registration of such products in low- and middle-income countries, while the registration processes are lengthy in some countries.

105. One study found that nearly three quarters of the 144 known instances where low- and middle-income countries used TRIPS flexibilities in 2001–2016 were for HIV treatment.[104] Of those, 100 uses of TRIPS flexibilities were for compulsory or public noncommercial use licenses, 40 invoked the least-developed country pharmaceutical transition measure, 1 involved parallel importation and 3 involved research exceptions.

106. Respondents in the current study singled out four interventions that are increasingly important for addressing patent barriers. Three of them involve IP:
    - voluntary licensing, especially through the MPP;
    - promoting public health-sensitive use of patentability criteria, whether through examination or through the use of opposition or invalidation procedures; and
    - the use of the research exception to enable the development and testing of generic versions of new, patented medicines.

107. In the absence of competition, price negotiation (including pooled procurement and access to key market data) is viewed as essential, especially for middle-income countries.

108. Respondents identified other trends that could present barriers to promoting and sustaining access to affordable medicines:
    - There are concerns that **drug donations** are still standard practice for some drug companies. WHO does not recommend the use of drug donations except in limited circumstances. Drug donations can undermine long-term efforts to expand access to treatment;
    - **Bilateral voluntary licenses** negotiated between originator and generics firms are often not transparent and are shielded from government and public scrutiny. This includes bilateral agreements that apply to only one or a few territories and which therefore segment the generics market;
    - Some originator companies continue to use **tiered pricing programmes**. Empirical data, in particular for ARVs, show that tiered pricing seldom results in the kinds of price reductions that can be achieved through generic competition;[105]

- **Shortages and stock-outs** of ARVs continue to occur. There was a limited stock-out of paediatric LPV/r in India in 2017 due to a confluence of factors. In 2015, in spite of the presence of four suppliers of the adult formulation of LPV/r, there was a significant stock-out of the adult formulation of LPV/r in South Africa, as well as in El Salvador and Guatemala.[106] The drug was available only from the originator, backed by patent protection. Following the stock-out, the originator signed a voluntary license with the MPP for an adult formulation of LPV/r, limited to the African continent.[107] There were also widespread shortages of lamivudine and abacavir in South Africa through October 2018.[108] Some respondents claimed that efforts to reduce industrial pollution from plants manufacturing active pharmaceutical ingredients may have had the unintended effect of compromising the reliable supply of those ingredients and finished products[109], thereby contributing to the recent shortages of lamivudine and abacavir in South Africa.

109. Darunavir, an ARV used in salvage therapy and recommended as an alternative second-line treatment for HIV, illustrates the access challenges that emerge when an originator company employs donations and tiered pricing, does not sign public health-friendly voluntary licenses and pursues secondary patents.[110] The originator company did not agree to a voluntary license with the MPP, even though patents owned by the US National Institutes of Health for darunavir were licensed to the MPP.[111] Instead it offered a limited right to two generics companies to package and distribute the product in a limited number of countries.[112] In November 2012, the originator company stated it would not enforce patents in sub-Saharan Africa and least-developed countries.[113]

110. In 2016, a decade after approval by the US Food and Drug Adminstration, prices for darunavair remained unaffordably high for many countries. Generic versions for 600mg versions cost US$ 1,273, nearly twice as expensive as the originator's price.[114] This was due to limited and small markets for generics, a situation created partly by patent barriers. Secondary patents, particularly combinations patents, have enabled the originator to maintain a monopoly in some countries.[115] A paediatric donation programme for darunavir has provided the product to children with HIV in only a small group of countries.[116] The donation programme may have made the low-volume paediatric market even less enticing for generic producers that have already developed quality-assured versions of the medicine.[117] The prices for darunavir remains high. The lowest price for the 600 mg generic version is US$ 658, while the lowest price offered by the originator is US$ 663.[118]

111. Most respondents noted that delays and barriers to registration can unduly delay competition and access to health technologies. Not enough countries and companies use WHO prequalification and the Collaborative Registration Scheme. Companies are not allocating adequate resources for timely registration and strengthening of health regulatory capacities needs to be further prioritized. Approving fixed-dose combinations and new formulations of ARVs in India, for example, has been difficult due to requirements for clinical trials of novel presentations or combinations.

112. Pipeline drugs could present a range of access barriers that undermine scale-up in low- and middle-income countries, including patent barriers, regulatory challenges and unaffordable prices.

OPPORTUNITIES AND RISKS IN THE POLICY ENVIRONMENT

113. This section identifies opportunities and risks in the policy environment that affect access to affordable HIV technologies.

Opportunities in the policy environment

UN-led inter-governmental processes

114. There are multiple UN-led efforts to improve innovation and access to medicines. WHO, the World Intellectual Property Organization and World Trade Organization, via the Trilateral Cooperation, have intensified their collaboration on public health and IP to foster improved understandings of the linkages between IP policies and public health and to enhance mutually supportive implementation of such policies.

115. The UN High Level Panel on Access to Medicines produced recommendations for UN agencies, governments, industry and civil society. The UN Human Rights Council issued a new roadmap on human rights and HIV, including measures to promote access to medicines. The draft WHO Roadmap on Access to Medicines and Vaccines proposes ten areas for intervention to improve access to medicines and vaccines for the period 2019–2023. The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property has been extended until 2022.

116. Many recommendations and approaches featured in these processes are inspired by the successes of the AIDS response. They are also highly relevant to overcome existing and future barriers to affordable HIV treatment across low- and middle-income countries.

Delinked R&D models

117. Delinked models of R&D, or those that fully separate the cost of R&D from the end product price, are already used by some product development partnerships to develop new medicines and vaccines.

118. Children with HIV and people with TB are unable to secure equitable access to medicines due partly to a lack of needs-based R&D or adapted development of medicines. Delinked models could generate incentives to encourage increased and more effective R&D investment. One industry respondent supported innovation prizes while others noted that incentives, in particular for paediatric R&D, could accelerate development, registration and affordable access to child-friendly products.

Antimicrobial resistance

119. Drug-resistant TB is already viewed as a major expression of antimicrobial resistance: by 2050, up to one quarter of the anticipated 10 million deaths from antimicrobial resistance will be due to TB.[119] The international response to antimicrobial resistance could help boost resources to the AIDS and TB responses. The lack of novel antibiotics may encourage the introduction of delinked models of R&D. There is broad interest to develop and increase access to new diagnostics to improve prescribing practices at the point-of-care. Such platforms could be applied to HIV treatment.

120. Yet antimicrobial resistance could also create barriers to access to medicines in low- and middle-income countries. Some respondents expressed concern that key policy-makers are focused narrowly on preventing excess use of new and existing antibiotics and are not focusing sufficiently on increasing access to life-saving medicines, vaccines and diagnostics, especially in low- and middle-income countries.

Risks in the policy environment

Upwards harmonization of IP laws, policies and practices

121. Numerous respondents registered concerns about free trade agreements that introduce stricter IP rules in low- and middle-income countries, thereby delaying generic competition and increasing drug prices. One respondent noted that World Trade Organization accession negotiations have required that incoming members, including low-income countries, introduce IP rules that exceed existing obligations under TRIPS.

122. Other respondents noted concerns about efforts of high-income country patent offices to provide direct technical support to patent offices of low- and middle-income countries, sometimes with the intention of modifying patent offices' rules, standards and procedures. There are also efforts to fully harmonize patent examination between patent offices.

Flat-lining HIV funding and Global Fund transitions

123. There were also concerns about "flat-lining" or declining HIV financing in some countries. Some donors have reduced earlier commitments and domestic resource mobilization is not bridging the gap.

124. The process of transitioning from donor funding has accelerated in recent years, with the Global Fund set to withdraw the bulk of its programmatic support and core funding for HIV programmes from a range of middle-income countries. Transitioning risks reducing available funding for particular countries, some of which are witnessing a revival in HIV incidence. Some countries may also be unable to secure the lowest prices for medicines as companies recategorize them as "commercial territories". In addition, domestic regulatory, policy and procurement processes are yet not fully operational in some transitioning countries.

Framing the relationship between the AIDS response and Universal Health Coverage

125. Many policy makers and NGOs are focusing increasingly on achieving Universal Health Coverage, sometimes at the possible expense of attention to specific diseases. At the same, the AIDS response is increasingly integrated with other public health programmes, including those focused on TB and viral hepatitis.

126. Some respondents stated that UNAIDS should develop an integrated framework for addressing access barriers for other diseases affecting people with HIV, such as noncommunicable diseases. Others noted that, as resources and political attention for HIV decline, a diversion of the remaining resources would undermine the AIDS response when many countries face significant hurdles to achieving the 90–90–90 targets.

RECOMMENDATIONS REGARDING UNAIDS' ROLE IN ENSURING ACCESS TO MEDICINES

127. There has been significant success in increasing access to HIV treatment. However, persistent access barriers remain and new challenges loom, especially for new health technologies to prevent, diagnose and treat HIV infection and its coinfections and comorbidities. The UNAIDS Secretariat has an important role to promote lessons and support efforts to tackle the gaps and challenges.

128. The UNAIDS Secretariat should continue to use its convening and coordinating mandate to promote new data collection and analysis, advocate that governments and industry invest in innovation and access to affordable HIV-related health technologies, increase its institutional engagement through the Joint Programme and beyond, and support community mobilization around these issues.

129. Working closely with Cosponsors, the UNAIDS Secretariat can add unique value in facilitating and supporting strong networks among the communities, advocates and activists that work on demand creation and accountability. The Secretariat is well positioned to convene consultation processes with a large variety of stakeholders, including governments and the private sector, on issues related to access to HIV technologies and keep this is a high priority on it's agenda.

130. Some of the toughest challenges in expanding access to health technologies are political in nature; overcoming them requires sufficient political will on the part of governments. Yet the political and policy space for addressing such challenges appears to be diminishing. The UNAIDS Secretariat needs to continue working with Cosponsors and engaging governments to overcome such barriers.

131. Overcoming IP-related barriers to access will remain a key area of work for UNAIDS. The effective use of various tools and strategies has reduced some of the IP barriers that had prevented the introduction of low-cost generic HIV medicines in many low- and lower-middle-income countries. Yet high prices of new medicines and limited competition still create significant access problems for some countries, especially since voluntary licenses do not include some middle-income countries. "TRIPS-plus" IP rules continue to be introduced in many low- and middle-income countries, including through free trade agreements.

132. The Joint Programme should build on its existing efforts to provide technical assistance to governments and support civil society mobilization to encourage the introduction of public health-sensitive laws and policies, and it should advocate for measures that prevent or overcome IP barriers which hinder access to medicines.

133. Health regulatory requirements can be barriers to access. Efforts are underway to support and strengthen national medicines regulatory authorities. Yet gaps remain, including insufficient data on the registration status of medicines and delays in registration of key medicines, especially paediatric ARVs. The Joint Programme can work with other agencies to collect registration data in low- and middle-income countries. The Joint Programme should encourage industry and governments to avoid unnecessary delays to registration and strengthen the capacity of regulatory authorities.

134. Numerous data gaps exist. The UNAIDS Secretariat, in consultation with Cosponsors, could select specific new data to be gathered in existing data collection efforts, including: the registration status of particular products and the prices paid for HIV-related technologies in specific middle-income countries. The Joint Programme could convene interagency discussions to improve the collection and analysis of data.

135. Many countries experience periodic shortages and stock-outs. The Joint Programme can facilitate measures that prevent or mitigate shortages and stock-outs, such as a centralized database of existing producers that can assist governments to rapidly overcome temporary disruptions to supplies. UNAIDS can advocate for appropriate measures to mitigate the impact of supply breakdowns and can also employ the newly launched Health Situation Rooms to assist in an appropriate domestic and international response.

136. The UNAIDS Secretariat's advocacy to expand local production in African countries is important. The Joint Programme should take note of emerging producers worldwide and advocate with these producers to expand access to quality-assured, safe and affordable medicines.

137. The Joint Programme should encourage new approaches to R&D of HIV-related technologies, in particular those approaches that separate the cost of R&D from the final product price, and that can ensure a sustainable return on investment for producers. There are neglected needs that could be met through new approaches to R&D, such as medicines to treat paediatric HIV.

138. The Joint Programme needs to champion upper-middle-income countries' need for an equitable approach to promoting access to affordable HIV medicines. It could document the HIV responses in upper-middle-income countries in order to correct misperceptions of the level of development, state of health-care systems and abilities of such countries to pay for HIV treatment, especially in upper-middle-income countries transitioning from Global Fund support. The UNAIDS Secretariat is working with the Global Fund to assist countries in transition; the support should continue post-transition.

139. The Joint Programme should explore additional innovative collaborations with relevant partners such as UNITAID, MPP and the Clinton Health Access Initiative to address access challenges related to the pipeline of new medicines and existing medicines. The UNAIDS Secretariat can facilitate the participation of NGOs in those efforts.

140. The Joint Programme needs to continue to engage in discussions on antimicrobial resistance to promote policies and investments that support the AIDS response. Such policies and investments might encourage the development of diagnostics that improve prescribing practices at the "point-of-care", or encouraging the use of delinked R&D models to develop new antibiotics, including for TB treatment. The Joint Programme can also ensure the policy response to antimicrobial resistance promotes an appropriate balance between rational use and ensuring access.

141. The UNAIDS Secretariat has always supported NGOs and treatment advocates. However, there is concern that limited capacities will undermine their ability to analyse and respond to new access barriers. This is already evident in some countries transitioning from Global Fund support. NGOs are not sufficiently involved in priority setting for new technologies. The UNAIDS Secretariat can support NGOs and treatment advocates by assisting with resource mobilization, providing information and materials to build capacity, and using UNAIDS Secretariat's convening abilities to facilitate their access to decision makers.

142. The UNAIDS Secretariat should reinvest in policy processes hosted by intergovernmental agencies. It also needs to work with governments and the private sector to achieve political commitments that address access barriers. High-level advocacy by the UNAIDS Secretariat can create opportunities for partners in the Joint Programme and elsewhere to provide direct technical support to governments that seek to address barriers to competition, including IP barriers and registration delays.

143. The Joint Programme needs to intensify its dialogues with both generics and originator companies to persuade them to advance policies that can expand access to their products and address unmet needs.

144. The Secretariat needs to strengthen its internal technical expertise to play an active role in the access to medicines debate, whether in collaborating with other agencies, working

with UNAIDS regional and country offices or by improving coordination around these issues across the Joint Programme.

145. The UNAIDS Secretariat also should ensure that there are adequate resources available for addressing access-to-health-technology challenges, including at UNAIDS country and regional offices. This includes providing countries with relevant data and analyses to inform national decision-making in order to prevent negative impacts of trade legislation or free trade agreements on access to medicines. This may not demand additional resources but it does require that existing staff regard access to medicines as important components of their work.

ANNEX 1: KEY INFORMANT INTERVIEWEES

For this report, 25 key informants were interviewed across 22 entities. Key informants were selected from governments, industry, multilateral organizations, foundations and civil society on the basis of their expertise on intellectual property, broader access challenges related to the uptake and diffusion of new technologies, and for their particular insights on HIV, comorbidities and coinfections. The names and individual responses of the interviewees have been kept confidential. In some cases, more than one individual from an entity was interviewed.

1. AIDS Rights Alliance for Southern Africa
2. Cipla Pharmaceuticals
3. Coalition Plus
4. Gilead Sciences
5. Government of Brazil
6. Government of South Africa
7. Global Network of People Living with HIV
8. Joint United Nations Programme on HIV/AIDS
9. Medicines Patent Pool
10. Medecins Sans Frontieres/Doctors without Borders
11. Mylan
12. Office of the High Commissioner of Human Rights
13. Pan American Health Organization
14. South Centre
15. United Nations Conference on Trade and Development
16. United Nations Development Program
17. United Nations Industrial Development Organization
18. ViiV Healthcare
19. World Health Organization
20. World Intellectual Property Organization
21. World Trade Organization
22. UNITAID

REFERENCES

[1] 2 A/HRC/32/L.23. Access to medicines in the context of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. Geneva: United Nations Human Rights Council; July 2016 (http://www.un.org/ga/search/view_doc.asp?symbol=A/HRC/32/L.23/Rev.1)
[2] A/HRC/38/L.12A/HRC/38/L.12A. Human rights in the context of HIV and AIDS. Geneva: United Nations Human Rights Council; July 2018.
[3] 35th UNAIDS PCB Meeting: When 'Rights' cause wrongs: Addressing intellectual property barriers to ensure access to treatment for all people living with HIV; agenda item 1.4 UNAIDS/PCB (35)/14.19; November 2014. http://www.unaids.org/sites/default/files/media_asset/20141114_NGOreport_35PCB.pdf
[4] 35th UNAIDS PCB meeting: Decisions, recommendations and conclusions; agenda item 1.4, decision point 4.3. Geneva: UNAIDS; December, 2014. (http://www.unaids.org/sites/default/files/media_asset/20141212_Decisions_35PCB_meeting_EN.pdf)
[5] 39th UNAIDS PCB Meeting: Synthesis report of existing literature and research on intellectual property related and other factors impacting the availability, affordability and accessibility of treatment and diagnostics for HIV and coinfections in low- and middle-income countries; agenda item 6, UNAIDS/PCB (39)/ 16.22 Geneva: UNAIDS; November 2016. (http://www.unaids.org/en/resources/documents/2016/PCB39_16-22)
[6] 39th UNAIDS PCB meeting: Decisions, recommendations and conclusions; agenda item 6, decision point 7.3, 7.5. Geneva: UNAIDS; December, 2016. (http://www.unaids.org/en/resources/documents/2016/PCB39_Decisions)
[7] 35th UNAIDS PCB Meeting: Report by the NGO Representative: When 'Rights' cause wrongs: Addressing Intellectual Property barriers to ensure access to treatment for all people living with HIV; agenda item 1.4, UNAIDS/PCB (35)/14.19 Geneva: UNAIDS; November 2014. (http://www.unaids.org/sites/default/files/media_asset/20141114_NGOreport_35PCB.pdf
[8] 39th UNAIDS PCB Meeting: Synthesis report of existing literature and research on intellectual property related and other factors impacting the availability, affordability and accessibility of treatment and diagnostics for HIV and coinfections in low- and middle-income countries; agenda item 6, UNAIDS/PCB (39)/ 16.22 Geneva: UNAIDS; November 2016. http://www.unaids.org/en/resources/documents/2016/PCB39_16-22
[9] United Nations Secretary General High Level Panel on Access to Medicines. Report of the United Nations Secretary General's High Level Panel on Access to Medicines: UN; 2016. (http://www.unsgaccessmeds.org/final-report/)
[10] WHA 68.18. Global strategy and plan of action on public health, innovation and intellectual property. Geneva: World Health Assembly, May 2015. (http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf#page=27)
[11] WHA 71(8). Addressing the global shortage of, and access to, medicines and vaccines. Geneva: World Health Assembly, May 2018. (http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71(8)-en.pdf)
[12] UNAIDS, On the Fast-Track to end AIDS: 2016-2021 Strategy. [internet]. Geneva: UNAIDS; 2015. http://www.unaids.org/sites/default/files/media_asset/20151027_UNAIDS_PCB37_15_18_EN_rev1.pdf
[13] UN Women, Key Barriers to Women's Access to HIV Treatment: A Global Review. [internet]. New York: UN Women; 2017. http://www.unwomen.org/en/digital-library/publications/2017/12/key-barriers-to-womens-access-to-hiv-treatment
[14] Medecins Sans Frontieres (MSF). Untangling the Web of antiretroviral price reductions. [internet]. Geneva: MSF; 2018. https://msfaccess.org/utw
[15] World Intellectual Property Organization (WIPO). PAT-Informed: The Gateway to Medicine Patent Information. [internet]. Geneva: WIPO; 2018. http://www.wipo.int/pat-informed/en/
[16] Medicines, Law and Policy. WIPO and pharma industry launch global medicines patent database. [internet]. 2018. (https://medicineslawandpolicy.org/2018/09/wipo-and-pharma-industry-launch-global-medicines-patent-database/)
[17] Initiative for Medicines, Access, and Knowledge (I-MAK). Roadmap Special Edition report dolutegravir. [internet]. New York: I-MAK, 2017. http://www.i-mak.org/wp-content/uploads/2017/06/I-MAKRoadmapSEReportDTG20170619F.pdf
[18] Medecins Sans Frontieres (MSF). Patent Opposition Database dolutegravir. [internet]. Geneva: MSF, 2018. https://www.patentoppositions.org/en/drugs/dolutegravir
[19] Medicines Patent Pool (MPP). Voluntary license for dolutegravir. [internet]. Geneva: MPP, 2014. https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/
[20] Medicines Patent Pool (MPP). Voluntary license for dolutegravir. [internet]. Geneva: MPP, 2014. https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/
[21] UNAIDS. New high- quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low-and middle-income countries at reduced price. [internet]. Geneva: UNAIDS, 2017. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/september/20170921_TLD
[22] Interview with official at the Ministry of Health within the Government of Brazil; interview held on October 19th, 2018.
[23] Interviews with industry representatives and civil society representatives.

[24] ViiV, Viiv Healthcare and Desano Pharmaceuticals manufacturing agreement will allow competitive supply of dolutegravir in China and several developing countries. [internet]. London: ViiV, 2015. https://www.viivhealthcare.com/media/press-releases/2015/july/viiv-healthcare-and-desano-pharmaceuticals-manufacturing-agreement-will-allow-competitive-supply-of-dolutegravir-in-china-and-several-developing-countries.aspx
[25] Pharma Letter, ViiV to start production of dolutegravir in Russia. [internet]. Pharma Letter: 2016. https://www.thepharmaletter.com/article/viiv-healthcare-to-start-production-of-dolutegravir-in-russia
[26] Medecins Sans Frontieres (MSF). HIV and Opportunistic Infection Treatment: Spotlight on Gaps. [internet]. Geneva: MSF, 2017. https://msfaccess.org/sites/default/files/HIV_Brief_SpotlightOnAccessGaps_ENG_2017.pdf
[27] ViiV. Worldwide registration 10mg and 25 mg tablet Tivicay. [internet]. Viiv 2018. https://www.viivhealthcare.com/media/126335/tivicay-paed-wwrs-11oct2018-for-external-use.pdf
[28] World Health Organization (WHO). Statement on DTG. [internet]. Geneva: WHO, 2018. http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf
[29] UNITAID. New partnership to help fast-track affordable HIV medicine for children living with HIV. [internet]. Geneva: UNITAID, 2018. https://unitaid.org/news-blog/new-partnership-to-help-fast-track-affordable-hiv-medicine-for-children-living-with-hiv/#en
[30] World Health Organization (WHO). Hepatitis C fact sheet [internet]. Geneva: WHO; 2018. http://www.who.int/news-room/fact-sheets/detail/hepatitis-c
[31] Gilead Sciences. Gilead Sciences to acquire Pharmasset, Inc. for US$ 11 billion. [internet]. Foster City: Gilead, 2011. http://investors.gilead.com/phoenix.zhtml?ID=1632335&c=69964&p=irol-newsArticle
[32] World Health Organization (WHO). Progress report on access to Hepatitis C treatment. [internet]. WHO: Geneva, 2018. http://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf;jsessionid=062458C0870AAA901820A41F6182241E?sequence=1
[33] Initiative for Medicines, Access, and Knowledge (I-MAK). America's Overspend: How the pharmaceutical patent problem is fueling high drug prices. New York: I-MAK, 2017. http://www.i-mak.org/wp-content/uploads/2017/10/Excess-Costs-Briefing-Paper-FINAL_-2017-10-24.pdf
[34] Medicines Patent Pool (MPP). MedsPaL patent database search for sofosbuvir. [internet]. Geneva: MPP: 2018. http://www.medspal.org/?product_standardized_name=Sofosbuvir%20400%20mg
[35] Iyengar S., Tay-Teo K., Vogler S., Beyer P., Wiktor S., de Joncheere K., Hill S., Prices, Costs, and Affordability of new medicines for Hepatitis C in 30 countries: An economic analysis, PLOS Med. 2016 May; 13(5): e1002032
[36] Hill A., Simmons B., Gotham D., Fortunak J., Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat Hepatitis C. J. Virus Erad. 2016 Jan; 2(1): 28-31.
[37] Gilead. Gilead announces generic licensing agreements to increase access to hepatitis C treatments in developing countries. [internet]. New Delhi: Gilead, 2014. http://www.gilead.com/news/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries
[38] The Atlantic. Why Egypt is at the forefront of Hepatitis C treatment. [internet]. Atlantic, 2018. https://www.theatlantic.com/health/archive/2018/05/why-egypt-is-at-the-forefront-of-hepatitis-c-treatment/561305/
[39] World Health Organization (WHO). Progress report on access to Hepatitis C treatment. [internet]. WHO: Geneva, 2018. http://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf;jsessionid=062458C0870AAA901820A41F6182241E?sequence=1
[40] Reuters. Brazil court strips Gilead of hepatitis C drug patent. [internet]. Reuters: Sao Paulo, 2018. https://www.reuters.com/article/us-gilead-sciences-brazil/brazil-court-strips-gilead-of-hepatitis-c-drug-patent-idUSKCN1M426U
[41] World Health Organization (WHO). Progress report on access to Hepatitis C treatment. [internet]. WHO: Geneva, 2018. http://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf;jsessionid=A159B7BD4A4CAA08A594227E692D244D?sequence=1
[42] Intellectual Property Watch. Malaysia grants compulsory license for generic sofosbuvir despite Gilead license. [internet]. IP-Watch: Geneva, 2017. http://www.ip-watch.org/2017/09/15/malaysia-grants-compulsory-licence-generic-sofosbuvir-despite-gilead-licence/
[43] Fierce Pharma. Gilead prices hepatitis C giant Solvadi at one-fifth the US price. [internet]. Fierce Pharma, 2017. https://www.fiercepharma.com/financials/gilead-prices-hep-c-giant-sovaldi-china-at-one-fifth-u-s-price-report
[44] Initiative for Medicines, Access, and Knowledge (I-MAK). China patent challenge compels Gilead to withdraw key patent claims on sofosbuvir base compound, opening life-saving Hepatitis C treatment for millions. I-MAK: New York, 2018. http://www.i-mak.org/2018/08/09/china-patent-challenge-compels-gilead-withdraw-key-patent-claims-sofosbuvir-base-compound-opening-life-saving-hepatitis-c-treatment-access-millions/
[45] Drugs for Neglected Diseases Initiative (DNDi). A public health approach to the Hepatitis C epidemic. [internet]. Geneva: DNDi, 2018. https://www.dndi.org/wp-content/uploads/2018/07/DNDi_HCV_2018.pdf
[46] Haryana Medical Services Corporation. Price of sofosbuvir. Haryana: India, 2018. http://hmscl.org.in/DrugRC.html
[47] Medecins Sans Frontieres (MSF). Bedaquiline FDA approval fact sheet. [internet]. Geneva: MSF; 2012. https://www.msf.org/bedaquiline-first-new-tuberculosis-drug-50-years
[48] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[49] Medicines Patent Pool (MPP). MedsPaL patent database search for bedaquline. [internet]. Geneva: MPP: 2018. http://www.medspal.org/?product_standardized_name=Bedaquiline%20100%20mg

[50] Medecins Sans Frontieres (MSF). Patent Opposition Database bedaquiline.[internet]. Geneva: MSF, 2018. https://www.patentoppositions.org/en/drugs/bedaquiline
[51] Treatment Action Group (TAG). Reality Check: The price of bedaquiline. [internet]. TAG: New York, 2018. http://www.treatmentactiongroup.org/sites/default/files/reality_check_bedaquiline_10_16_18.pdf
[52] Medecins Sans Frontieres (MSF). First new TB drugs in half a century reach just 2% of people who need them. [internet]. MSF: Cape Town, 2015. https://msfaccess.org/first-new-tb-drugs-half-century-reach-just-2-people-who-need-them
[53] Gotham D., Fortunak J., Pozniah A., Khoo S., Cooke G., Nytko III F.E., Hill A., Estimated generic prices for novel treatments for drug-resistant tuberculosis. Journal of Antimicrobial Chemotherapy, 72(4), 1 April 2017: 1243-1252. https://doi.org/10.1093/jac/dkw522
[54] USAID. USAID's bedaquiline donation program in partnership with Johnson & Johnson. [internet]. USAID: Washington, 2018. https://www.usaid.gov/what-we-do/global-health/tuberculosis/technical-areas/bedaquiline-donation-program
[55] Janssen. Janssen joins partnership in China to provide access to bedaquiline for the treatment of multidrug resistant tuberculosis. [internet]. Janssen: Beijiing, 2018. https://www.xian-janssen.com.cn/en/news/639
[56] Pharmstandard. Pharmstandard and Janssen broaden collaboration to advance ongoing efforts to tackle multidrug resistant tuberculosis. |internet]. Pharmstandard: Moscow, 2018. https://pharmstd.com/archivedetails_64_2747.html
[57] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[58] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[59] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[60] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition online supplement). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_Supplement_UTM_ENG_2018.pdf
[61] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[62] World Health Organization (WHO). WHO implementation tool for pre-exposure prophylaxis of HIV infection. [internet]. WHO: Geneva, 2017. http://apps.who.int/iris/bitstream/handle/10665/258509/WHO-HIV-2017.27-eng.pdf?sequence=1
[63] Medecins Sans Frontieres (MSF). Patent Opposition Database Tenofovir disoproxil fumarate. [internet]. Geneva: MSF, 2018. https://www.patentoppositions.org/en/drugs/tenofovir-disoproxil-fumarate
[64] Gilead. Gilead offers voluntary licenses for manufacturing of Viread in developing world. [internet]. Gilead: Foster City, 2006. http://www.gilead.com/news/press-releases/2006/5/gilead-offers-voluntary-licenses-for-manufacturing-of-viread-in-developing-world-
[65] Medicines Patent Pool (MPP). Tenofovir Disoproxil Fumarate. [internet]. MPP: Geneva, 2011. https://medicinespatentpool.org/licence-post/tenofovir-disoproxil-fumarate-tdf/
[66] Intellectual Property Watch. Truvada case shows civil society success with pregrant oppositions. [internet]. IPW 2018. http://www.ip-watch.org/2018/05/08/truvada-case-shows-civil-societys-success-pre-grant-opposition/
[67] IHS Markit. Indonesia issues compulsory licenses against seven HIV, hepatitis drugs. [internet]. IHS Markit 2012. https://ihsmarkit.com/country-industry-forecasting.html?ID=1065972339
[68] Medicines Patent Pool (MPP). Tenofovir/Emtricitabine. [internet]. MPP: Geneva, 2011. http://www.medspal.org/?product_standardized_name=Tenofovir/Emtricitabine%20150/100%20mg
[69] Wall Street Journal (WSJ). U.K. Health Service turns to clinical trial to make cheaper HIV drug available.[internet]. WSJ 2017. See: https://www.wsj.com/articles/englands-nhs-turns-to-clinical-trial-to-make-cheaper-hiv-drug-1502441145
[70] McDermett, Will and Emery. CJEU issues landmark decision on patent term extensions for medicinal products. [internet]. 2018. http://www.mondaq.com/unitedstates/x/733216/Patent/CJEU+Issues+Landmark+Decision+On+Patent+Term+Extensions+For+Medicinal+Products
[71] National Public Radio (NPR). Rising cost of PrEP to prevent HIV infection pushes it out of reach for many. [internet]. NPR: 2018. https://www.npr.org/sections/health-shots/2018/06/30/624045995/rising-cost-of-prep-a-pill-that-prevents-hiv-pushes-it-out-of-reach-for-many
[72] UNICEF. Pediatric care and treatment. |internet]. UNICEF: New York, 2018. https://data.unicef.org/topic/hivaids/paediatric-treatment-and-care/
[73] Penazzato M., Irvine C., Vicari M., Essajee S.M., Sharma A., Puthanakit T., Abrams E.J., Doherty M., A global research agenda for pediatric HIV. Acquir Immune Defic Syndro. Volume 78, Supplement 1. August 15, 2018. https://www.who.int/hiv/pub/journal_articles/jaids2018-03.pdf
[74] UNAIDS. Preventing mother-to-child transmission of HIV. [internet]. UNAIDS : Geneva 2016. http://www.unaids.org/en/resources/presscentre/featurestories/2016/october/20161024_EMotherToChildT
[75] Penazzato M., Irvine C., Vicari M., Essajee S.M., Sharma A., Puthanakit T., Abrams E.J., Doherty M., A global research agenda for pediatric HIV. Acquir Immune Defic Syndro. Volume 78, Supplement 1. August 15, 2018. https://www.who.int/hiv/pub/journal_articles/jaids2018-03.pdf
[76] Scroll.in, An HIV medicine for toddlers is out of stock across India. [internet]. Scroll: New Delhi, 2017. https://scroll.in/pulse/830682/an-hiv-medicine-for-toddlers-is-out-of-stock-across-india

[77] UNITAID. HIV portfolio. [internet]. UNITAID: Geneva. https://unitaid.org/assets/Unitaid-HIV-Portfolio.pdf
[78] Young R, Bekele T, Gunn A, Chapman N, Chowdary V, Corrigan K et al. Developing new technologies for neglected diseases: A pipeline portfolio review and cost model. *Gates Open Res* 2018, 2:23 (https://gatesopenresearch.org/articles/2-23/v2).
[79] Gavi, Human papillomavirus support.[internet]. Gavi: Geneva. https://www.gavi.org/support/nvs/human-papillomavirus/
[80] Clendinen C, Zhang Y, Warburton R, Light D, Manufacturing costs of HPV vaccines for developing countries. Vaccine. Volume 34 (48), 21 November 2016, 5984-5989. (https://www.sciencedirect.com/science/article/pii/S0264410X16308568).
[81] PAHO. Revolving Fund vaccine prices. [internet]. PAHO: Washington, 2018 (https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=vaccines-9979&alias=43314-revolving-fund-vaccine-prices-2018-314&Itemid=270&lang=en).
[82] Médecins Sans Frontières. The right shot: Bringing down barriers to affordable and adapted vaccines 2nd Edition. Geneva: MSF; 2015 (https://msfaccess.org/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines-2nd-ed-2015).
[83] Médecins Sans Frontières. The Right Shot: Bringing down barriers to affordable and adapted vaccines 2nd Edition. [internet]. MSF: Geneva, 2015 (https://msfaccess.org/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines-2nd-ed-2015).
[84] Médecins Sans Frontières. A fair shot for vaccine affordability. [internet]. MSF: Geneva, 2017. (https://msfaccess.org/sites/default/files/VAC_report_A%20Fair%20Shot%20for%20Vaccine%20Affordability_ENG_2017.pdf).
[85] Young R, Bekele T, Gunn A, Chapman N, Chowdary V, Corrigan K et al. Developing new technologies for neglected diseases: A pipeline portfolio review and cost model. [version 2; referees: 3 approved]. *Gates Open Res* 2018, 2:23 (https://gatesopenresearch.org/articles/2-23/v2)
[86] Young R, Bekele T, Gunn A, Chapman N, Chowdary V, Corrigan K, Dahora L, et al. Developing new technologies for neglected diseases: A pipeline portfolio review and cost model. *Gates Open Res* 2018, 2:23 (https://gatesopenresearch.org/articles/2-23/v2).
[87] Owen A, Rannard S, Jackson A, Dickinson L, Giardielle M, Siccardi M et al. Human confirmation of oral dose reduction potential of nanoparticle ARV formulations. Abstract 39. CROI, February 13–16, 2017 Seattle, Washington. Available from: http://www.croiconference.org/sessions/human-confirmation-oral-dose-reduction-potential-nanoparticle-arv-formulations
[88] Medicines Patent Pool. The Medicines Patent Pool signs a collaborative agreement with the University of Liverpool to develop HIV nanomedicines. Geneva: MPP; 2015 (https://medicinespatentpool.org/mpp-media-post/the-medicines-patent-pool-signs-a-collaborative-agreement-with-the-university-of-liverpool-to-develop-hiv-nanomedicines/).
[89] Medicines Patent Pool. The Medicines Patent Pool signs a collaborative agreement with the University of Liverpool to develop HIV nanomedicines. Geneva: MPP; 2015 (https://medicinespatentpool.org/mpp-media-post/the-medicines-patent-pool-signs-a-collaborative-agreement-with-the-university-of-liverpool-to-develop-hiv-nanomedicines/).
[90] Marmora, L Casas C, Grubb I, McClure C, Long-acting technologies for infectious diseases in LMICs.The Lancet.D-18-06212 S0140-6736(18)32544-3.
[91] Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamcer D et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet [Online]. 2017;390(10101):1499-1510.
[92] Rajoli RK, Back DJ, Rannard S, Freel Meyers CL, Flexner C, Owen A, Siccardi M. Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV. Clin Pharmacokinet. [Online] 2015 Jun [Cited 2018 July 1];54(6):639-50. Available from: 10.1007/s40262-014-0227-1. (https://www.ncbi.nlm.nih.gov/pubmed/25523214)
[93] Flexner C. Long acting Antiretroviral Therapy: a Shot in the Dark or a Paradigm Shift? (Abstract 147) CROI [Online] February 13–16, 2017 [Cited 2018 July 16] Seattle, Washington. Available from: http://www.croiwebcasts.org/portal;jsessionid=ACF8A18B25FFFBC2A647B417402CF141
[94] Marmora, L. Casas C., Grubb I., McClure C., Long-acting technologies for infectious diseases in LMICs.The Lancet.D-18-06212 S0140-6736(18)32544-3. (http://dx.doi.org/10.1016/ S0140-6736(18)32544-3)
[95] USFDA, FDA approves new HIV treatment for patients who have limited options. [internet]. FDA: Washington, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599657.htm?
[96] FDA Drug Watch, Drug Watch : Ibalumizab. . [internet]. JAMA 2018]. https://www.jwatch.org/na46459/2018/04/10/drug-watch-ibalizumab
[97] Young R., Bekele T., Gunn A., Chapman N., Chowdary V., Corrigan K., Dahora L., Martinez S., Permar S., Persson J., Rodriguez B., Schaferhoff M., Schulman K., Singh T., Terry R.F., Yamey G., Developing new technologies for neglected diseases: A pipeline portfolio review and cost model. [version 2; referees: 3 approved]. *Gates Open Res* 2018, 2:23 (https://gatesopenresearch.org/articles/2-23/v2)
[98] Third World Network (TWN).Biological Drugs: Challenges to Access. [internet]. TWN: Geneva, 2018. https://www.twn.my/announcement/biologicaldrugs/Biologics%20English.pdf
[99] Financial Times. Fall in number of patents filed by big pharma. Financial Times, 18 March 2012, https://www.ft.com/content/0912c0ea-70f9-11e1-a7f1-00144feab49a
[100] Third World Network (TWN).Biological Drugs: Challenges to Access. [internet]. TWN: Geneva, 2018. https://www.twn.my/announcement/biologicaldrugs/Biologics%20English.pdf

[101] Barry, F (2015) Filgastrim biosimilar is first Latin copy biologic, says Brazil. [internet]. BioPharma Reporter, 24 November 2015, http://www.biopharma-reporter.com/Markets-Regulations/Filgrastim-biosimilar-is-first-Latin-copy-biologic-says-Brazil
[102] Accessibsa. Pharmaceutical patent grants in India: How our safeguards against evergreening have failed, and why the system must be reformed. [internet]. Accessibsa: Delhi,2018. https://www.accessibsa.org/media/2018/04/Pharmaceutical-Patent-Grants-in-India.pdf
[103] Medecins Sans Frontieres (MSF). DR-TB drugs under the microscope (5th edition). [internet]. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-10/TB_IssueBrief_UTM_ENG_2018.pdf
[104] 't Hoen Ellen FM, Veraldi J., Toebesc B., Hogerzeil H.,Medicine procurement and the use of flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights, 2001–2016. Bulletin of the World Health Organization; Type: Policy & practice Article ID: BLT.17.199364. (http://www.who.int/bulletin/online_first/BLT.17.199364.pdf)
[105] Moon S., Jambert E., Childs M, von Schoen-Angerer T. A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. Globalization and Health. 2011; 7: 39 (https://doi.org/10.1186/1744-8603-7-39).
[106] Medicins Sans Frontieres (MSF). South Africa should override patent on key HIV medicine after widespread stock-out problems. [internet]. South Africa: MSF, 2015. https://www.msf.org/south-africa-should-override-patent-key-hiv-medicine-after-widespread-stock-out-problem
[107] Medicines Patent Pool, The Medicines Patent Pool and Abbvie sign licensing agreement to increase access to crucial HIV treatments throughout Africa. [internet]. MPP: Geneva, 2015. https://medicinespatentpool.org/mpp-media-post/the-medicines-patent-pool-and-abbvie-sign-licensing-agreement-to-increase-access-to-crucial-hiv-treatments-throughout-africa/
[108] IOL, Patients worried over shortage of live-saving meds. [internet]. IOL: Durban, 2018. https://www.iol.co.za/thepost/patients-worried-over-shortage-of-life-saving-meds-17634592
[109] Pharmabiz. China crackdown on polluting firms leaves India pharma industry in quandary as API prices rise 40% in 4 months.[internet]. Pharmabiz: New Delhi, 2018. http://www.pharmabiz.com/NewsDetails.aspx?aid=109959&sid=1
[110] Medecins Sans Frontieres (MSF), Untangling the web of ARV price reductions. [internet]. MSF: Geneva, 2016. https://msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/UTW_Drug_Profiles_DRV.pdf
[111] Medicines Patent Pool (MPP), Patents related to darunavir. [Internet]. MPP: Geneva, 2010. https://medicinespatentpool.org/fr/licence-post/darunavir/
[112] Medecins Sans Frontieres (MSF), Untangling the web of ARV price reductions. [internet]. MSF: Geneva, 2016. https://msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/UTW_Drug_Profiles_DRV.pdf
[113] Johnson and Johnson. Janssen announces intent not to enforce patents for darunavir in resource-limited settings. [internet]. J&J 2012. https://www.jnj.com/media-center/press-releases/janssen-announces-intent-not-to-enforce-patents-for-darunavir-in-resource-limited-settings
[114] Medecins Sans Frontieres (MSF), Untangling the web of ARV price reductions. [internet]. MSF: Geneva, 2016. https://msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/UTW_Drug_Profiles_DRV.pdf
[115] Medecins Sans Frontieres (MSF), Untangling the web of ARV price reductions. [internet]. MSF: Geneva, 2016. https://msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/UTW_Drug_Profiles_DRV.pdf
[116] Johnson and Johnson (J&J), Janssen, the pharmaceutical companies of Johnson and Johnson, announces first of its kind drug donation program for HIV treatment-experienced children. J&J: Cape Town 2013. https://www.jnj.com/media-center/press-releases/janssen-the-pharmaceutical-companies-of-johnson-johnson-announces-first-of-its-kind-drug-donation-program-for-hiv-treatment-experienced-children
[117] Medecins Sans Frontieres (MSF), Untangling the web of ARV price reductions. [internet]. MSF: Geneva, 2016. https://msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/UTW_Drug_Profiles_DRV.pdf
[118] Medecins Sans Frontieres (MSF). Stopping senseless deaths: Overcoming access barriers to affordable, lifesaving diagnostics and treatments for HIV and opportunistic infections. MSF: Geneva, 2018. https://msfaccess.org/sites/default/files/2018-07/HIV_Brief_Stopping_SenselessDeaths_ENG_2018.pdf
[119] Stop TB Partnership. AMR Review releases final recommendations urging new investments to prevent a catastrophic rise of drug-resistant tuberculosis and other infections. [internet]. Stop TB Partnership: Geneva, 2016. http://www.stoptb.org/news/stories/2016/ns16_019.asp