‘Do not go gentle into that good night’. Lessons learned from our slide into the post-antibiotic era

Marc Mendelson
Division of Infectious Diseases & HIV Medicine
University of Cape Town
Antimicrobial Stewardship describes the multi-disciplinary, systematic approach to optimising the appropriate use of antimicrobials to improve patient outcome and limit emergence of resistant pathogens whilst ensuring patient safety.

While drivers of resistance and treatment failure differ between microbes unifying themes exist.
Extremophiles (thermophiles)

Blue and clear waters are extremely hot and at times may exceed the boiling point (199°F [93°C] at this elevation).

- Archaea
- 144°F (62°C) or lower Fungi
- 133°F (56°C) or lower Protozoa
- 80°F (27°C) or lower Trout
- 163°F (73°C) or lower Cyanobacteria
- 140°F (60°C) or lower Algae
- 122°F (50°C) or lower Mosses, crustaceans, and insects
Antibiotic resistance is ancient

Metagenomic analysis of 30,000 year old permafrost samples

- $\beta$-Lactam resistance - $\text{bla}_{\text{TEM}}$
- Tetracycline resistance - $\text{TetM}$
- Vancomycin resistance - $\text{VanX}$
- Aminoglycoside-antibiotic-modifying acetyltransferase $\text{AAC}(3)$ ribosome methyltransferase
- Macrolide, lincosamide and type B streptogramin antibiotic resistance – $\text{Erm}$
Bacterial resistance mechanisms

- Decreased permeability
- Antibiotic
- Antimicrobial resistance mechanisms
  - Antibiotic degrading enzyme
  - Antibiotic resistance genes
  - Antibiotic altering enzyme
  - Plasmid
  - Efflux pump

Alteration in Target Molecule
Antibiotic resistance is transferable

Slide courtesy of Adrian Brink
Selection of antibiotic resistant bacteria

- Sensitive bacterium
- Resistant bacterium

Antibiotic replication
Antimicrobial use drives the emergence of antimicrobial resistance

Simultaneous prescription of antibiotics in South African ICUs

Example: 1 patient simultaneously received:
- Cloxacillin
- Teicoplanin
- Metronidazole
- Amikacin
- Ceftazadime
- Meropenem
- Levofloxacin
- Erythromycin
- Co-trimoxazole
- Fluconazole
Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

36% increase in global antibiotic consumption between 2000 – 2010
75% of that increase occurred in BRICS countries
Increasing hospital sector use of carbapenems 2005-2010
Per capita total carbapenem use; retail sector 2005 - 2010

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
International Tourism 2013

International tourist arrivals (ITA): 1,087 million
International tourism receipts (ITR): US$ 1,159 billion

Share in the world (%)

Americas
ITA: 168 million (15%)
ITR: 229 US$ bn (20%)

Europe
ITA: 563 million (52%)
ITR: 489 US$ bn (42%)

Asia Pacific
ITA: 248 million (23%)
ITR: 359 US$ bn (31%)

Middle East
ITA: 52 million (5%)
ITR: 47 US$ bn (4%)

Africa
ITA: 56 million (5%)
ITR: 34 US$ bn (3%)

UN World Tourism Organization 2014 Report
Global spread of NDM-1-producing *Klebsiella pneumoniae*, as of June 2012.
Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Tolman


- E. coli
- K. pneumoniae
- P. aeruginosa
- P. putida
- P. pseudoalcaligenes
- P. aryzihabitans
- S. boydii
- S. indologenes
- A. caviae
- S. maltophilia
- V. cholerae
- C. freundii
- Achromobacter spp
- Kingella dentricans
## Surgery Cost Chart
(Medical Tourism Association 2010 Survey)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>US</th>
<th>India</th>
<th>Thailand</th>
<th>Malaysia</th>
<th>Mexico</th>
</tr>
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<tbody>
<tr>
<td>Heart bypass</td>
<td>$144,000</td>
<td>$5,200</td>
<td>$15,121</td>
<td>$11,430</td>
<td>$27,000</td>
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<td>Heart valve replacement</td>
<td>170,000</td>
<td>5,500</td>
<td>21,212</td>
<td>10,580</td>
<td>18,000</td>
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<td>Hip replacement</td>
<td>50,000</td>
<td>7,000</td>
<td>7,879</td>
<td>7,500</td>
<td>13,000</td>
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<tr>
<td>Dental implant</td>
<td>2,800</td>
<td>1,000</td>
<td>3,636</td>
<td>354</td>
<td>1,800</td>
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<tr>
<td>Face lift</td>
<td>15,000</td>
<td>4,000</td>
<td>3,697</td>
<td>3,440</td>
<td>4,900</td>
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<tr>
<td>IVF treatments</td>
<td>14,500</td>
<td>3,250</td>
<td>9,091</td>
<td>3,819</td>
<td>3,950</td>
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<tr>
<td>Kidney transplant (bring donor)</td>
<td>8,000</td>
<td>21,212</td>
<td></td>
<td>45,000</td>
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</table>
High rate of hospital-acquired infections in developing countries

- Meta-analysis: developing-country adult ICUs had infection rates 3x higher than those in the United States
- Surgical site infections higher (5.6 vs. 1.6-2.9 per 100 surgical procedures)
- Rates of device-associated infections high

19 cases from 5 states

All female 18-59 years

12 underwent surgery at same clinic, 7 at others

Liposuction (74%), abdominoplasty (58%), breast implants (32%)

14 hospitalized in US – multiple surgeries & Abx

M. abscessus (16), M. fortuitum (2)
Inter-relationship of AMR

Diagram based on Linton (1977), as adapted by Rebecca Irwin, Health Canada (Prescott 2000) and IFT
Antimicrobial Consumption in the USA

- 81 million kilograms used per annum
- 15.75 million kilograms used per annum
- Feed Animals
- Pets
- Human

10 million kilograms used for pets and human consumption.
Residential Proximity to Large Numbers of Swine in Feeding Operations Is Associated with Increased Risk of Methicillin-Resistant *Staphylococcus aureus* Colonization at Time of Hospital Admission in Rural Iowa Veterans

Margaret Carrel, PhD; Marin L. Schweizer, PhD; Mary Vaughan Sarrazin, PhD; Tara C. Smith, PhD; Eli N. Perencevich, MD, MS

Among 1,036 patients, residential proximity within 1 mile of large swine facilities was associated with nearly double the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization at admission (relative risk, 1.8786 [95% confidence interval, 1.0928–3.2289]; \( P = .0239 \)) and, after controlling for multiple admissions and age, was associated with nearly triple the odds of MRSA colonization (odds ratio, 2.76 [95% confidence interval, 1.2728–5.9875]; \( P = .0101 \)).

*Infect Control Hosp Epidemiol* 2014;35(2):190–192
World population to reach ~8 billion by 2025 with increasing urbanization
Demand for meat is increasing in developing countries
Projected Change in Agricultural Productivity by 2080 due to climate change, incorporating the effects of carbon fertilization

Different forms of antibiotics sold for animal use during 2002 - 2004

- **In-feeds (69%)**
  1. Macrolides, lincosamides and pleuromutilins (61.60%)
  2. Tetracyclines (14.00%)
  3. Polypeptides (9.10%)
  4. Quinoxalines (8.20%)
  5. Lonophores (6.70%)
  6. Glycolipids (0.40%)

- **Water solubles (12%)**
  1. Sulphonamides (95.40%)
  2. Penicillins (1.80%)

- **Parenterals (17.5%)**
  1. Penicillins (60.00%)
  2. Tetracyclines (32.00%)
  3. Cephalosporins (4.50%)
  4. Sulphonamides (3.20%)
  5. Quinolones (0.20%)
  6. Aminoglycosides (0.10%)

- **Intramammaries (4%)**
  1. Penicillins (98%)

- **Other dosage forms (1.5%)**

Eagar et al. J S Afr Vet Assoc. 2012;83(1)
MRSA bloodstream infections


72% HA-MRSA at Red Cross Hospital, 2007-2011  (Naidoo et al. PLoS ONE. 2013; 8(10); e78396)
## ESBL rates in South Africa

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th><em>K. pneumoniae</em></th>
<th><em>E. coli</em></th>
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<tbody>
<tr>
<td>SMART(^1) * 2004-2009*</td>
<td>Complicated intra-abdominal infections</td>
<td>41.2%</td>
<td>7.6%</td>
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<tr>
<td>SASCM(^2) public sector hospitals, 2010</td>
<td>Blood cultures</td>
<td>55-74%</td>
<td>3-17%</td>
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<tr>
<td>GERMS-SA(^3) Sentinel sites Jan-Jul 2012</td>
<td>Blood cultures</td>
<td>75%</td>
<td>-</td>
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</tbody>
</table>


*Study for the Monitoring of Antimicrobial Resistance Trends*
Spread of Carbapenemase Producing *Enterobacteriaceae* (CPE) in South Africa

SAMJ 2012; 102(7): 599-601

J Clin Micro 2013; 51(1): 369-72
Emergence of OXA-48 and OXA-181 Carbapenemases among *Enterobacteriaceae* in South Africa and Evidence of *In Vivo* Selection of Colistin Resistance as a Consequence of Selective Decontamination of the Gastrointestinal Tract

- Unstable patient admitted MVR & CABG
- OXA-181-producing *Klebsiella pneumoniae*
  - S - tigecycline and colistin from urine
- Colistin monotherapy
- Still colonized 15 days later
- Cardiac surgery postponed
- Colistin 2MU 8hrly + Meropenem
  + SDD (oral colisitin & tigecycline 22 days)
- Pan-resistant *K. pneumoniae*
The true cost of antimicrobial resistance

Richard Smith and Joanna Coast argue that current estimates of the cost of antibiotic resistance are misleading and may result in inadequate investment in tackling the problem.

Richard Smith professor of health system economics, Joanna Coast professor of health economics

1 London School of Hygiene and Tropical Medicine, London WC1H 9SH, UK; 2 School of Health and Population Sciences, University of Birmingham, Birmingham, UK

“We estimate that without antimicrobials, the rate of postoperative infection in [total hip replacements] is 40-50% and about 30% of those with an infection will die.”
Outbreak of Oxa-181 *Klebsiella pneumoniae* on a Haematology Transplant Unit

Slide courtesy of Colleen Bamford
Outbreak of Fatal MDR *Pseudomonas aeruginosa* on a Haematology Transplant Unit

Slide courtesy of Colleen Bamford

- **+= Died**
- **= Survive**
- **X = Ward X**
- **R = Radiotherapy ward**
Combating antimicrobial resistance, including antibiotic resistance

Draft resolution proposed by Australia, China, Costa Rica, Ghana, Japan, Libya, Mexico, Netherlands, Qatar, Sweden, Thailand, United Kingdom of Great Britain and Northern Ireland and United States of America
Responsibilities of members states

1. Political awareness and leadership to enable appropriate use
2. Strengthening of Infection prevention and control
3. Develop national strategic plans and international collaboration
4. Strengthen pharmaceutical management systems
5. Mobilize human and financial resources
6. Improve awareness of threat posed and required interventions
7. R&D through collaborative financial models
8. Collaborate with WHO secretariat to develop the GAP
9. Develop AMR surveillance in hospital inpatients; outpatients and community; animals and non-human usage
The South African strategic plan for AMR

Impact: Rational Antimicrobial use and improved patient outcomes

Antimicrobial Resistance Governance

Enhance surveillance
Antimicrobial stewardship
Prevention including IPC and vaccination

Education and Communication/ Public awareness
Adult Infectious Diseases Specialists

Paediatric Infectious Diseases Specialists

Microbiologists

Pharmacists

Infection Control Practitioners

Surgeons & Intensivists

Animal Health microbiologists & Veterinarians

Epidemiologists
What lessons have we learned [are we learning] from the loss of antibacterials that have relevance to the future of antiretroviral use?
Lesson 1
The international mindset still sees antimicrobials as private goods
Responsible use requires acknowledging that antimicrobials are a Global Public Good

A ‘Global Public Good’ is both non-excludable and non-rival in consumption

Global governance failure exists because of ‘free riders’
Lesson 2
Complacency and Profits
“Tuberculosis will be eradicated”

Funding for TB research and treatment 1960 = $40 million → 1989 = $283,000
Percentage of TB Cases Among Foreign-born Persons, United States*

**2000**

- Purple: ≥50%
- Beige: 25%–49%
- White: <25%

**2010**

- Purple: ≥50%
- Beige: 25%–49%
- White: <25%

*Updated as of July 21, 2011.*
Discovery of drugs for tuberculosis

1940s
- 1943: Streptomycin
- 1948: PAS

1950s
- 1951: Thiacetazone
- 1952: Isoniazid
- 1954: Pyrazinamide
- 1955: Cycloserine
- 1957: Kanamycin

1960s
- 1960: Ethionamide
- 1961: Ethambutol
- 1963: Capreomycin

1970s
- 1961: Ofloxacin

1980s
- 1963: Rifampicin

1990s
- 1992: Gatifloxacin
- 1996: Moxifloxacin
- 2000: PA-824
- 2005: TMC-207
- 2006: OPC-67683

2010s
- Potential new regimen

Timeline:
- 1946: First randomised trial: streptomycin monotherapy led to streptomycin resistance
- 1952: First regimen: streptomycin, aminosalicylic acid, and isoniazid
  - 18 months of treatment
- 1960s: Aminosalicylic acid replaced with ethambutol: streptomycin, isoniazid, and ethambutol
  - 18 months of treatment
- 1970s: Addition of rifampicin: streptomycin, isoniazid, rifampicin, pyrazinamide, ethambutol
  - 6–8 months of treatment
- 1980s: Streptomyacin replaced with pyrazinamide: isoniazid, rifampicin, pyrazinamide, ethambutol
  - 6–8 months of treatment
Dates of discovery of distinct classes of antibacterial drugs

Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

WHO AMR Report 2014
The Gram negative antibiotic pipeline for the next 10-15 years

Antiretroviral Pipeline 1987 - 2003
<table>
<thead>
<tr>
<th>Generic Name (Acronym)</th>
<th>Brand Name</th>
<th>Sponsor</th>
<th>Status</th>
<th>Date</th>
<th>Class</th>
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<tbody>
<tr>
<td><strong>Approved (16)</strong></td>
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</tr>
<tr>
<td>atazanavir</td>
<td>Reyataz</td>
<td>BMS</td>
<td>Approved</td>
<td>2003</td>
<td>PI</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>Emtriva</td>
<td>Gilead</td>
<td>Approved</td>
<td>2003</td>
<td>NRTI</td>
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<tr>
<td>entefuvirtide (T-20)</td>
<td>Fuzeon</td>
<td>Roche</td>
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<td>2003</td>
<td>PI</td>
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<td>fosamprenavir</td>
<td>Lexiva</td>
<td>GSK</td>
<td>Approved</td>
<td>2003</td>
<td>PI</td>
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<tr>
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<td>2003</td>
<td>NRTI 2-FDC</td>
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<td>emtricitabine/tenofovir (FTC/TDF)</td>
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<td>Gilead</td>
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<td>2004</td>
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<td>2005</td>
<td>PI</td>
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<td>Prezista</td>
<td>Janssen</td>
<td>Approved</td>
<td>2006</td>
<td>PI</td>
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<td>efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF)</td>
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<td>maraviroc</td>
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<td>nevirapine-XL</td>
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<td>rilpivirine/emtricitabine/tenofovir</td>
<td>Complera</td>
<td>Janssen/Gilead</td>
<td>Approved</td>
<td>2011</td>
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<td>Gilead</td>
<td>Approved</td>
<td>2012</td>
<td>PI/PI PK booster/NNRTI 4-FDC</td>
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<td><strong>Submitted (3)</strong></td>
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<td>elvitegravir</td>
<td>–</td>
<td>Gilead</td>
<td>Submitted</td>
<td>2012</td>
<td>InI (single-agent approval postponed; approved in Stribild 2012)</td>
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<td>Gilead</td>
<td>Submitted</td>
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<td>dolutegravir</td>
<td>–</td>
<td>ViiV/GSK</td>
<td>Submitted</td>
<td>2013</td>
<td>InI</td>
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<td><strong>Active in Phase III (1) or Phase II (9)</strong></td>
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<td>tenofovir alafenamide (TAF)</td>
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<td>AI</td>
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<td>cencriviroc</td>
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<td>Tobira</td>
<td>In phase II</td>
<td>2013</td>
<td>CCR5R</td>
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<td>doravirine (MK-1439)</td>
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<td>Merck</td>
<td>In phase II</td>
<td>2013</td>
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<td>In phase II</td>
<td>2013</td>
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<td>rilpivirine-LA</td>
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<td>Janssen</td>
<td>In phase II</td>
<td>2013</td>
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<td>darunavir/cobicistat/emtricitabine/tenofovir alafenamide</td>
<td>–</td>
<td>Janssen/Gilead</td>
<td>In phase II</td>
<td>2013</td>
<td>PI/PI PK booster/NNRTI 4-FDC</td>
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<td>GS/GSK</td>
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<td>2013</td>
<td>PI/NNRTI 3-FDC</td>
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<tr>
<td>elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide</td>
<td>–</td>
<td>Gilead</td>
<td>In phase II</td>
<td>2013</td>
<td>InI/PI PK booster/NNRTI 4-FDC</td>
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</table>
Table 1B. HIV treatment pipeline, 2003–2013: drugs stopped or stalled in phase II/III

<table>
<thead>
<tr>
<th>Generic Name (Acronym)</th>
<th>Sponsor</th>
<th>Last Active Year</th>
<th>Class</th>
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<tr>
<td>Stopped in Phase III (3)</td>
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<td>capravirine (AG-1549)</td>
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<td>vicriviroc (SCH 417690)</td>
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<td>lersivirine (UK-453,061)</td>
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<td>2010</td>
<td>AI mAb</td>
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<td>anti-CD4 mAb</td>
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<td>NRTI</td>
</tr>
<tr>
<td>bevirimat (PA-457)</td>
<td>Panacos/Myriad</td>
<td>2010</td>
<td>AI</td>
</tr>
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</table>
Typical Pharmaceutical Economic Model: Return is driven by sales volume

Investment is largely controlled by need to demonstrate safety & efficacy

Price (somewhat) controlled by authorities/payers

Volume (somewhat) driven by company and competition

Slide courtesy of James Anderson, GSK
De-linked or de-coupled model

“Buy-out”

“Staged Buy-out”

Slide courtesy of James Anderson, GSK
Recommendations for new models of pharmaceutical R&D by the WHO Consultative Expert Working Group

- De-linking revenues from sales
- New incentives or re-purposing off-patent medicines
- Milestone payments and advanced purchase commitments for new priority antibacterials
- Global contract for stewardship
- Agreement on tiered pricing
Actual and projected numbers of people receiving ART in LMICs, and by WHO region, 2003-2015

2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)
Relationship between transmitted resistance to NNRTI drugs & antiretroviral therapy coverage

![Graph showing the relationship between transmitted resistance to NNRTI drugs and antiretroviral therapy coverage. The x-axis represents the percentage of people living with HIV receiving ART, while the y-axis shows the prevalence of NNRTI resistance mutations as a percentage of genotypes. The graph has data points for different regions, indicating a general trend of increasing resistance with increasing treatment coverage.]

WHO HIV Drug Resistance Report 2012
Lesson 3
Healthcare professionals and the public have difficulty identifying with AMR
EBOLA

Signs and Symptoms

If you have fever, diarrhoea and vomiting with or without bleeding, go immediately to the nearest health facility.

For more information call 117 (Call free)
Patients will be 1st in U.S. with Ebola

The concern began just as news broke that a long-range business jet left the U.S. for Liberia, where it was to evacuate two Americans infected with Ebola. **FULL STORY**

- Jet outfitted with isolation pod
- What's risk of Ebola on planes?
- Photos: Outbreak | Explainer
- Sick doc gives Ebola serum away
How do you develop the narrative?

What do the consequences of antiretroviral treatment failure look like to you, your patients and their support networks?
26 year old cachexic HIV-HBV coinfected man

- 1\textsuperscript{st} line ART after PTB diagnosis – defaulted and re-started
- Developed virological failure, 2\textsuperscript{nd} line switch
- Re-presented with presumptive disseminated TB
- Alluvia not boosted
- Deteriorating on TB treatment, unidentified cause
  - rifampicin boosting and addition of MDR therapy
- Re-admitted with [probable] disseminated TB, disseminated cryptococcosis, pseudomembranous colitis
26 year old male HIV-HBV coinfected

<table>
<thead>
<tr>
<th>Tuberculosis</th>
<th>HIV, HBV</th>
<th>Cryptococcus</th>
<th>C. difficile</th>
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<tr>
<td>Rifampicin</td>
<td>Tenofovir</td>
<td>Amphotericin</td>
<td>Vancomycin</td>
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<td>Isoniazid</td>
<td>Emtricitabine</td>
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<td>[oral]</td>
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<td>Ethambutol</td>
<td>Aluvia (DD)</td>
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<td>Prazinamide</td>
<td>Cotrimoxazole</td>
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<td>Moxifloxacin</td>
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<td>Ethionamide</td>
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<td>Kanamycin</td>
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</table>

Potential nephrotoxicity
Potential hepatic toxicity
Lesson 4
The need to work effectively as a multi-disciplinary team
Microbiologists

Infectious Diseases Specialists

Registars

GSH Antibiotic Stewardship Team

Pharmacists

Nurses

IPC

Intensivists

Statistician
Antiretroviral Stewardship Team

- ART Prescriber
- Adherence Counsellor
- [Psychologist/Psychiatrist]
- Nurses
- Social Worker
- Treatment supporter(s)
- Others; Who would they be?
Lesson 5
Asking the right question
5 D'S
OF DODGEBALL
Duck Dodge Dip Dive Dodge
The 5 D’s of Antibiotic Stewardship

• Drug [Is an antibiotic indicated at all?]
• Dose
• Dosing interval
• Duration
• De-escalation

[And an ‘R’ – Route of administration]
What antiretroviral combination should I use?

That’s the easy part
“Why did we fail?”
Take Home Messages

• History has a horrible way of repeating itself, particularly when it comes to the control of infectious diseases.

• Although much is being done to address ARV treatment failure, too often, the wrong question is being asked.

• We need to be smarter about defining patients at risk and ensuring members of our ARV stewardship teams have the skills and time to fulfill their role.
Do not go gentle into that good night
Old age should burn and rave at close of day
Rage, rage against the dying of the light

Though wise men at their end know dark is right,
Because their words had forked no lightning they
Do not go gentle into that good night

Good men, the last wave by, crying how bright
Their frail deeds might have danced in a green bay,
Rage, rage against the dying of the night

Wild men who caught and sang the sun in flight
And learn, too late, they grieved it on its way
Do not go gentle into that good night

Grave men, near death, who see the with blinding sight
Blind eyes could blaze like meteors and be gay,
Rage, rage against the dying of the light.

And you my father, there on the sad height,
Curse, bless, me now with your fierce tears I pray,
Do not go gentle into that good night.
Rage, rage against the dying of the light.

Dylan Thomas, 1914 - 1953
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