THE ACCESS AND DELIVERY PARTNERSHIP

New Health Technologies for TB, Malaria and NTDs

The impact of WTO TRIPS Agreement on access to medicines

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UNDP
Presentation Outline

- TRIPS, Doha and access to medicines
- What have we learnt?
- Future challenges and emerging issues
- An enabling environment for innovation and access
- Introducing the Access and Delivery Partnership
Cost of ARV treatment in 2000 = US$10,439 per year
BUT in 2001, Indian company, Cipla, introduced
generic ARVs at US$350 a year
Introduction of generic ARVs have reduced prices up
to 99% = $65 a year
22-fold increase in global ARV coverage has been
possible due to competition from generic medicines
Introduction of generic medicines ➔ market
competition ➔ reduced medicine prices
The competition effect: Prices drop with generic introduction
The case of India demonstrates how strategic use of flexibility in TRIPS Agreement contributed to development of India’s pharmaceutical industry.

Transition period under TRIPS allowed India not to grant patents for pharmaceutical products until 2005, permitted Indian manufacturers to produce **generic medicines**.

The 2005 transition period is an example of a flexibility available under TRIPS Agreement.

LDCs have another important flexibility – no pharmaceutical patents until 2016; no TRIPS implementation until 2021.
The ability to produce and supply generic medicines will be limited in the future, as TRIPS Agreement implementation requires patent protection for pharmaceutical.

Majority of new medicines are now patented in many countries, including those with capacity to produce affordable ARVs and other generic medicines, such as India, Thailand and China.

Use of TRIPS flexibilities will be crucial to ensure continued ability to produce generic medicines and ensure access to affordable medicines.
Price comparisons of first-line, second-line and possible third-line

- **First-line**:
  - Lowest generic price TDF/3TC+EFV*: $143
  - Multiplied by 19.3

- **Second-line**:
  - Lowest generic price AZT/3TC+ATV+r: $442
  - Multiplied by 6.3

- **Possible third-line**:
  - RAL+DRV+r+ETV: $2766

**US$ per patient per year**
India’s Patent Act: Impact on generic production and access

- India supplies over 80% of generic ARVs used in LMICs
- Patents on new medicines will affect ability of generic manufacturers to produce future ARVs and medicines to treat NCDs
- Drug resistance requires switch to second generation ARVs: some under patent 3.4 times more expensive, 3rd generation up to 23.4 times more expensive
- Exporting countries like India will need to maximise use of TRIPS Flexibilities
- Importing countries will need to take full advantage of safeguards and flexibilities
- This is especially important given eventual shift to 2nd & 3rd generation ARVs
India’s Patent Act: Impact on exports and patent grants

U.S. Pharmaceutical Exports to India, Millions USD

<table>
<thead>
<tr>
<th>3520</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical patents granted in India, 2007-2012 (Source: Indian Patent Office)</td>
<td>Compulsory license for a German pharmaceutical product</td>
<td>Compulsory licenses for U.S. pharmaceutical Products</td>
</tr>
</tbody>
</table>
Doha Declaration on TRIPS and Public Health

- Backdrop of HIV/AIDS epidemic
- Legal challenges to developing countries legislation
  - South Africa: Pharmaceutical company challenge of amendment to Medicines and Related Substances Act (1997)
  - Brazil: US complaint to WTO Dispute Settlement on local working provision (2000)
- The culmination of debate at WTO, arising from developing country proposal to examine impact of TRIPS on access to medicines – WTO 4th Ministerial Conference in Doha, 14 November 2001
The Doha Declaration

“We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health … we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members’ right to protect public health and in particular, to promote access to medicines for all”

- Clarification that TRIPS Agreement does not prevent WTO Members from taking measures to protect public health
  - Interpretative guide to TRIPS
  - Affirmation of right to use flexibilities in TRIPS
  - Expeditious solution for countries with insufficient or no manufacturing capacities
  - Extension of LDC transition period (now up to 2016)
Policy options for affordable medicines

Import of medicines

- **Compulsory licence** = government grants a compulsory licence to allow a drug company to import from a foreign produce. **Example:** Drug company or distributor in Country A imports generic medicine from India under a CL.

- **Government use licence** = government is licensed to import from foreign producer for “public use”. **Example:** MOH in Country A imports generic medicine from Thailand under GU licence for use in public hospital.

- **Parallel importation** from a country where the branded medicine is sold at a cheaper price. **Example:** Patented drug X is sold for $10 a tablet in Country A but sold for $5 in Malaysia. If national law in Country A allows for parallel import, drug X can be imported into the country at the cheaper price.
Policy options for affordable medicines

Domestic R&D and local production

- **Patentability standards** = to ensure grant of high-quality patents
- **R&D exception** = to allow for research and development on patented chemical compounds
- **Bolar exception** = allows preparation and testing of patented product for drug regulatory approval, so that generic medicine can be ready for approval by FDA once patent expires
- **Compulsory licence** = a drug company is granted a CL to manufacture generic version of patented medicine in the country and to sell the generic version on the private market
- **Government use licence** = government grants a GU licence to a drug company in Country A to manufacture generic for use in the public sector
<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Nation</th>
<th>National Income Group</th>
<th>Disease</th>
<th>Disease Group</th>
<th>Total Products</th>
<th>Outcome</th>
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<tr>
<td>2001</td>
<td>Brazil</td>
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<td>HIV/AIDS</td>
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<tr>
<td>2001</td>
<td>Canada</td>
<td>HIC</td>
<td>Anthrax</td>
<td>CD</td>
<td>1</td>
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<td>Discount</td>
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<td>2002</td>
<td>Egypt</td>
<td>LIC</td>
<td>Erectile dysfunction</td>
<td>NCD</td>
<td>1</td>
<td>CL</td>
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<td>2003, 2007</td>
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<td>LDC</td>
<td>Pandemic flu</td>
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<td>Ghana</td>
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<td>HIV/AIDS</td>
<td>HIV/AIDS</td>
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<td>2005</td>
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<td>LIC</td>
<td>HIV/AIDS</td>
<td>HIV/AIDS</td>
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<tr>
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<td>Taiwan</td>
<td>HIC</td>
<td>Pandemic flu</td>
<td>CD</td>
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<td>VL</td>
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<td>2006–2007</td>
<td>India</td>
<td>LIC</td>
<td>Cancer</td>
<td>NCD</td>
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<td>None</td>
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<td>2010</td>
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<td>UMIC</td>
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<td>HIV/AIDS</td>
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<td>CL</td>
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</table>

Totals: 24 Episodes, 17 Nations, 40 Unique Drug-Nation Combinations +2 Categorical CLs. Years in parentheses indicate CL renewals. CVD, cardiovascular disease.
doi:10.1371/journal.pmed.1001154.t001

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001154
## Price impact of compulsory licences

*Source: Global Commission on HIV and the Law (2012), UNDP*

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of License and medicine</th>
<th>Impact on prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>Government-use order for the production of combination of generic stavudine + didonasine + nevirapine</td>
<td>Resulted in price reduction of 83%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Government-use order to locally manufacture generic lamivudine, nevirapine</td>
<td>Resulted in price reduction of 53.3%</td>
</tr>
<tr>
<td>Thailand</td>
<td>Government-use order to import or locally produce generic lopinavir/ritonavir</td>
<td>Projected price reductions of 80.2%</td>
</tr>
<tr>
<td>Brazil</td>
<td>Compulsory licence issued by Government to import generic efavirenz</td>
<td>71.8% price reduction</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Compulsory license to import and, if necessary, locally produce generic ritonavir</td>
<td>Patent holder reduced price of branded medicine by 70%</td>
</tr>
<tr>
<td>India</td>
<td>Compulsory license to locally produce sorafenib tosylate to treat kidney cancer and liver cancer</td>
<td>Price set by Patent Controller will result in 97% reduction</td>
</tr>
</tbody>
</table>
Indonesia – Government use licence

- 2004: Indonesian Presidential Decree authorised local production of nevirapine and lamivudine.

- 2013: Indonesian Presidential Decree authorising local production of 6 medicines to meet the availability and urgent need of the Antiviral and Antiretroviral Medicines for the treatment of Human Immunodeficiency Virus-Acquired Immune Deficiency Syndrome (HIV / AIDS) and Hepatitis B.

<table>
<thead>
<tr>
<th>No</th>
<th>NAME OF ACTIVE SUBSTANCES</th>
<th>NAME OF PATENT HOLDER</th>
<th>PATENT NUMBER</th>
<th>TERM OF THE PATENT</th>
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</thead>
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<tr>
<td>1</td>
<td>Efavirenz</td>
<td>Merck &amp; Co. INC</td>
<td>ID 0 005 812</td>
<td>Until the end of the Patent, August 7, 2013</td>
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<td>2</td>
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<td>Glaxo Group Limited</td>
<td>ID 0 011 387</td>
<td>Until the end of the Patent, May 14, 2018</td>
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<td>Didanosin</td>
<td>Bristol – Myers Squibb Company</td>
<td>ID 0 010 163</td>
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<td>4</td>
<td>Combination of Lopinavir and Ritonavir</td>
<td>Abbot Laboratories</td>
<td>ID P 0023461</td>
<td>Until the end of the Patent, August 23, 2018</td>
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<td>5</td>
<td>Tenofovir</td>
<td>Gilead Sciences, Inc</td>
<td>ID 0 007 658</td>
<td>Until the end of the Patent, July 23, 2018</td>
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<tr>
<td>6</td>
<td>Combination of Tenofovir and Emtricitabin - Combination of Tenofovir, Emtricitabin and Eyafirenz</td>
<td>Gilead Sciences, Inc</td>
<td>ID P0029476</td>
<td>Until the end of the Patent, November 3, 2024</td>
</tr>
</tbody>
</table>
## Comparison of originator vs. generic drug prices

<table>
<thead>
<tr>
<th>Drug specification</th>
<th>Price (USD)</th>
<th>% of price reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
<td>Generic</td>
</tr>
<tr>
<td>1. EFV 600mg</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>2. LPV/r 133mg/33mg</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>3. Clopidogrel 75mg</td>
<td>2.3</td>
<td>0.1</td>
</tr>
<tr>
<td>4. Letrozole 2.5mg</td>
<td>7.0</td>
<td>0.2</td>
</tr>
<tr>
<td>5. Docetaxel 80mg</td>
<td>863</td>
<td>37.9</td>
</tr>
<tr>
<td></td>
<td>237.71</td>
<td>9.1</td>
</tr>
<tr>
<td>6. Erlotinib 150mg</td>
<td>83.7</td>
<td>22.4</td>
</tr>
<tr>
<td>7. Imatinib 400mg</td>
<td>111.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Rate of use of Lopinavir/Ritonavir, 200/50mg (bottles) under Universal Health Coverage scheme.
Rate of use of Efavirenz, 600 mg. (bottles) under Universal Health Coverage Scheme
Impact of patents on innovation and access

Triple therapy ARV FDCs:

- 2003 WHO Treatment Guidelines advocated use of FDCs to promote adherence and limit resistance, as a strategy for WHO 3x5 campaign

- FDCs from originator companies at the time did not reflect WHO-recommended regimens for first-line treatment - difficulties posed by patents on each component held by different parties

- Absence of product patents enabled Indian manufacturers to produce required FDCs - WHO prequalified first triple ARV FDCs from Indian generic manufacturers

- By 2009, USFDA and WHO PQ approved 57 adult FDCs, 31 paediatric ARVs from Indian generic manufacturers, compared to 8 adult FDCs and 14 paediatric ARVs by non-Indian and originator companies
Global campaign against HIV/AIDS

Lessons learnt?
- Impact of patents on medicine prices
- Generic competition enabled access
- Impact of patents on innovation and access

Going beyond HIV/AIDS
"Is this going to have a big effect on our business model? No, because we did not develop this product for the Indian market, let’s be honest. We developed this product for Western patients who can afford this product, quite honestly."

Marijn Dekkers, Bayer CEO December 2013, referring to a decision by an Indian patent court that granted a compulsory license to a local company to reproduce Bayer’s drug. Under Indian patent laws, if a product is not available locally at a reasonable cost, other companies may apply for licenses to reproduce those products at a more affordable price. Nexavar costs an estimated $69,000 for a full year of treatment in India, 41 times the country’s annual per capita income.
Dearth of R&D for NTDs

- January 2014, AstraZeneca announces withdrawal from all early R&D for TB, Malaria and NTDs to focus efforts on drugs for cancer and hypertension

- Pfizer stopped R&D into all anti-infective drugs in 2012

- In 2012, only a third of funding required to undertake R&D for new TB products was made available
<table>
<thead>
<tr>
<th>New drugs for diseases that disproportionately affect developing countries</th>
<th>New drugs to replace ineffective or toxic treatments</th>
<th>New drugs for emerging diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>The “10/90 gap”: 5% of global resources being applied to low and middle-income countries, where 93% of preventable deaths occur</td>
<td>Drug resistance to existing HIV, TB, malaria treatments</td>
<td>Over 20 diseases have emerged in past decade; including new strains of cholera, SARS, avian flu, H1N1</td>
</tr>
<tr>
<td>Only 1% drugs in last 25 years for tropical diseases and TB (which make up 11% of the GDB)</td>
<td>More effective HIV, TB and malaria drugs and combinations still needed</td>
<td>Urgent need for new treatments and vaccines</td>
</tr>
<tr>
<td>Vaccines for HIV/AIDS, malaria, etc. are still not available</td>
<td>New drugs are needed to replace current toxic treatments for diseases, such as trypanosomiasis and leishmaniasis</td>
<td></td>
</tr>
</tbody>
</table>
R&D Landscape for TB, Malaria and NTDs 2000 – 2011

- 850 new therapeutic products registered in 2000-2011
- 37 (4%) were indicated for neglected diseases
- 336 new chemical entities
- only four new chemical entities (1%) were approved for neglected diseases (three for malaria, one for diarrhoeal disease)
- 148,445 clinical trials registered
- only 2016 (1%) were for neglected tropical diseases
Emerging Issues

Re-examining IP, innovation & public health

- Recognition that current system for stimulating R&D has failed to deliver, particularly for diseases disproportionately affecting poor people
- IP protection alone does not guarantee innovation
- International policy debate over the past decade on the twin problems of market failure and dearth of health technologies for diseases of the poor
- Global process at WHO → CIPIH, WHO GSPOA, WHO CEWG
- What are the alternative mechanisms for increasing R&D and innovation?
TRIPS has failed to encourage and reward the kind of innovation that makes more effective pharmaceutical products available to the poor, including for neglected diseases.

Countries must therefore develop, agree and invest in new systems that genuinely serve this purpose, prioritising the most promising approaches including a new pharmaceutical R&D treaty and the promotion of open source discovery.
IP and innovation

Source: Swiss Federal Institute of Intellectual Property, October 2006
Impact of TB, Malaria and NTDs on development outcomes

- Tuberculosis kills 1.3 million people per year
- 207 million cases of malaria globally every year, resulting in more than 620,000 deaths per year
- The 17 NTDs identified by WHO are endemic in 149 countries
  - at least 100 countries are endemic for two or more diseases
  - 30 countries are endemic for six or more NTDs
- NTDs kill fewer people than HIV/AIDS, TB and malaria
- BUT they account for 11.7% of the global disease burden
- And are responsible for high morbidity and premature death and disability in developing countries
NTD treatments, outdated & ineffective

- MDR-TB treatment takes 2 years and includes:
  - 8 months of daily injections
  - 14,000 tablets to swallow
  - Toxic side effects (deafness, psychosis, severe nausea)

- Less than 50% of patients are cured
- Treatment can still cost in excess of $5,000 per patient per year

- Human African trypanosomiasis, Chagas disease, leishmaniasis all need new and safer medicines

- Innovation is one piece of the puzzle
- The other is the capacity of a health system to absorb a new product

- Depends on various factors:
  - Sustainable financing
  - Legal and policy environment
  - Medicines regulatory capacity
  - Supply chain management
  - Health care delivery systems
  - Appropriate pricing policies
  - Adequate human resources
New partnerships for TB, malaria and NTDs

  - This calls for a “new approach” & new partnerships to stimulate R&D in TB, malaria and NTDs

2 complementary and synergistic projects:

- GHIT Fund: GOJ partnership with BMGF & Japanese research organizations to create a fund to promote engagement of Japanese research organizations in product development for global health
- Access & Delivery Partnership: GOJ funding to strengthen capacities of LMICs to access and absorb new health technologies as they become available
GLOBAL HEALTH INNOVATION TECHNOLOGY (GHIT) FUND

JAPANESE PHARMACEUTICAL SECTOR  BMGF

WHO TDR  PATH

NATIONAL PARTNERS

UNDP

GLOBAL HEALTH INNOVATION TECHNOLOGY (GHIT) FUND

ACCESS AND DELIVERY PARTNERSHIP

TECHNICAL AND POLICY ADVICE  CAPACITY BUILDING FOR ABSORPTION

PDPS FOR NEW HEALTH TECHNOLOGIES  PPPs FOR NEW HEALTH TECHNOLOGIES

IMPROVED ACCESS AND DELIVERY OF NEW HEALTH TECHNOLOGIES FOR TB, MALARIA AND NTDs
Access and Delivery Partnership

- Government of Japan funded:
  - US$3.5 million per annum over 2013-2018
  - Comprising 3 implementing global initiatives bodies + partner LMICs + other stakeholders
    - UNDP (HIV, Health and Development Unit, BDP)
    - WHO (The Special Programme for Research and Training in Tropical Diseases)
    - PATH

Aims:
- To provide technical and policy advice on how to improve access and delivery of health technologies in LMICS and to strengthen capacity in LMICs to achieve this result
- To develop relevant capacity in LMICs to absorb new health technologies
Access and Delivery Partnership

Strategic Objectives:
- Promoting appropriate linkages between innovation and access
- Promoting an enabling environment for innovation in developing countries
- Facilitating strategic South-South collaboration
- Ensuring sustainable and affordable access to health technologies
- Building synergies and adding value to existing initiatives
Integrated public health, innovation and industrial policies

Disease control programmes & drug regulatory frameworks

Financing for procurement & innovation

Procurement and supply chain management

OUTPUT 1
Policy & legal frameworks

OUTPUT 2
Evaluation of epidemiological studies

OUTPUT 3
Monitoring of Phase IV clinical trials

OUTPUT 4a
Financing for new health technologies

OUTPUT 4b
Commercialization pricing and supply

OUTPUT 5
Supply chain and delivery systems

Led by UNDP

Led by WHO/TDR

Led by PATH

IMPROVED ACCESS AND DELIVERY FOR TB, MALARIA AND NTDs
17 Neglected diseases as identified by WHO

- Buruli Ulcer (*Mycobacterium ulcerans* infection)
- Chagas disease
- Dengue/Severe dengue
- Dracunculiasis (Guinea-worm disease)
- Echinococcosis
- Foodborne trematodiases
- Human African Trypanosomiasis (Sleeping sickness)
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis (River blindness)
- Rabies
- Schistosomiasis
- Soil transmitted helminthiases
- Taeniasis/Cysticercosis
- Trachoma
- Yaws (Endemic treponematoses)