Professor Andrew Lever
University of Cambridge
5 papers to change clinical practice

AMLLever

BHIVA 2013
Dolutegravir (DTG; S/GSK1349572) + abacavir/lamivudine once daily statistically superior to Tenofovir/emtricitabine/efavirenz: 48 week results
Walmsley, et al. *ICAAC* 2012; Abstract H-556b

Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

Short-Course Antiretroviral Therapy in Primary HIV Infection
The SPARTAC Trial Investigators

Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial
Sax et al for the GS-236-0103 Study Team

*Morb Mortal Wkly Rep*. 2011 Dec 2; 60:1618
Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA; Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc; A. David Paltiel, PhD; and Bruce R. Schackman, PhD


50% reduction in drug costs and a savings of $960 million in care costs in 1 year

Reduced treatment efficacy, resulting in 4.4 months of life lost per patient lifetime
Study questions generic HIV drug use

Rises in the use of cheaper, non-branded HIV drugs could potentially see more patients with treatment failure, claim US researchers
Model study paradigm

1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART).

versus

Once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, branded tenofovir)
Comparison of CEPAC Model outcomes and data reported from WIHS.

Kaplan–Meier survival curves based on data from WIHS were compared with preliminary, model-estimated survival over 36 mo. Lines with symbols represent model-based projections, whereas those without symbols represent WIHS data. CEPAC = Cost-Effectiveness of Preventing AIDS Complications; WIHS = Women's Interagency HIV Study.
Comparative cost/benefit
Potential savings

Potential annual cost savings in the United States with 3-pill or 2-pill, generic-based ART compared with branded ART.
Validity of assumptions

Assumption of inferior efficacy of 3TC versus FTC

WHO report 2013 – no difference in efficacy or safety

Poorer adherence because of separate pills

Fixed dose combinations of generic TDF+FTC+EFV

TDF on patent in US - $9,200/patient/year

Generic TDF = $200/patient/year

- Trade off between cost and efficacy misleading
Patent expiry dates of HAART drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Manufacturer</th>
<th>Expiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC (lamivudine)</td>
<td>NRTI</td>
<td>GlaxoSmithKline</td>
<td>2010</td>
</tr>
<tr>
<td>Abacavir</td>
<td>NRTI</td>
<td>GlaxoSmithKline</td>
<td>2012</td>
</tr>
<tr>
<td>Efavirenz*</td>
<td>NNRTI</td>
<td>Bristol-Myers Squibb</td>
<td>2013</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>NNRTI</td>
<td>Pfizer</td>
<td>2013</td>
</tr>
<tr>
<td>Darunavir</td>
<td>PI</td>
<td>Tibotec</td>
<td>2015</td>
</tr>
<tr>
<td>FTC (emtricitabine)*</td>
<td>NRTI</td>
<td>Gilead</td>
<td>2015</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>PI</td>
<td>Boehringer Ingelheim</td>
<td>2015</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>PI</td>
<td>Abbott</td>
<td>2016</td>
</tr>
<tr>
<td>Tenofovir*</td>
<td>NRTI</td>
<td>Gilead</td>
<td>2017</td>
</tr>
</tbody>
</table>

(*Atripla)

“In ten years this will be a disease treated for $200 per year, or less”

John Bartlett
Generic drugs and HIV

WHO – ‘generic antiretroviral therapy is safe and effective’
Treatment of HCV Infection by Targeting MicroRNA


NEJM 27th May 2013

Use of a ‘locked’ nucleic acid (LNA) to target a virus infection
Hepatitis C

170 million chronic carriers

Major cause of cirrhosis, liver failure and HCC

20% HIV infected people are HCV infected

85% HIV+ people with Haemophilia

DAD study 14% deaths liver related 66% had HCV
MicroRNAs (miRNAs)

Small, endogenous, noncoding RNAs

Posttranscriptional regulation of gene expression by binding to partially complementary sites within the 3' untranslated region of target messenger RNAs (mRNAs),

Cause translational repression or mRNA deadenylation and degradation.

miRNA 122

Highly abundant miRNA expressed in the liver

Involved in control of cholesterol metabolism in liver

Essential to the stability and propagation of HCV RNA
Locked nucleic acid
Miravirsen

Phase 2a study

15-nucleotide locked nucleic acid–modified antisense oligonucleotide
Complementary to and with a high affinity and specificity for the 5′ region of mature miR-122

Patients

36 treatment naïve
HCV genotype 1
HBV/HIV negative
Compensated disease
HCV RNA > 75,000 IU/ml

4 groups of 9
Placebo, 3mg/kg, 5mg/kg, 7mg/kg
5 weekly doses over 29 days

PEG/IFN ribavirin at week 7 (3mg, n= 5) or 10 (5mg, n=3, 7mg, n=2)
Results

Sustained decrease in transaminases

No biochemical toxicity of note

Decrease in serum cholesterol

No evidence of viral resistance
LNA against HCV effective

Pharmacokinetics

Safety

Other applications
Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa
Klopper et al EID Volume 19, Number 3—March 2013
Countries that had reported at least one XDR-TB case by Oct 2011

Argentina, Armenia, Australia, Austria, Azerbaijan, Bangladesh, Belarus, Belgium, Benin, Botswana, Brazil, Burkina Faso, Cambodia, Canada, Chile, China, Colombia, Czech Republic, Dominican Republic, Ecuador, Egypt, Estonia, France, Georgia, Germany, Greece, India, Indonesia, Iran (Islamic Rep. of), Ireland, Israel, Italy, Japan, Kazakhstan, Kenya, Kyrgyzstan, Latvia, Lesotho, Lithuania, Luxembourg, Macedonia, Malawi, Malaysia, Malta, Mexico, Mongolia, Mozambique, Namibia, Nepal, Netherlands, New Zealand, Nigeria, Norway, Pakistan, Panama, Peru, Philippines, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Rwanda, Senegal, Sierra Leone, Slovenia, South Africa, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Togo, Tanzania, Thailand, The Former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Arab Emirates, United Kingdom, United Republic of Tanzania, United States of America, Uruguay, Uzbekistan, Viet Nam, Yemen, Zimbabwe.
<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migliori (Italy)</td>
<td>2 patients with TDR-TB</td>
</tr>
<tr>
<td><em>Euro Surveill.</em> 2007</td>
<td></td>
</tr>
<tr>
<td>Velayati (Iran)</td>
<td>146 MDR-TB assessed</td>
</tr>
<tr>
<td><em>Chest</em> 2009</td>
<td>8 XDR</td>
</tr>
<tr>
<td></td>
<td>15 TDR resistant to all first-line (INH, RF, SM, ETB, and PZA) and second-line drugs tested (OFC, CYC, PTH, AMK, KAN, ETH, PAS, and CAP)</td>
</tr>
<tr>
<td>Udwadia (India)</td>
<td>4 patients with TDR-TB</td>
</tr>
<tr>
<td><em>CID</em> 2011</td>
<td></td>
</tr>
<tr>
<td>2012 WHO consultation</td>
<td>TDRTB not clearly defined</td>
</tr>
<tr>
<td>2013 WHO</td>
<td>Annual need of at least US$ 1.6 billion in international funding for treatment and prevention of drug resistant TB (and malaria)</td>
</tr>
</tbody>
</table>
TB South Africa

9.6% MDR-TB

One of highest burden MDR-TB countries in the world

One of highest HIV burden countries in the world

Epidemic driven by transmission

Culture conversion rates for XDR-TB <20%

Streicher et al
Infection, Genetics and Evolution
Volume 12, Issue 4, June 2012, Pages 686–694
Study

Molecular analysis of 309 drug-susceptible and 342 multidrug-resistant TB (MDR-TB) isolates collected from 2008 to 2009 from Eastern Cape Province,

Results

69% of MDR-TB were Beijing subtype

92% of these 236 MDR-TB strains belonged to an atypical Beijing genotype resistant to 10 (4 first-line and 6 second-line) anti-TB drugs

INH, RF, SM, ETB, PZA, OFX, AMK, KAN, ETH, and CAP (some PAS resistant)
Cause of high levels of resistance

Absence of routine second line drug testing

2004 guidelines 6/12 KAN ETH PZA OFX CYC/ETB then 18/12 ETH PZA OFX CYC/ETB

May have led to undertreatment of ‘pre-XDR’ TB

2007 Second line DST introduced, CAP and PAS available
## 2010 Guidelines

<table>
<thead>
<tr>
<th></th>
<th>MDR TB</th>
<th>XDR TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive phase</td>
<td>Kanamycin (IM)</td>
<td>Capreomycin (IM)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>Ethionamide</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Ethionamide</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td></td>
<td>Terizidone/cycloserine</td>
<td>Terizidone/cycloserine</td>
</tr>
<tr>
<td>Continuation</td>
<td>Ethionamide</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>phase</td>
<td>Pyrazinamide</td>
<td>$p$-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Terizidone/cycloserine</td>
<td>Terizidone/cycloserine</td>
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</table>
### Zithulele hospital, Eastern Cape, South Africa

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR-TB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2(c)</td>
<td>5</td>
<td>24</td>
<td>(13)</td>
<td>44</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td>5</td>
<td>23</td>
<td>(1)</td>
<td>29</td>
</tr>
<tr>
<td>Defaulted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td><strong>XDR-TB</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1 (died)</td>
<td>(4)</td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Eastern Cape 2004-2009 6211 MDRTB 488 XDRTB
HIV Prevention in Action on the Football Field: The Whizzkids United Program in South Africa

Louise Balfour, Thomas Farrar, Marcus McGilvray, Douglas Wilson, Giorgio A. Tasca, Johanna N. Spaans, Catherine Mathews, Lungile Maziya, Siphosihle Khanyile, Tracy L. Dalgleish, William D. Cameron

AIDS Behav 2013
South African national surveys indicate that 12.6% of youth have initiated sex before age 14

Sex education should be offered as early as age 10
Aims to impart knowledge and life skills critical to HIV prevention

The Africaid Trust, has been operating a 12-week educational soccer program in elementary schools in Pietermaritzburg, South Africa
“On The Ball” WhizzKids United

Using the game of soccer as an analogy for life (e.g., not using a condom during sex is like playing soccer without a goalkeeper)
Aims

WKU compared HIV knowledge, stigma and health care seeking behaviours of elementary youth (grades 5–8) who had received the WKU OTB program in addition to traditional classroom-based HIV education to students who had only received traditional HIV education.

Establish the baseline level of HIV knowledge, sexual behaviors and health seeking behaviors of older youth in grades 9–12.

Method

Survey was administered in schools using a novel, cell phone based technology that allowed for the secure reporting and uploading of sensitive information.

Participants

972 participants (99% South African black, 498 boys and 472 girls grades 5-12)

267 WKU programme (142 boys, 119 girls)

Edendale Township HIV prevalence of 42.3% among pregnant women presenting at antenatal clinics.
Differences between WKU and non-WKU participants in grades 5–8 (n = 629)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Received WKU program</th>
<th>Did not receive WKU program</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 5–8</td>
<td>Mean (%) SD (%)</td>
<td>Mean (%) SD (%)</td>
<td></td>
</tr>
<tr>
<td>HIV stigma</td>
<td>27 21</td>
<td>33 23</td>
<td>&gt;0.001*</td>
</tr>
<tr>
<td>HIV general knowledge</td>
<td>49 28</td>
<td>37 28</td>
<td>&gt;0.001*</td>
</tr>
<tr>
<td>Grade 8 participants only</td>
<td>(n = 41)</td>
<td>(n = 46)</td>
<td></td>
</tr>
<tr>
<td>HIV general knowledge</td>
<td>70 24</td>
<td>66 29</td>
<td>0.074</td>
</tr>
<tr>
<td>HIV sex-related knowledge</td>
<td>59 27</td>
<td>49 26</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

Means for HIV knowledge are presented as mean percent correct
* Statistical significance
Descriptive Statistics: Grades 9–12

55.6% respondents in grades 9–12 reported being sexually active

29% self-reported use of a condom during the most recent sexual encounter

31% HIV counselling within the last 6 months

Less than one-third of survey respondents tested for HIV in previous 6 months

90% would use a youth friendly health clinic affiliated with the WKU clubhouse if available
Systematic identification of synergistic drug pairs targeting HIV

Xu Tan, Long Hu, Lovelace J Luquette III Geng Gao, Yifang Liu, Hongjing Qu, Ruibin Xi Zhi John Lu, Peter J Park & Stephen J Elledge

Nature Biotechnology Vol 30 No11 Nov 2012 p1125
Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen

Abraham L. Brass,1,2 Derek M. Dykxhoorn,3* Yair Benita,4* Nan Yan,3 Alan Engelman,5 Ramnik J. Xavier,4* Judy Lieberman,2 Stephen J. Elledge3†

siRNA based screening approaches for cellular factors that assist viral replication

1. Cells seeded in microtiter plates
2. Robotic transfection of arrayed siRNAs
3. 48/72h
4. Virus infection
5. 24/48h
6. Reporter readout
Fig. 5. Model of HDF roles in the HIV life cycle. With the stages of the HIV life cycle as a framework, each HDF was placed at the position most likely to elicit HIV dependency. The function and subcellular location of HDFs were determined with the use of multiple databases (rationale, table S4). Some proteins are in multiple locations to represent more than one possible role in the HIV life cycle. Newly identified HDFs (red or blue, the latter if they inhibited HIV in part two only); previously implicated HDFs detected in the screen (green), or not detected but with a relevant interaction (gray); HIV protein (black): matrix (MA), reverse transcriptase (RT), integrase (IN), envelope (gp120, gp41) (ENV). Unfolded protein response, UPR.
Method

1,000 FDA approved drugs

500,000 pairwise combinations

Eliminated:

Cytotoxic
Topical
HAART
Antivirals
Structural duplicates
Results

Enrichment of anti-inflammatory drugs in combinations that synergise against HIV

Glucocorticoids and Nitazoxanide synergise by targeting different steps in lifecycle
Low dose combinations of known approved drugs may have powerful anti-HIV effects with minimal side effects.

This strategy is applicable to other infections.