



UNIVER  ALLIED
ESSENTIAL MEDICINES

Introduction to Access & Research Gaps

Aria Ilyad Ahmad
UAEM Conference 2010, UNC/Duke



- Imagine: you are Canadian, and have just been diagnosed with **chronic hypertension**
- Can lead to: stroke, aneurysm, **heart attack**, heart and kidney failure
- Consider your treatment options...



Pick one...

- **Diuretics**

- Chlorthalidone- Hygroton
- Hydrochlorothiazide- Hydrodiuril, Microzide, Esidrix
- Indapamide- Lozol
- Metolazone- Mykrox, Zaroxolyn
- **Loop diuretics**
- Bumetanide- Bumex
- Ethacrynic acid- Edecrin
- Furosemide- Lasix

- **Alpha-blockers**

- Doxazosin mesylate- Cardura
- Prazosin hydrochloride- Minipress
- Terazosin hydrochloride- Hytrin

- **Beta-blockers**

- Acebutolol- Sectral
- Atenolol- Tenormin
- Betaxolol- Kerlone
- Bisoprolol fumarate- Zebeta

- **Direct vasodilators**

- Hydralazine hydrochloride- Apresoline
- Minoxidil- Loniten

- **Calcium antagonists - nondihydropyridines**

- Diltiazem hydrochloride- Cardizem SR, Cardizem CD, Dilacor XR, Tiazac
- Verapamil hydrochloride- Isoptin SR, Calan SR Verelan, Covera HS

- **Calcium antagonists - dihydropyridines**

- Amlodipine besylate- Norvasc
- Nifedipine- Procardia, Adalat, Procardia XL, Adalat XL, Procardia ER, Adalat ER

54 drugs

Effective
Relatively safe
Widely available
Tolerable side effects
Easy to administer
Well understood
Affordable

- **Peripheral adrenergic inhibitors**

- Reserpine- Serpasil

- **Central alpha-agonists**

- Clonidine hydrochloride- Catapres
- Guanabenz acetate- Wytensin
- Guanfacine hydrochloride- Tenex
- Methyl dopa- Aldomet

- **Timolol - Visken**

- Propranolol hydrochloride- Inderal, Inderal LA
- Timolol maleate- Blocadren

- **Combined alpha- and beta-blockers**

- Carvedilol- Coreg
- Labetalol hydrochloride- Normodyne, Trandate

- Lisinopril- Zestrin, Lisin
- Moexipril- Univase
- Quinapril hydrochloride- Accupril
- Ramipril- Altace
- Trandolapril- Mavik

- **Angiotensin II receptor blockers**

- Losartan potassium- Cozaar
- Valsartan- Diovan
- Irbesartan- Avapro

- Next, imagine: you are Kenyan, and you have just been diagnosed with **visceral leishmaniasis (kala azar)**
- Leads to: disfiguring skin lesions, liver & spleen failure, blindness, almost certain **death** in a matter of weeks if left untreated
- Consider your treatment options...



Pick one...

4 drugs

Highly toxic
Low effectiveness
Difficult to administer
Not well studied
Unaffordable

Sodium stibogluconate IM
Amphotericin B: IV suspensions,
liposomal formulations
Miltefosine oral
Paromomycin IV

A tale of two worlds...



>



Global neglected disease burden



- Most neglected diseases (ND) affect over **1,000,000,000** people worldwide
 - *Neglected* refers to when treatment options don't exist or are inadequate (MSF, 2009)
 - All low-income countries are affected by **> 5 NDs** simultaneously (WHO, 2010)

The “Big Three”:

HIV/AIDS, Tuberculosis & Malaria

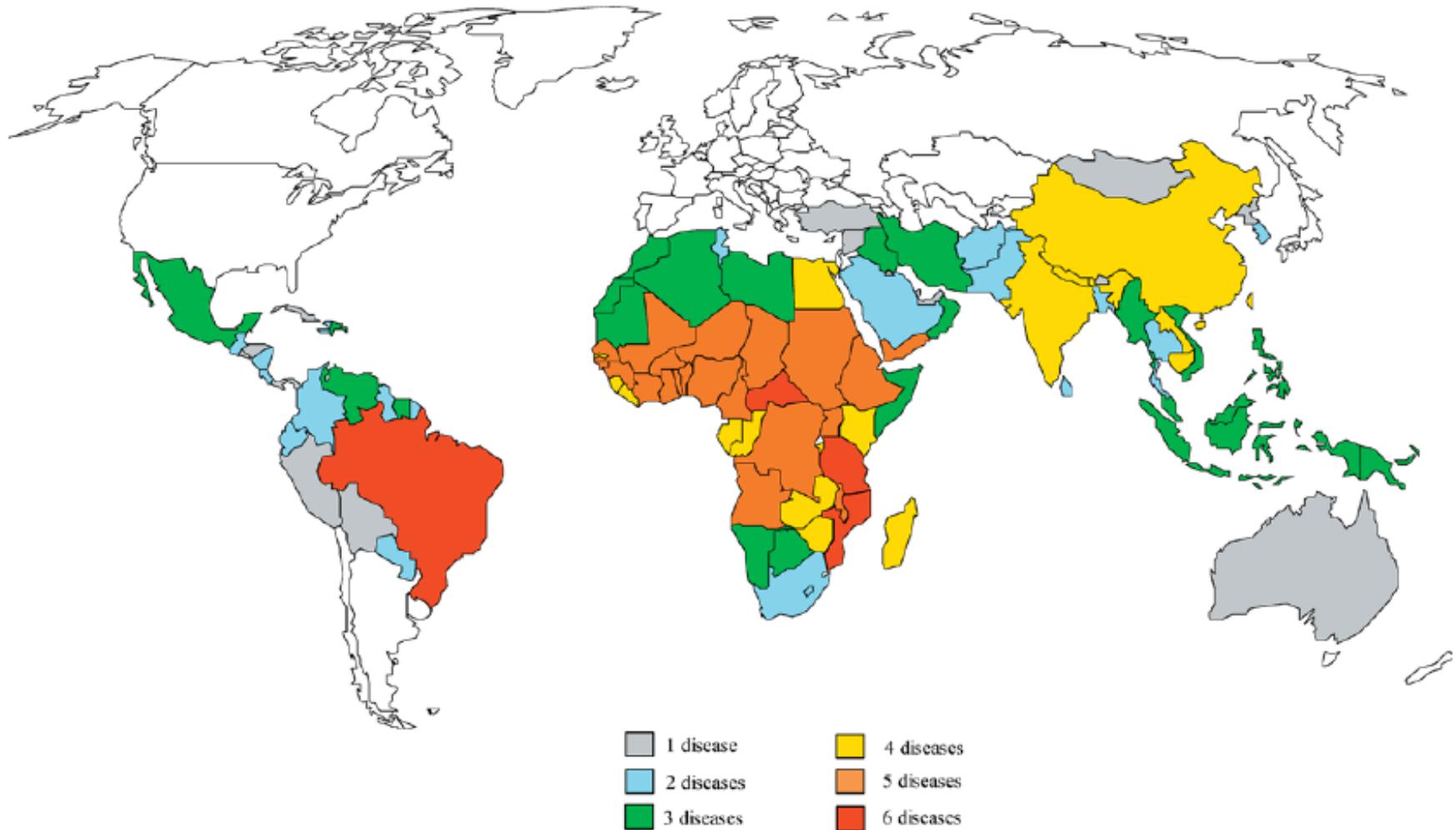
>6 million deaths annually
10% of global disease burden

1 billion currently infected
10% of global disease burden

“Most Neglected” Diseases:

African trypanosomiasis
Lymphatic filariasis
Schistosomiasis
Chagas Disease
Onchocerciasis
Leishmaniasis
Dengue fever
Buruli ulcer
Trachoma
Leprosy
Yaws

Global distribution of neglected diseases



DOI: 10.1371/journal.pmed.0020336.g001

Figure 1. Geographic Overlap of the Neglected Tropical Diseases
(Figure: Molly Brady, Emory University)

Moral significance of medicines



- Pharmaceuticals are not ordinary “goods”
 - ✦ Have life-saving and life-enhancing properties
- Symbolic importance, indicator of development
- Access to medicines (A2M) internationally recognized as a human right
 - ✦ **Universal Declaration of Human Rights** (1948) "inalienable and universal"
 - ✦ **International Covenant on Economic, Social and Cultural Rights** (1966) Article 12 gives States the right to protect the right of its populations to the “highest attainable standard of physical and mental health”
 - ✦ **UN Economic and Social Council Commission on Human Rights** (2001) calls on States to promote the right to health through access to affordable treatments and...(the) provision of *essential drugs*
 - Furthermore stresses that intellectual property rights more "akin to a privilege"
 - ✦ **WHO Model Essential Medicines List** as of 2010, adapted by over 156 countries

What is the global drug gap?



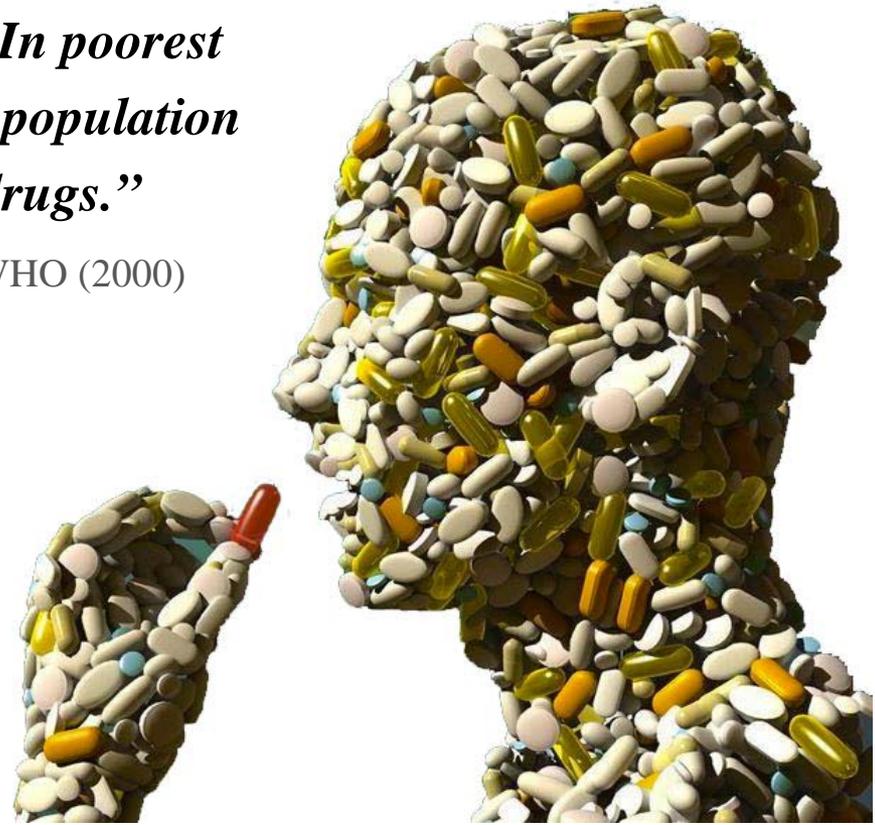
“At the beginning of the 21st century, one-third of the world’s population still lacks access to the essential drugs it needs for good health. In poorest parts of Africa and Asia, over 50% of the population do not have access to the most vital drugs.”

Gro Harlem Brundtland, Former Director-General, WHO (2000)

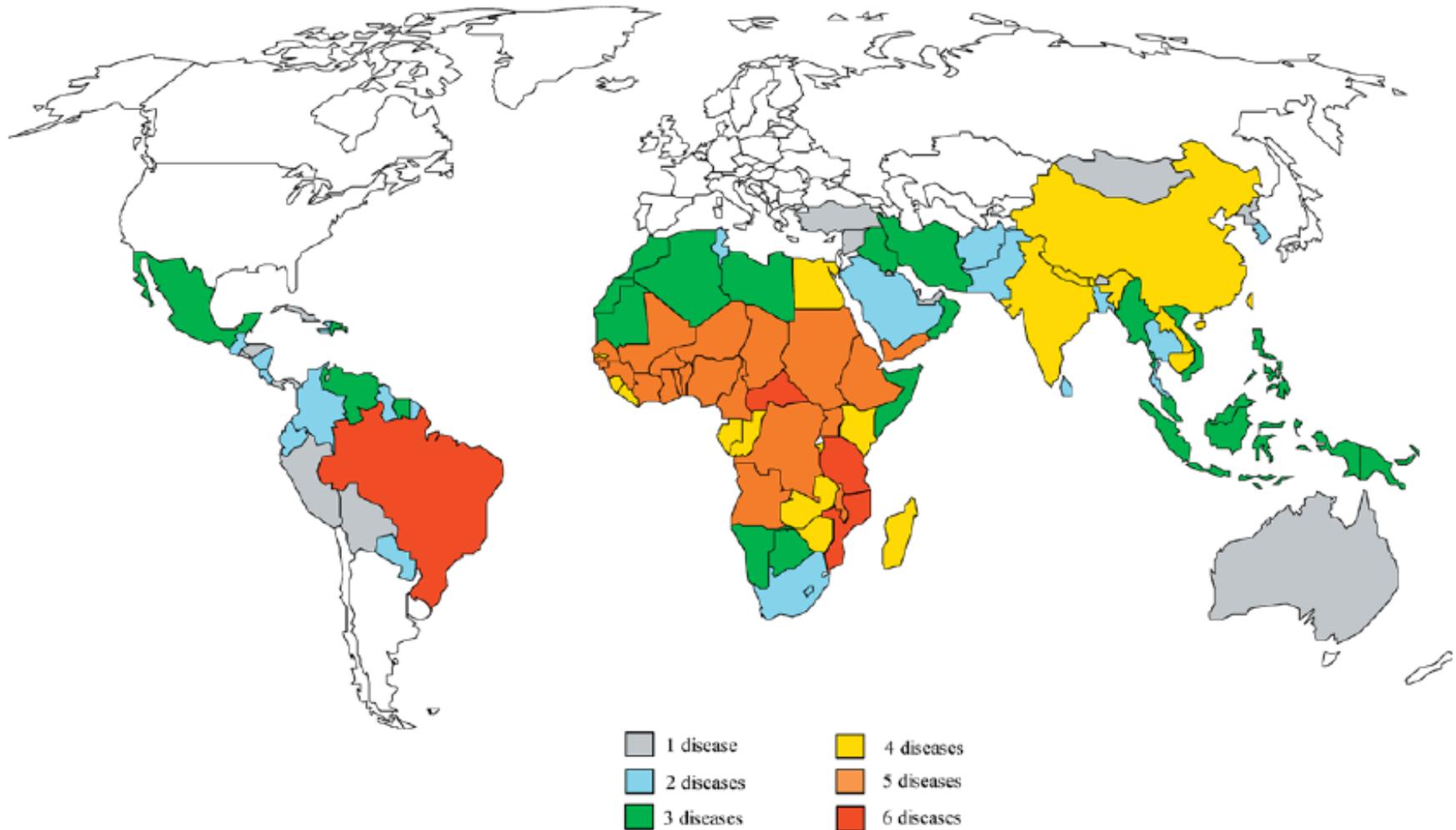


**World Health
Organization**

“...10,000,000 people die each year because they do not have access to existing medicines.”



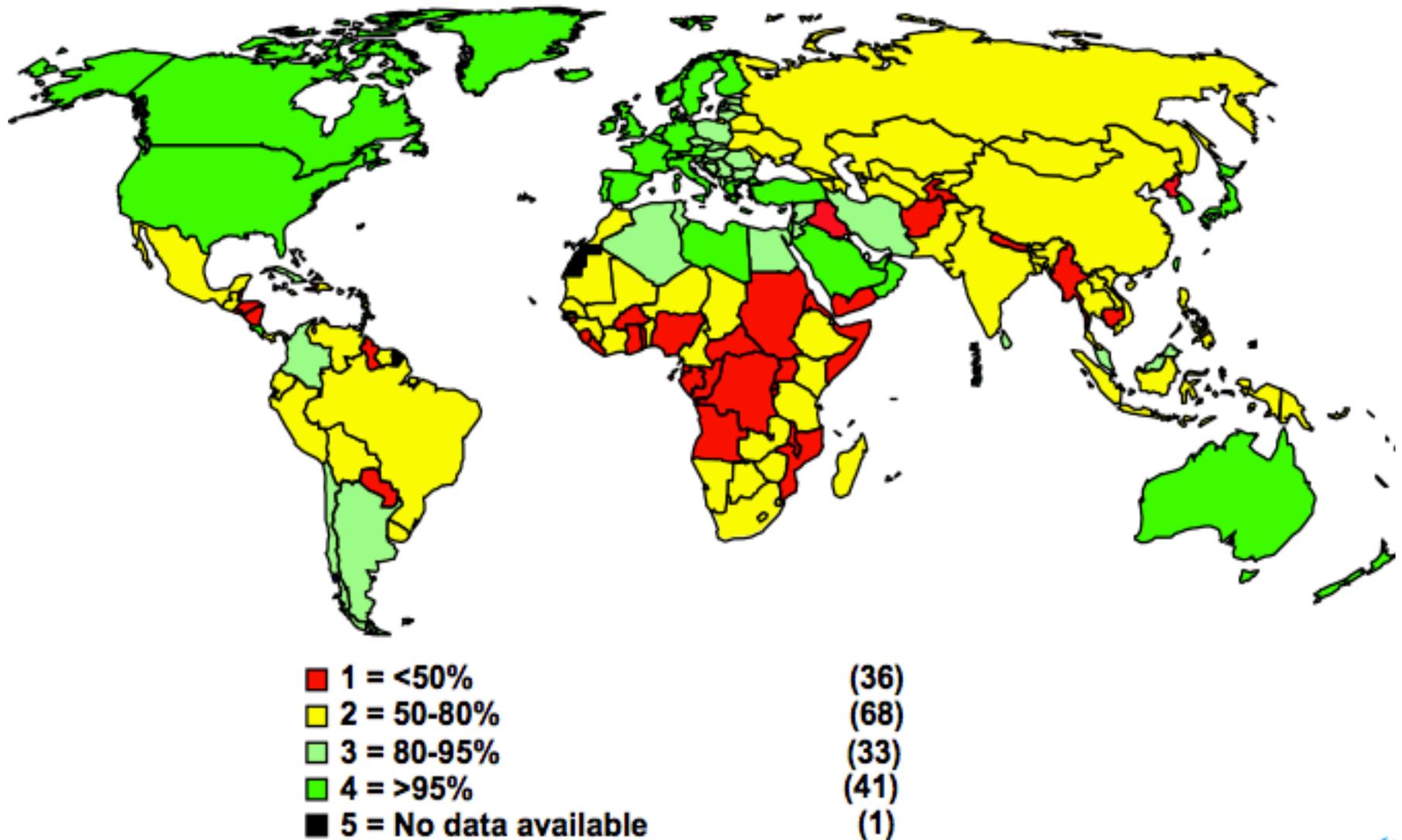
Global distribution of neglected diseases



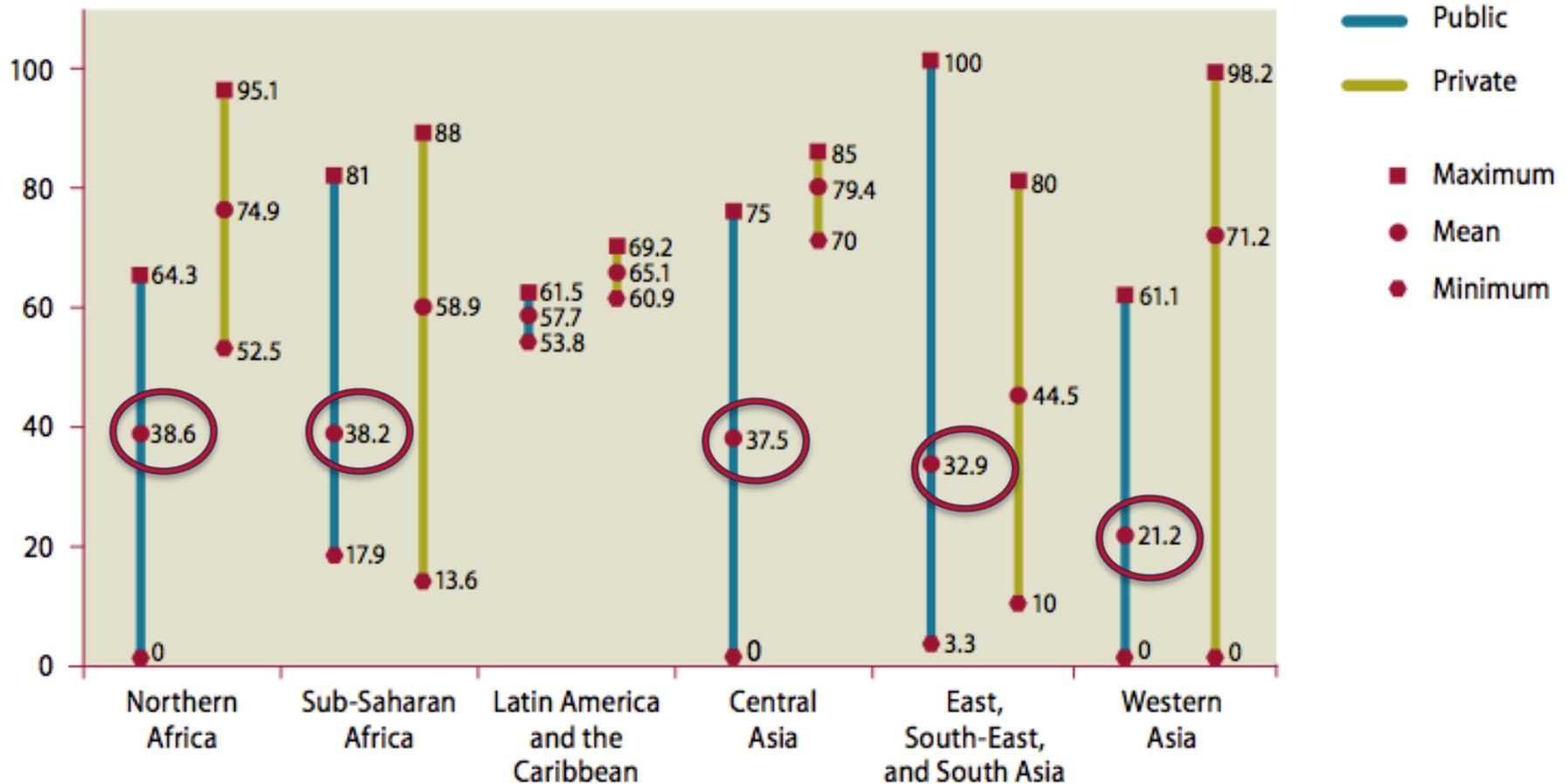
DOI: 10.1371/journal.pmed.0020336.g001

Figure 1. Geographic Overlap of the Neglected Tropical Diseases
(Figure: Molly Brady, Emory University)

Global (in-)access to essential medicines



Availability of selected medicines in public and private health care facilities (2001-2007)



Price as a determinant of drug access



- Large margins between *manufacturing cost* and *market price*
 - **Pricing ratio**: can be upwards of 200 to 1 (Outterson and Smith, 2005)
- Markets are “notoriously defective” in dealing with public goods
 - With drugs, eventually create an artificial and unpredictable scarcity leading to “market failure of undersupply” (Sen, 1999)
- Cost of originator antiretrovirals: \$10,439 pp/year (approx. **\$30/day**)
 - But more than **2 billion** people live on **<\$2 a day** (WHO, 2005)
 - HICs allocate **\$230** pp/yr for meds vs. **\$6** by sub-Saharan African countries
- **80/20 Gap**: developing countries comprise 80% of the global population but represent less than 20% of worldwide drug sales

Global pharmaceutical markets

(by region, US\$ billion)



Region	2004	2005	Global Share of Sales (%)
North America	249.0	268.8	44.4
Europe	169.2	180.4	29.8
Japan	66.1	69.3	11.4
South-East Asia	25.3	28.8	4.6
Latin America	24.4	26.6	4.4
Oceania	7.1	7.7	1.3
Indian Subcontinent	6.6	7.2	1.2
Africa	6.3	6.7	1.1
Commonwealth of Indep. States	4.2	5.0	0.8
Middle East	4.7	4.9	0.8
Total World Market	562.9	605.4	100.0

85.6%



Drug development pipeline

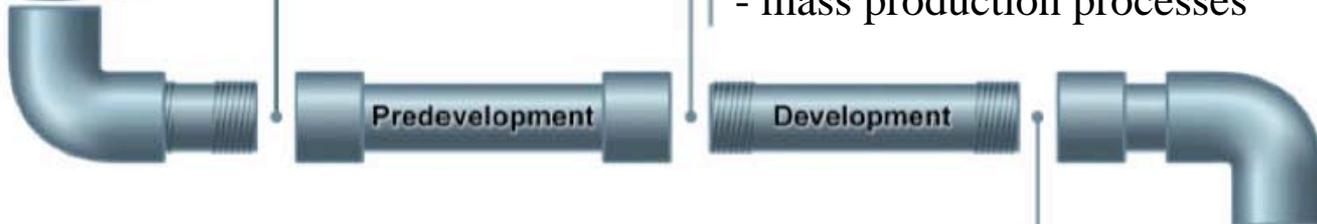


1. Discovery:

- basic research
- discover therapeutic targets
- possible candidate molecules

2. Development:

- formulation
- assess safety and efficacy (\$\$\$)
- mass production processes



3. Delivery:

- registration
- manufacturing
- sale
- distribution

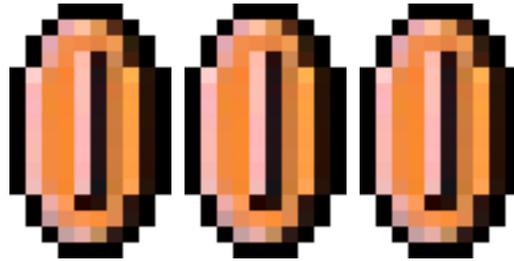


WORLD 1

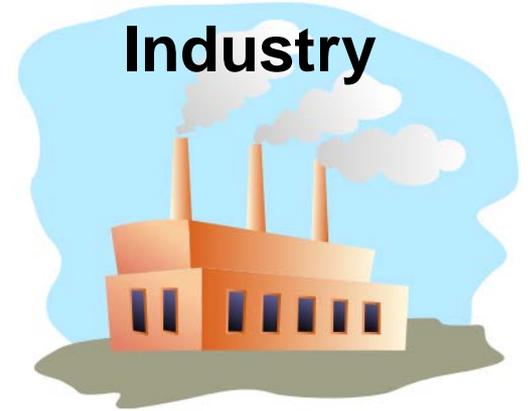
Advocacy groups/charities



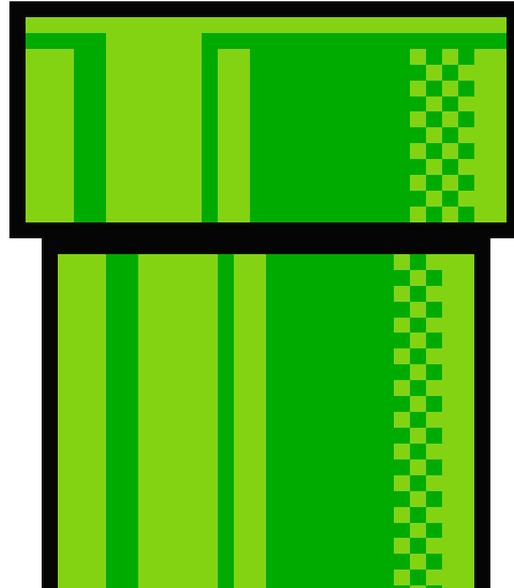
Government

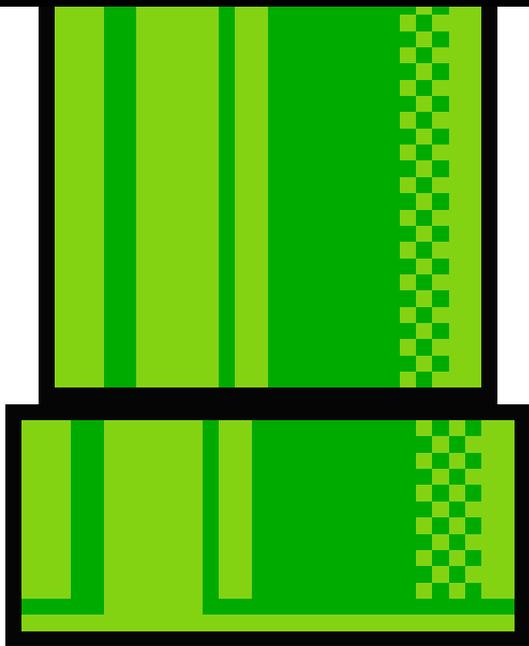


Industry

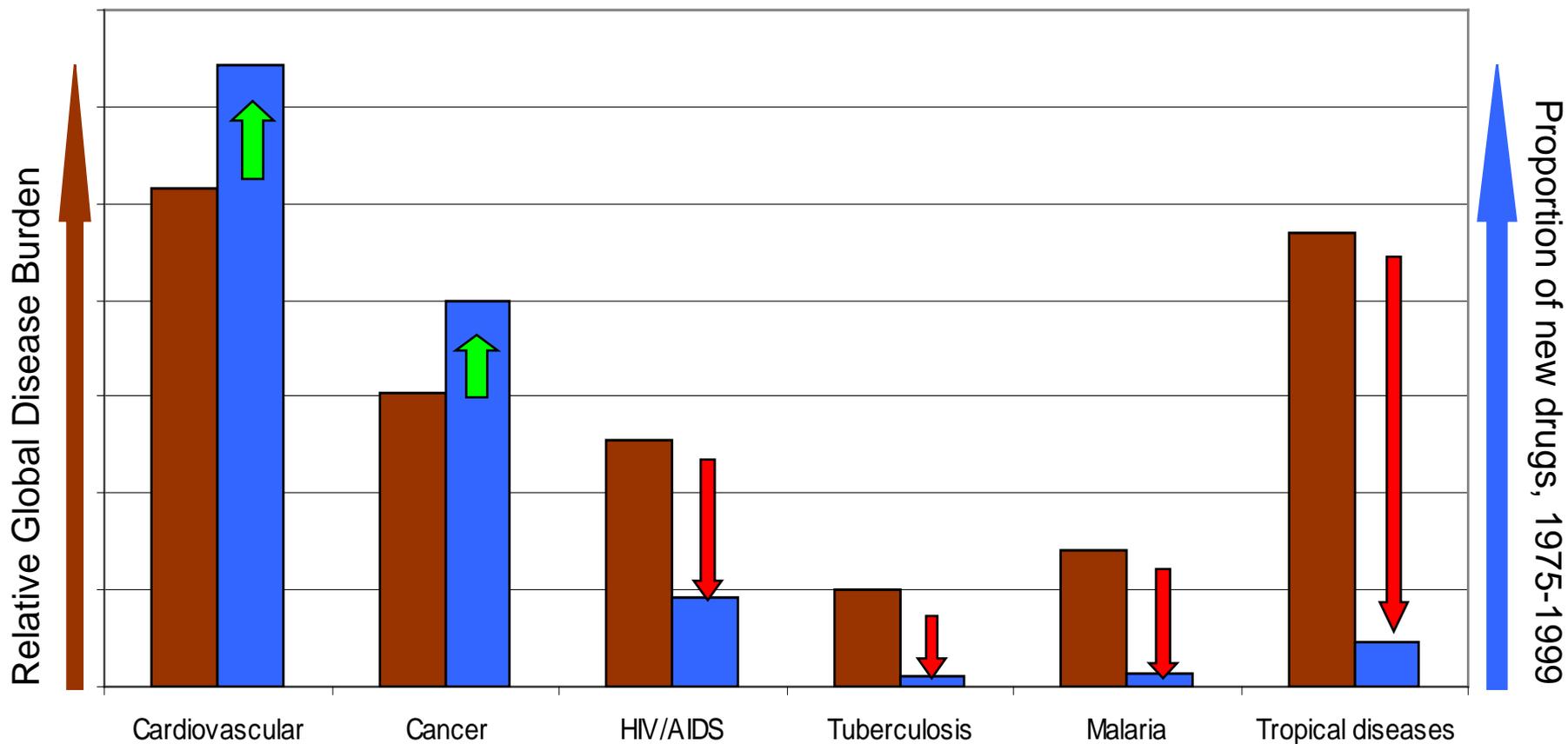


Patients





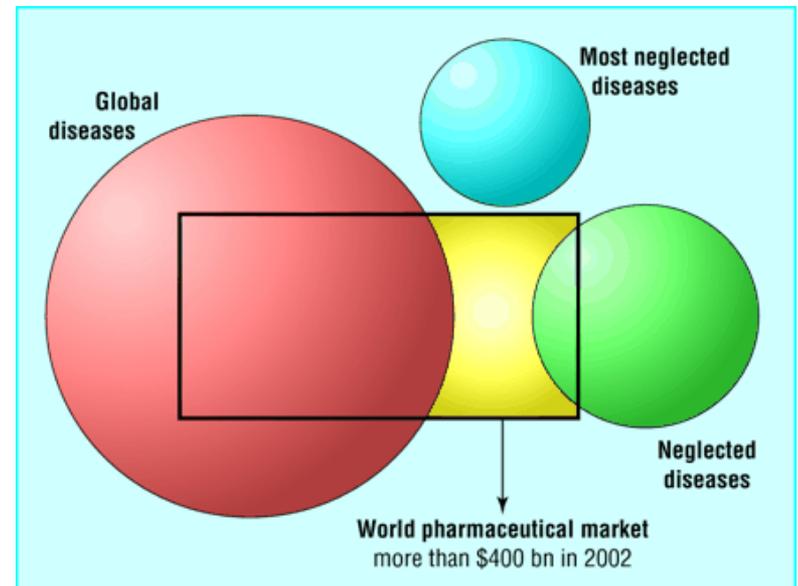
Global disease burden vs. innovation



Incentives for ND drug development

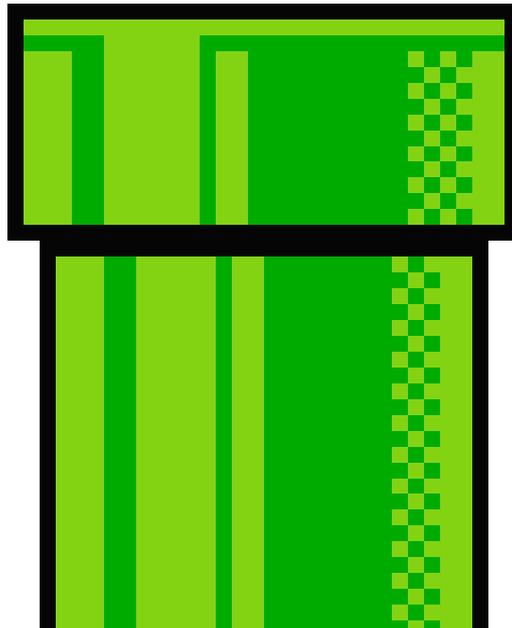


- **90/10 Gap**: <10% of world's resources for health research are applied to the health problems facing countries facing >90% of the global disease burden
- Shift in global R&D to e.g. **blockbuster** (>\$1b) and **'me-too'** drugs
 - “Stream of new drugs has slowed to a trickle, and few are innovative...” (Angell, 2004)
- Pharmaceutical R&D not “that into” tropical (neglected) diseases (Troullier et al, 2002)
 - Of 1223 new chemical entities commercialized from 1975-1990, 379 were therapeutic innovations, only 13 specifically for tropical diseases
 - Update for 1990-2004: out of 163 novel chemical entities, only 4 were for NDs (malaria and leishmaniasis)



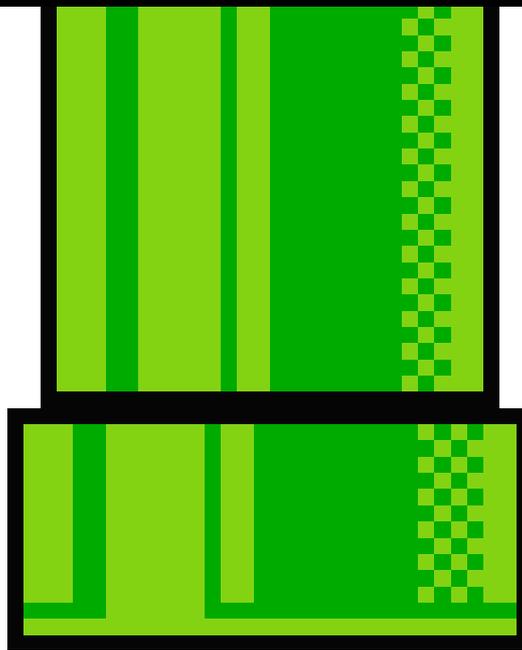
Yarney, G. (2007) “World’s Most Neglected Diseases” *BMJ*

WORLD 3



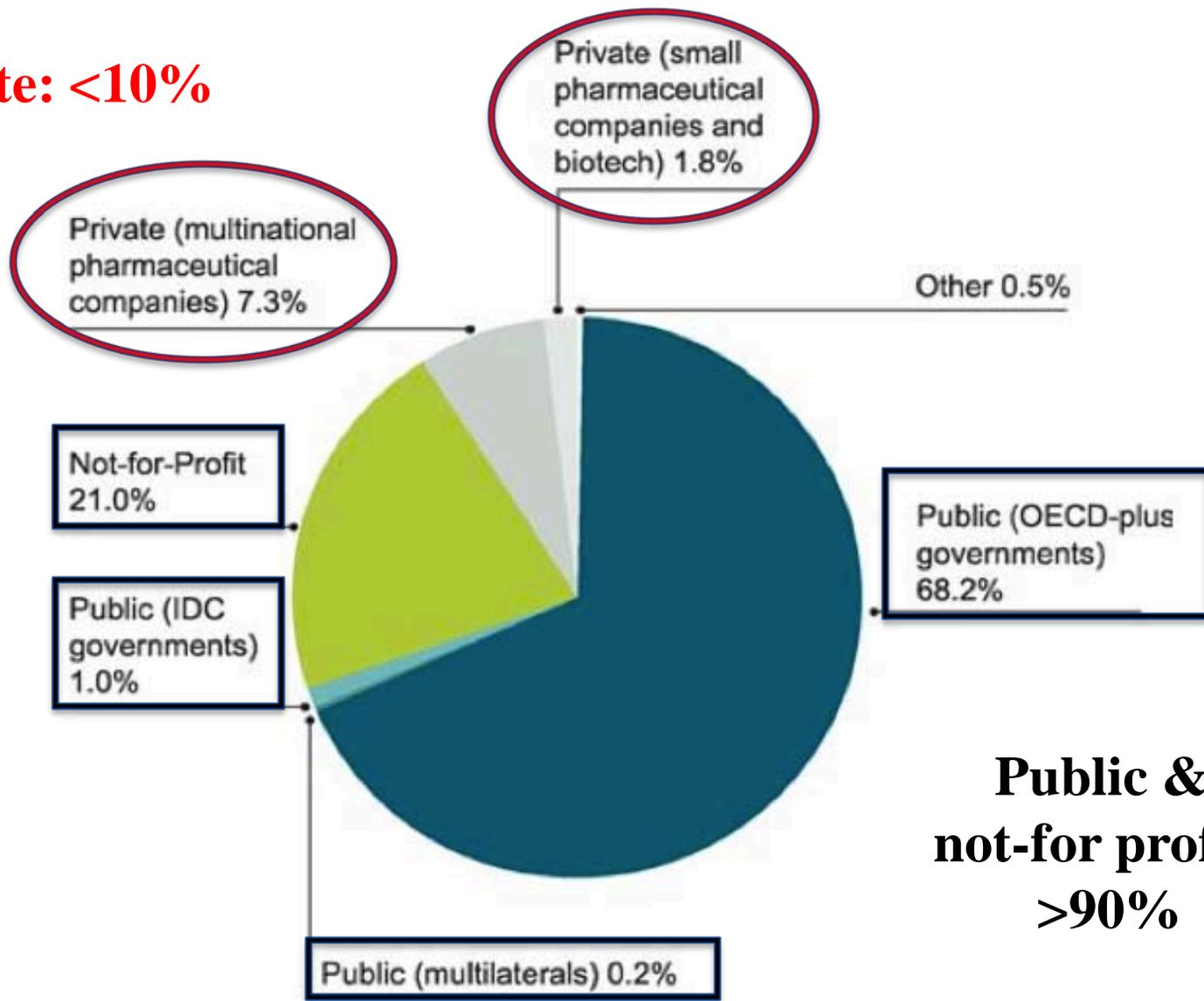
Patients





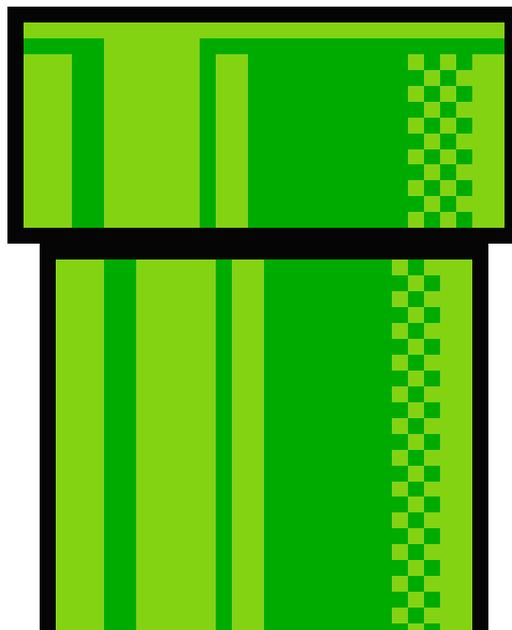
Total ND R&D Funding Type, 2007

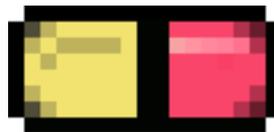
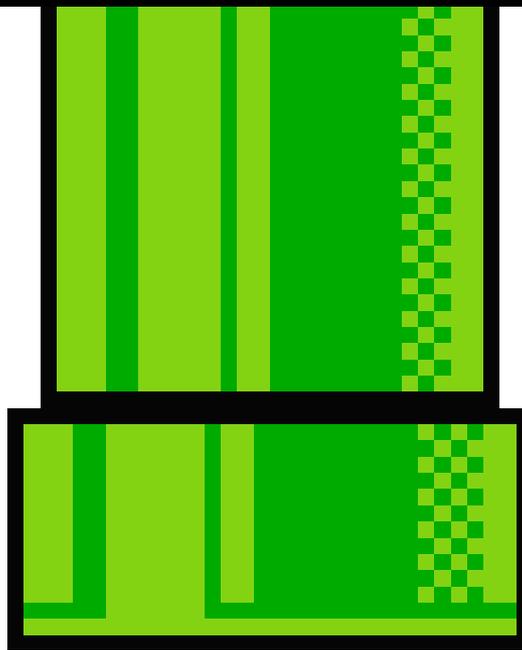
Private: <10%



**Public &
not-for profit:
>90%**

BILL & MELINDA
GATES *foundation*



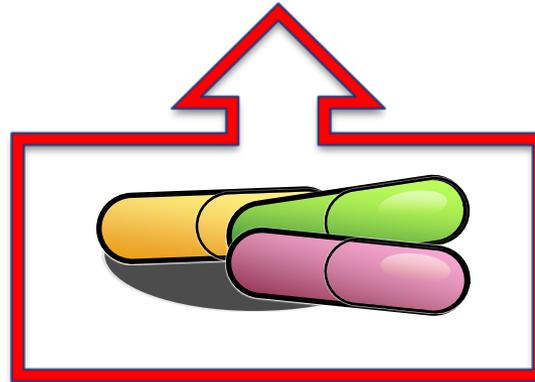


Intellectual property rights (IPRs)

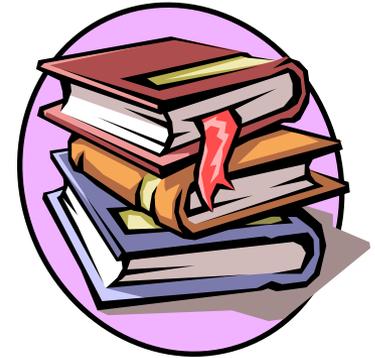


Novel? Useful?
Non-obvious?

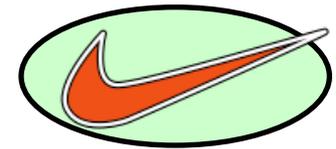
Patent



©



TM



- **Patent:** value-free rights to exclude someone from using your technology

Why do we patent?



- Would you invest in a product that could be freely copied?
 - Exclusion = Monopoly
- But, without a real market
 - Exclusion = Deprivation
- Patents create incentives (32+ ARVs!), **but** not in places without markets (0 TB research!)
 - HIV/AIDS is exceptional (illuminates + obscures)



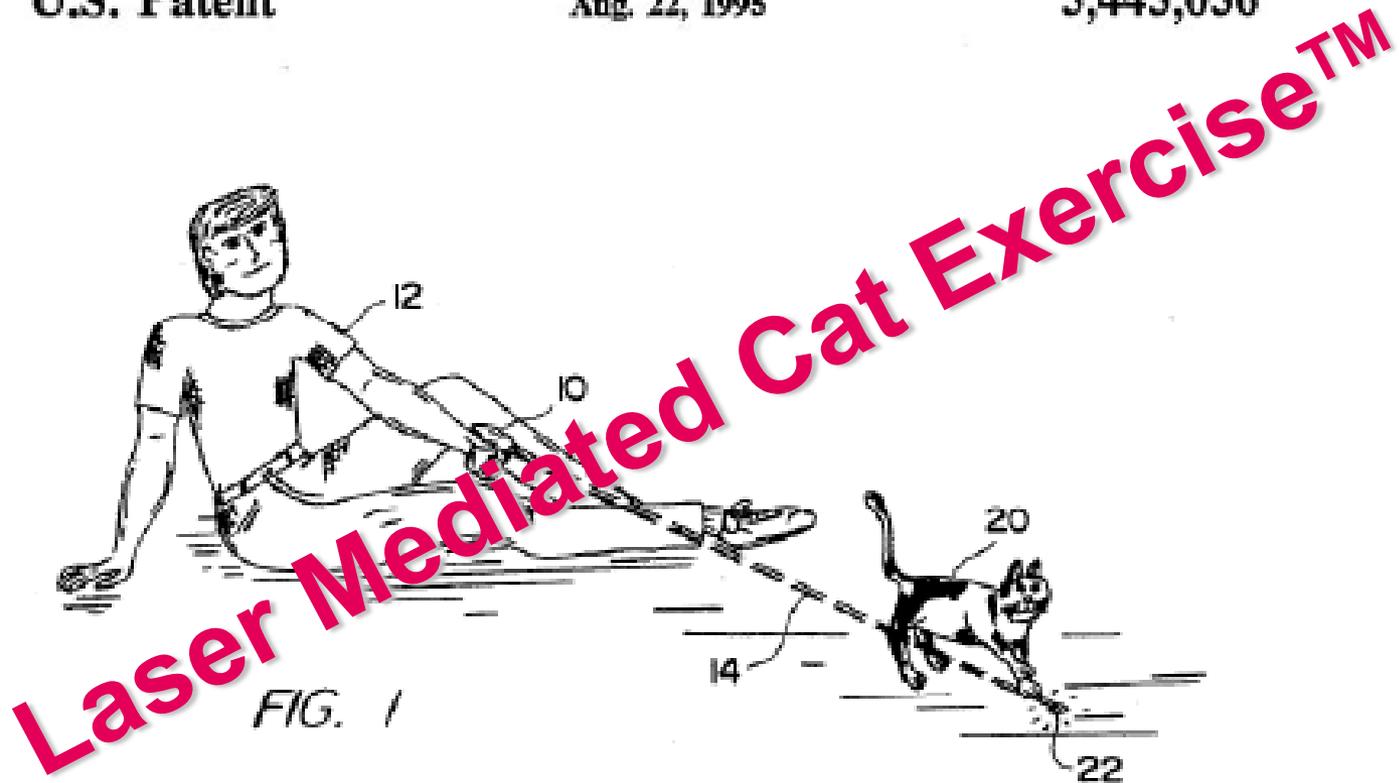
Some patents are asinine...



U.S. Patent

Aug. 22, 1995

5,443,036



...other patents are amazing!

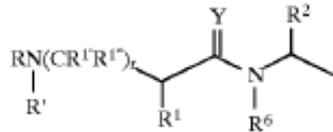


pro-
vide-
itor
etro-
virus
e.g.,
as to
nter-

compounds are characterized as sulfonamide-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retrovirus protease inhibiting compound of the formula:



(I)

and
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tural
ursor
: pol
e.g.,
been
is by
nfec-
: shift
HIV
also
artic
: gag
been

or a pharmaceutically acceptable salt thereof wherein:

R represents hydroxyethyl, aralkoxycarbonyl, alkylcarbamoyl, cycloalkylalkoxycarbonyl, alkanoyl, aralkanoyl, aryloxy carbonylalkyl, heterocyclylcarbonyl, heterocyclylalkanyl, heteroalkanyl, heteroalkoxy, heteroaryloxy carbonyl, he-

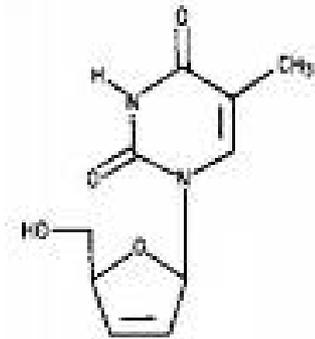
United States Patent [19] Vazquez et al.

[54] α -AND β -AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

[75] Inventors: **Michael L. Vazquez**, Gurnee; **Richard A. Mueller**, Glencoe, both of Ill.; **John J. Talley**, St. Louis, Mo.; **Daniel Getman**, Chesterfield, Mo.; **Gary A. DeCrescenzo**, St. Peters, Mo.; **John N. Freskos**, Clayton, Mo.

[73] Assignee: **G.D. Searle & Co.**, Skokie, Ill.

d4T!



US005843946A

[11] **Patent Number:** 5,843,946
[45] **Date of Patent:** Dec. 1, 1998

[52] **U.S. Cl.** 514/252; 514/253; 546/168
[58] **Field of Search** 546/168; 514/252; 514/253, 237.2

[56] References Cited

U.S. PATENT DOCUMENTS

4,548,926	10/1985	Matsueda et al.	514/19
4,757,050	7/1988	Natarajan et al.	514/18
5,122,514	6/1992	Boger et al.	514/19
5,134,123	7/1992	Branca et al.	514/18
5,140,011	8/1992	Branca et al.	514/18

Primary Examiner—Johann Richter

International intellectual property law



- All patent law is domestic, but there are international floors
- *Trade Related Aspects of Intellectual Property Rights (TRIPS)*
 - Agreement among WTO states in 1994 to globalize IPRs
 - States must provide 20 year patents for pharmaceuticals
- *Doha Declaration on TRIPS and Public Health (2001)*
 - **Paragraph 4:** TRIPS should not prevent states to protect public health, “in particular, to promote access to medicines”
 - **Paragraph 5:** a state has the “right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted”
 - **Paragraph 6** (*August 30th Decision*): absence of manufacturing capacity...



‘Public Health, Innovation & IPRs’



Public health

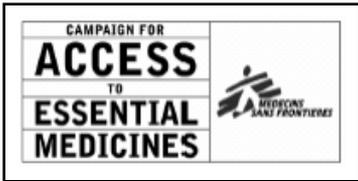
innovation and
intellectual property rights

REPORT OF THE COMMISSION ON
INTELLECTUAL PROPERTY RIGHTS, INNOVATION
AND PUBLIC HEALTH

“Where the market has very limited purchasing power, as is the case for diseases affecting millions of poor people in developing countries, patents are not a relevant factor or effective in stimulating R&D and bringing new products to market.” (p34)



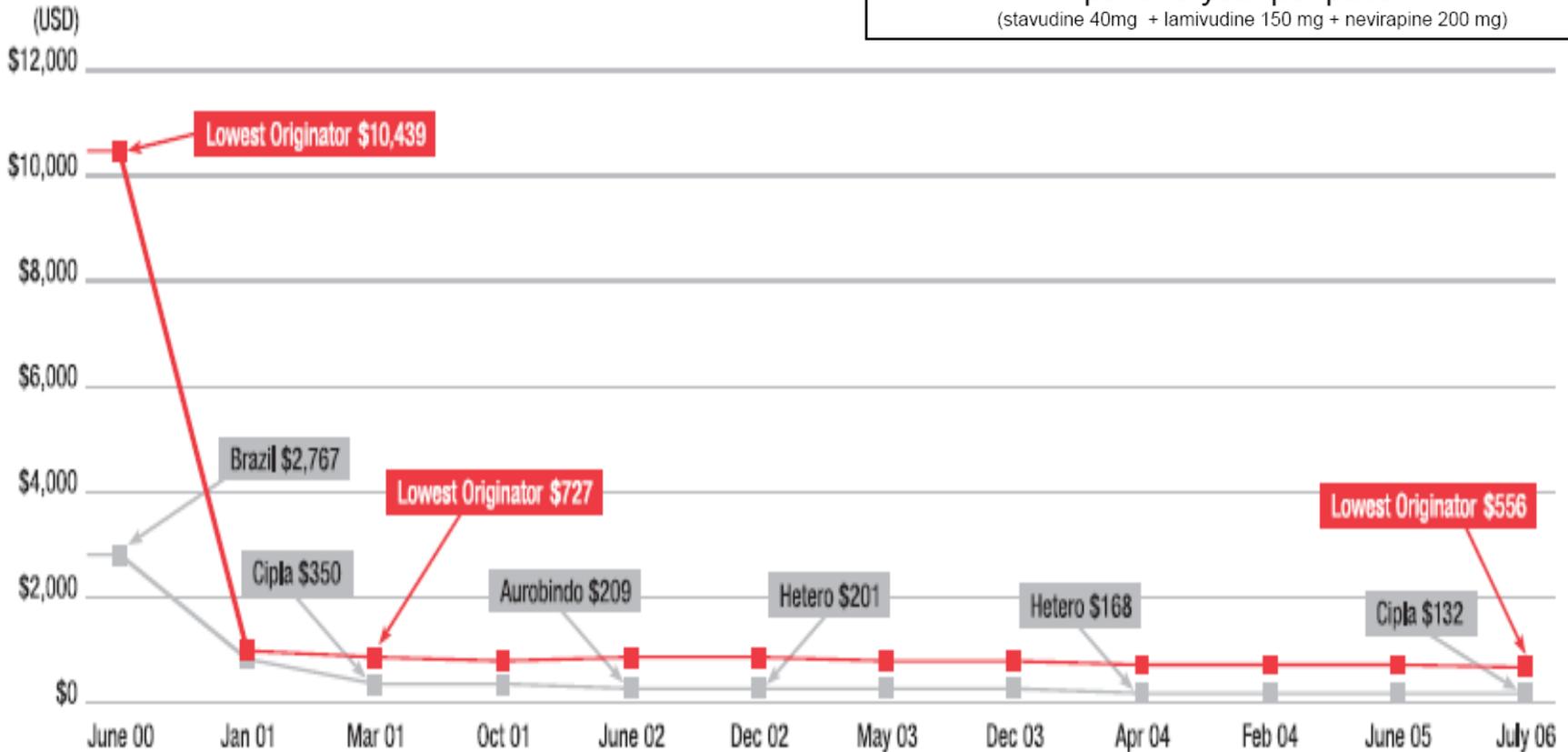
World Health
Organization



Effect of generic competition

(d4t+3tc+NVP)

Sample AIDS triple-combination: lowest world prices
per one year per patient
(stavudine 40mg + lamivudine 150 mg + nevirapine 200 mg)



Sample of ARV triple-combination: stavudine + lamivudine + nevirapine, Lowest world prices per patient per year, Generic competition has shown to be the effective means of lowering drug prices, During the last five years, originator companies have often responded to generic competition.

What is the Role of Universities?



University basic science research



- Universities play an increasingly important role in R&D and patenting/licensing in Canada and US, especially “health-related innovations”
 - 80 out of 86 Nobel winners in medicine from academia
- Shift from corporate to campus labs
 - “...at least a third of drugs marketed by major drug companies are licensed from universities or small biotech companies... tend to be most innovative”
- U.S. universities responsible for >50% basic science research (Mowery et al, 2001)
 - 40% of \$100b spent on biomedical research annually is publically funded
- 15 of 21 drugs with the greatest therapeutic impact from 1965-92 were developed using publically funded research, universities
 - Every vaccine in past 25 years has university contribution

University commercialization



Global Biotech Assignees

1	<i>University of California</i>	543
2	US Government	443
3	University of Texas	277
4	Johns Hopkins University	154
5	Stanford University	148
6	Columbia University	137
7	University of Pennsylvania	133
8	University of Florida	132
9	Duke University	110
10	Wisconsin	102
11	University of Michigan	100
12	MIT	100
13	University of Washington	96
14	Yale University	93
15	University of Minnesota	84
16	New York University	80
17	University of Illinois	79
18	Harvard University	75

University ARV contributions:

Abacavir – Minnesota

AZT – NCI

FTC/3TC – Emory

Enfuvirtide – Duke/UCSF

Darunavir – U Ill Chicago, NIH

Didanosine – NIH

Stavudine – Yale



How do universities measure success?



- **AUTM Annual Licensing Surveys**
- **AUTM Better World Project**
- Milken Institute: Mind to Market Report
- NSF: Science and Engineering Indicators; Academic R&D Survey
- AUCC: Momentum Report
- Canada: Commercialization of Intellectual Property in Higher Education
- UNICO: UK University Commercialization Survey
- Library House: Metrics for Evaluation of Knowledge Transfer at Univ.
- HEFCE: Higher Education-Business and Community Interaction Survey

American University Technology Managers



- E.g. AUTM Annual Licensing Surveys
 - Licensing Revenue
 - Invention Disclosures
 - Patent Applications
 - Patents Issued
 - Licenses Executed
 - Startup Companies Formed

Strategic misalignment...



“If you measure success in terms of social impact or awareness and you count things such as gifts, research collaborations, global impact and boost to your reputation, it changes your orientation. If you measure success only by the amount of royalties and fees you bring in, then your licensing practices will reflect that.”

Carol Mimura, Assistant Vice Chancellor, Intellectual Property and Industry Research Alliances, UC Berkeley



Appendix

“Second-line” ARVs



- Necessary after 3-5 years, or immediately
- Newer, more complicated to make, more expensive
- Patented in more countries
 - Boehringer never enforced NVP
- Demand rising sharply

High Prevalence of Antiretroviral Drug Resistance Mutations in HIV-1 Non-B Subtype Strains From African Children Receiving Antiretroviral Therapy Regimen According to the 2006 Revised WHO Recommendations

“TRIPS-Plus” agreements and pressures



- **Free Trade Agreements**

- Extended monopoly periods
- Limit TRIPS flexibilities

- **Unilateral Trade Sanctions**

- Korea, Mexico, Chile, Thailand, Indonesia, Bolivia, Columbia, Ecuador, Peru, Venezuela, India, Argentina, Brazil, Taiwan, ...

- **Corporate Litigation**

- Kenya, Uganda, Ghana, Thailand, Brazil, China, South Africa, ...

- **Anti-Counterfeiting Trade Agreement (ACTA)?**

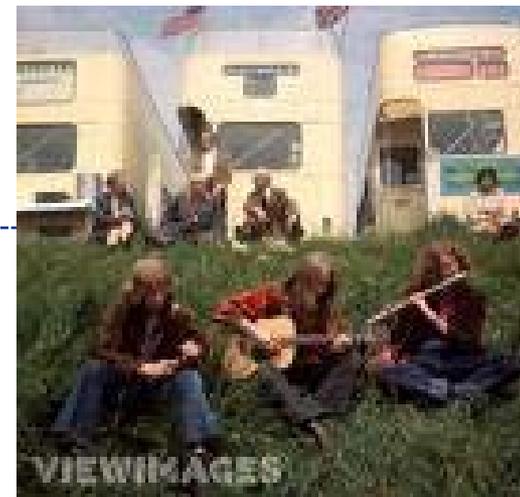


The Story of UAEM

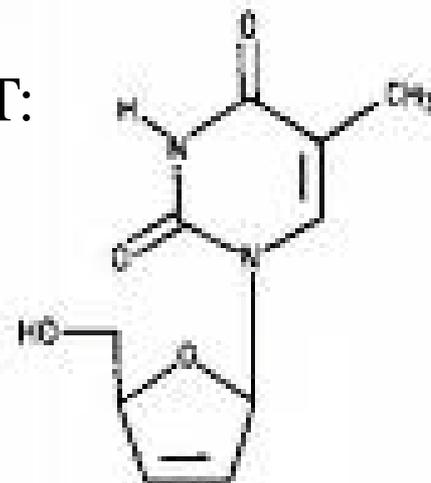
In the mid-1960s . . .



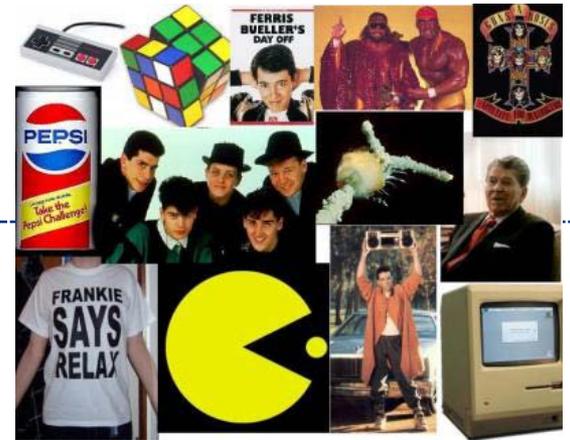
Michigan Cancer Center



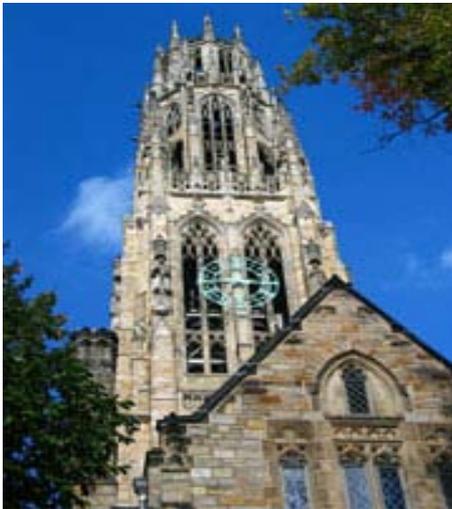
d4T:



In the mid-1980s . . .



Yale

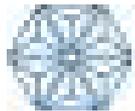


d4T
→



Bristol-Myers Squibb

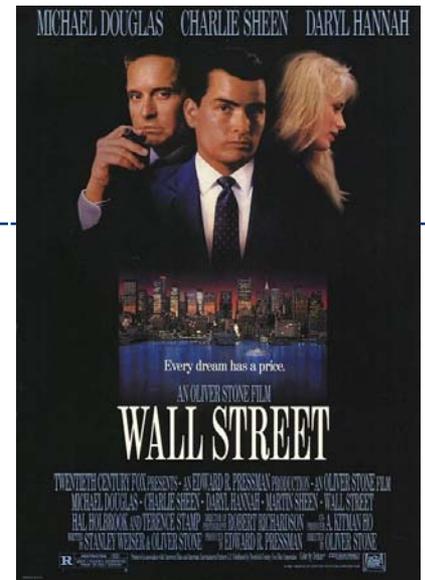
In the mid-1990s . . .



Bristol-Myers Squibb

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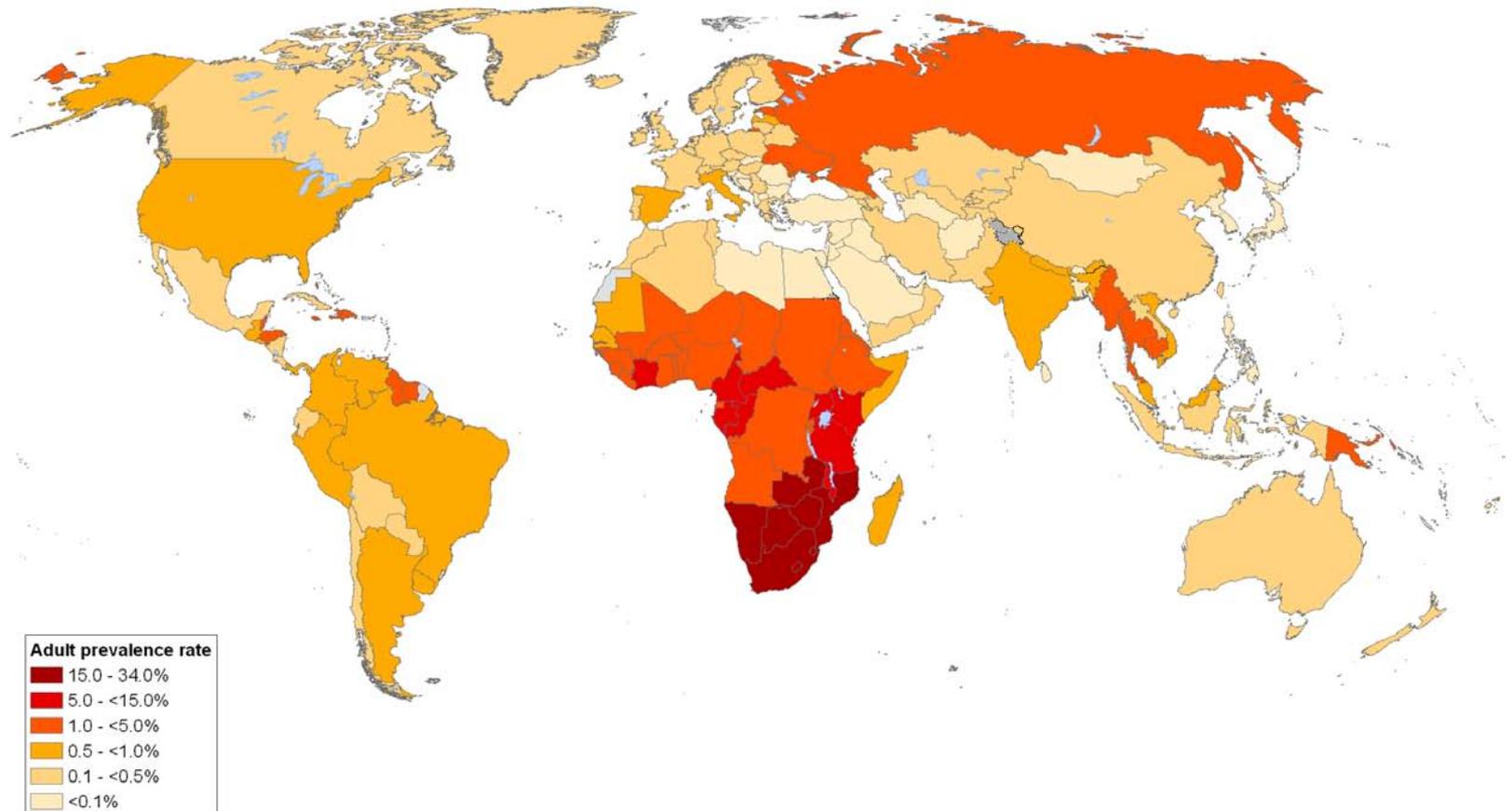
Federal Drug Agency



Stavudine



Emerging HIV/AIDS Pandemic



A Snapshot of ARVs in 2000

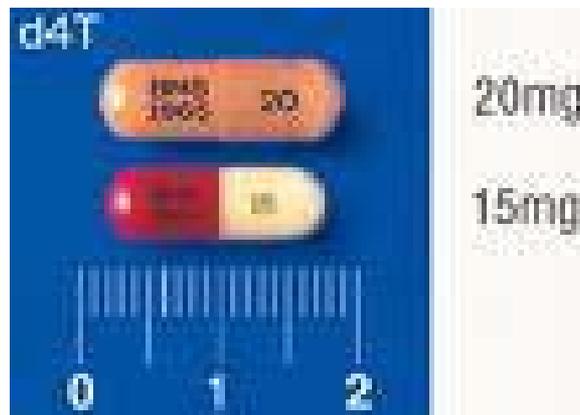
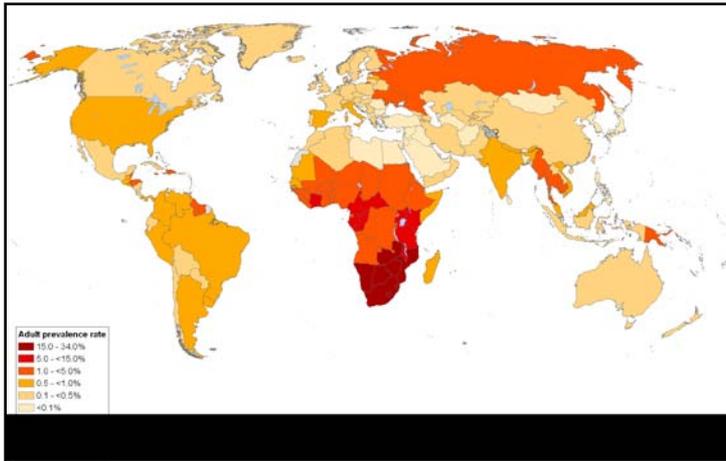


- Cost upwards of \$10,000pp/year
- WHO & UNAIDS:
 - Treatment unwise given cost
- No international funding
- Limited price concessions
- Access in developing countries: 5%
- Access in sub-Saharan Africa: < 1%



Joseph Jeune, Partners in Health

In 2001 . . .







~~\$1,600~~

\$55

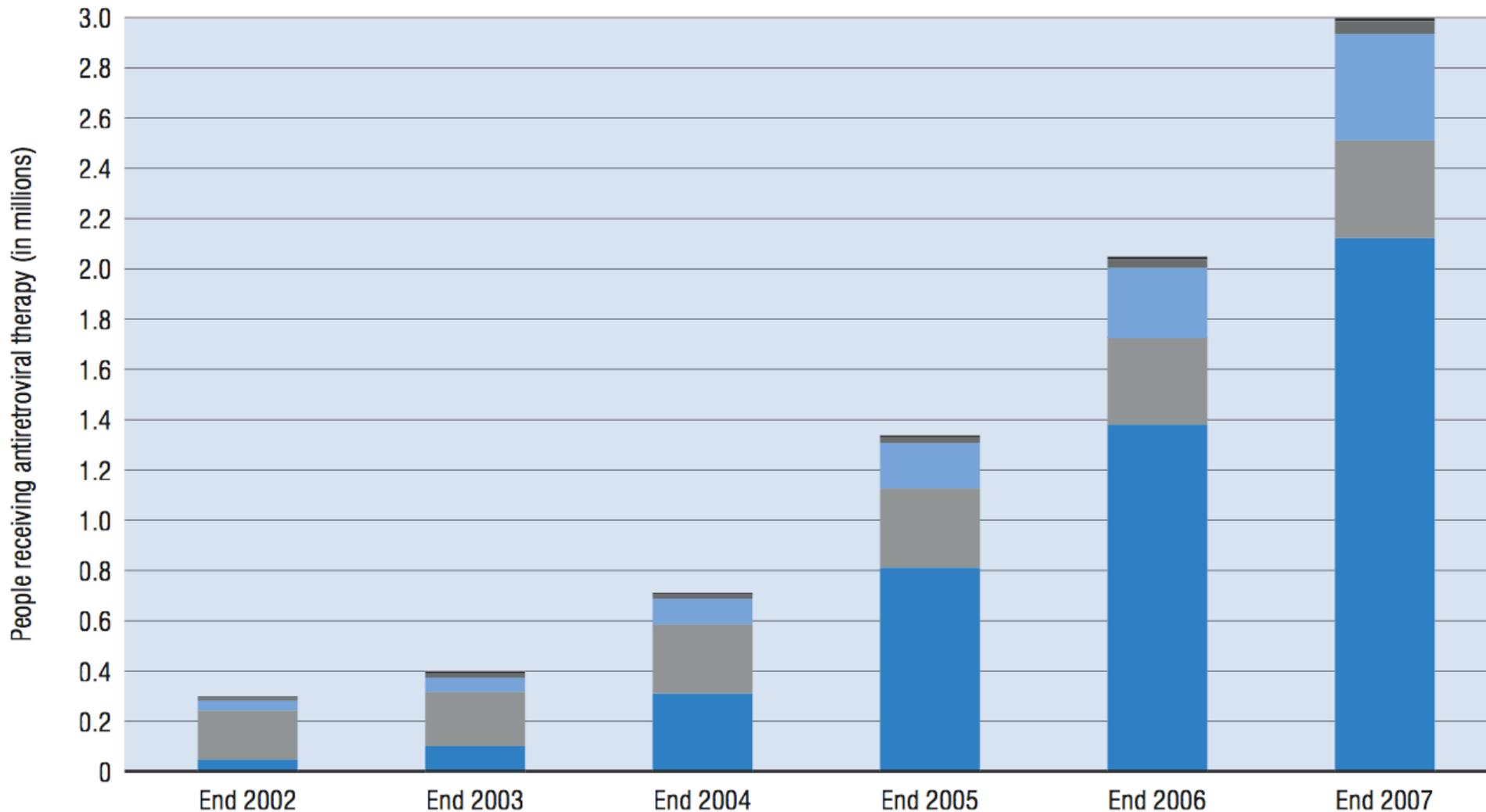


Before ARV therapy



After 6 months on ARV therapy

ARV Coverage, 2002-2007



Expert Opinion

1. Introduction
2. Body
3. Conclusion
4. Expert opinion

Safety of stavudine in the treatment of HIV infection with a special focus on resource-limited settings

Alain Makinson, Vincent Le Moing, Charles Kouanfack, Christian Laurent[†] & Eric Delaporte

[†]University of Montpellier, Institut de Recherche pour le Développement, Montpellier, France

Background: Western randomized trials and prospective cohorts in resource-limited settings have proven virological success with stavudine-based highly active antiretroviral therapy. However, stavudine is no longer recommended in first-line treatments in these two settings due to its intrinsic toxicities and side effects. Yet it remains a cornerstone of treatment in resource-limited settings, due to lack of alternatives and its availability in generic fixed-dose combinations. **Objective:** To review the toxic effects of stavudine and their prevention and management strategies, especially in resource-limited settings. **Methods:** Data from clinical and pharmacological trials in Western countries, as well as prospective cohorts in resource-limited settings, were reviewed. **Conclusion:** Initiating or switching to less toxic nucleoside analogues whenever possible, or lowering stavudine doses to 30 mg b.i.d., is strongly recommended.

Keywords: antiretroviral therapy, d4T, HIV, resource-limited settings, safety, stavudine, toxicity



Universities Allied for Essential Medicines

Our labs. Our drugs. Our Responsibility.

A non-profit organization with 90+ chapters at research universities around the world, founded and maintained by students of law, medicine, public policy, public health, etc.

VISION - Universities and publicly funded research institutions will be part of the solution to the access to medicines crisis by promoting medical innovation in the public interest and ensuring that all people regardless of income have access to essential medicines and other health-related technologies.

Nobel Laureate Signatories: MSF, 1999 Peace -- Peter Agre, 2003 Chemistry -- Kenneth Arrow, 1972 Economics -- Craig Mello, 2006 Medicine -- **John Polanyi**, 1986 Chemistry -- Oliver Smithies, 2007 Medicine -- Jack Steinberger, 1988 Physics -- Sir John Sulston, 2002 Medicine -- Harold Varmus, 1989 Medicine -- Reverend Desmond Tutu, 1984 Peace

Distinguished Signatories: **James Orbinski**, Former President MSF -- **Julio Montaner**, President of International AIDS Society -- **Stephen Lewis**, Former UN Special Envoy for HIV/AIDS in Africa -- Paul Farmer, President, Partners in Health -- Jeffrey Sachs, Earth Institute, Columbia, UN Millennium Project -- Edwin Cameron, South African Supreme Court Justice -- ...

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Hull York Medical School
Imperial College London
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Peninsula Medical School
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Boston University
Case Western Reserve University
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Claremont Colleges
Columbia University
Cornell University
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University of Western Australia, Australia
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