Challenges of HIV/AIDS in Africa
New Challenges
New Answers
Introduction
What are the pressing HIV/AIDS needs in Africa?

- **New Therapeutics**
  - New Drugs
    - Dolutegravir
  - Improved Drugs
    - TAF
  - New Strategies
    - Monthly administration
    - Quarterly administration

- **Improved Diagnostic Technologies**
  - Infant diagnosis
  - Tuberculosis diagnosis
Dolutegravir Key Characteristics

- Pharmacokinetics
  - Once daily dosing ($t_{1/2} = 15$ h)
  - Low milligram dose (50 mg)
  - Low PK variability
  - No significant food effect
  - No renal effect
  - No CYP induction or inhibition

- Unique resistance profile
  - Limited cross-resistance to raltegravir and elvitegravir
  - Potential for higher genetic barrier to resistance

Dolutegravir: Antiviral Activity

Mean Change from Baseline in HIV-1 RNA (log_{10} copies/mL)

Day

Mean Change from Baseline in HIV-1 RNA (log_{10} copies/mL)

Dosing period

Follow-up period

-2.5
-2.0
-1.5
-1.0
-0.5
0.0
0.5

12
3
4
7
8
9
10
11
14
21

(BL)

(FU)

2 mg
10 mg
50 mg
PBO
Monotherapy Antiviral Activity

# Clinical Summary: Dolutegravir

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Arms (all arms get cART)</th>
<th>N</th>
<th>Naïve or Experienced</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRING 2</td>
<td>DTG vs Raltegravir</td>
<td>822</td>
<td>Naïve</td>
<td>88% vs 86% &lt;50 c/mL at W48 (non-inferior)</td>
</tr>
<tr>
<td>SINGLE</td>
<td>DTG/abac/3TC vs Efavirenz/TDF/FTC (ATRIPLA)</td>
<td>833</td>
<td>Naïve</td>
<td>88% vs 81% &lt;50 c/mL at W48 (Superior; p&lt;0.05)</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG</td>
<td>484</td>
<td>Naïve</td>
<td>90% vs 83% &lt;50 c/mL at W48 (Superior; p=0.025)</td>
</tr>
<tr>
<td>SAILING</td>
<td>DTG vs Raltegravir</td>
<td>719</td>
<td>Experienced</td>
<td>79% vs 71% (Superior; P&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No prior INI</td>
<td></td>
</tr>
<tr>
<td>VIKING</td>
<td>DTG 50 mg BID</td>
<td>183</td>
<td>Experienced</td>
<td>1.4 log decrease at D10 63% &lt;50 c/mL at W24 Q148 + 2 mutations=VF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prior INI</td>
<td></td>
</tr>
</tbody>
</table>
Dolbutegravir Summary
This drug is significantly different

- Potent antiviral activity
  - $2.6 \log_{10} \text{cp/mL}$ median decline in HIV-1 RNA after 10-day monotherapy
  - Superior to ATRIPLA and Darunavir/r in treatment-naïve patients; non-inferior to Raltegravir
  - Superior to Raltegravir in treatment experienced (no prior INI)
  - Active in 63% of patients with prior INI exposure and treatment failure
  - Not active if Q148 plus 2 INI mutations present

- Safe and well tolerated
- Once daily dosing
- Small dose (50 mg)
- Steady pharmacokinetics (no boosting required)
- Few drug-drug interactions
- No dose adjustment in renal insufficiency
- Cost of goods: miniscule
Tenofovir Alafenamide Fumarate (TAF)  
A new and better version of a good drug

- Prodrug, NRTI class, converted to active tenofovir diphosphate or TFV-DP
  - *not* tenofovir disoproxil fumarate or TDF, the approved drug we know as tenofovir or Viread®
  - More active than TDF, 1.5 log vs 1.0 log VL reduction or 300% more active
  - Safer and better tolerated
  - Co-formulation possible
  - Dosed 10 mg per day
  - Cost of goods: very little
### Long Acting Formulations

*Monthly or quarterly therapy…a real possibility for prevention and treatment*

- **Rilpivirine LA**
  - Nanaosuspension non-nucleoside reverse transcriptase inhibitor
  - Intramuscular, monthly

- **GSK744 LAP**
  - Nanosuspension integrase inhibitor
  - Intramuscular and subcutaneous, monthly or quarterly
  - 200-1200 mg tested

- **Ibalizumab (monoclonal antibody entry inhibitor – intravenous, biweekly or monthly)**
Diagnostic Devices for the World
Focus on Tuberculosis and Infant HIV Diagnosis

- Models for traditional Western medical technologies

... Problems for Low and Middle Income Countries (LMICs)

- US, Japan and Europe and the main purchasers of medical devices and they are the main designers and distributors
- LMICs are sold the same products as high income countries
  - Expensive
  - Parts and service dependent on Western countries
  - The cost in the consumables/reagents

- Research & Development of new devices requires:
  - 5-10% annual growth
  - >$500 million USD in annual sales
  - 20% - 40% rate of return on investment
Device Development Needs for Africa

- Diagnostic devices for LMIC needs
  - Rapid tuberculosis and infant HIV diagnosis
  - Viral load testing at point of care
  - Digital radiologic imaging (HealthGreen)
- Devices that do not require a cold chain
- Point of Care operability
- Heat stable equipment and reagents
- Independence from electrical grid
- Equipment and reagents which can be manufactured in Africa
- Institutional support for design, development and commercialization of identified needs
Northwestern University
Center for Innovation in Global Health Technologies (CIGHT)
Low Cost Diagnostic Project

September 20, 2013
Northwestern University Background

Partnerships & Collaborations

Key Contributions:
- Project Coordination, New Technology, Market Research and Product Development, Field Experience

Current Partners:
- McCormick School of Engineering – Center for Innovation in Global Health Technology (CIGHT)
- Kellogg School of Management – Global Health Initiative (GHI)
- Feinberg School of Medicine
- University of Cape Town

Key Contributions:
- Technology, Manufacturing, Regulatory, Distribution, Current Partners:

Key Contributions:
- R&D Funding, Mission, Field Experience

Current Partners:
NU Background
In prior years, >100 MBA students & faculty have conducted medical diagnostics market research in >10 countries

Key Questions
- What tests are needed?
- What tests are currently available and in what format?
- What platform format is appropriate?
- What is the expected frequency of testing?
- Who are the key stakeholders and what role do they play in technology adoption?
- What are the acceptable tradeoffs to these key stakeholders?
Product Pipeline

- P24 infant HIV test
- IMCI Tablet
- HIV Viral Load Test
- TB Diagnostic Test
# p24 Infant HIV Test

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Duration</td>
<td>~40 minutes</td>
</tr>
<tr>
<td>Blood Collection Requirements</td>
<td>3 drops (~80 µL)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95% Sensitivity and 99% Specificity</td>
</tr>
<tr>
<td>Price</td>
<td>~ 7 - 15 USD per test*</td>
</tr>
<tr>
<td></td>
<td>~ 400 - 700 USD per device*</td>
</tr>
<tr>
<td>Power Source</td>
<td>Rechargeable Battery</td>
</tr>
<tr>
<td>Result</td>
<td>Visually Read, qualitative result</td>
</tr>
<tr>
<td>Availability</td>
<td>2013</td>
</tr>
</tbody>
</table>

* Assumes minimum manufacturing volumes are achieved across all customers
p24 Infant HIV Test

**Step 1: Collect blood**

**Step 2: Apply blood to LYNX Plasma Separator**

**Step 3: Plunge Plasma Collection Pad into the Reaction Tube**

**Step 4: Separate Reaction Tube from LYNX Plasma Separator**

10 minutes

**Step 5: Add LYNX Buffer**

**Step 6: Heat**

**Step 7: Insert LYNX Test Strip**

11 minutes

30 minutes

**Step 8: Read Test**

- 

+
How do we measure the value of and electronic Integrated Management of Childhood Illnesses (eIMCI)?

- Accuracy (diagnosis and/or treatment)
- Adherence (HC worker and/or patient adherence)
- Speed (time to diagnose)
- Throughput (# of patients per day)
- Supply chain (commodity forecasting)
- Cost (training, hard and soft costs)
Symptoms

Diarrhea

Start treatment for severe dehydration (Plan C, p. 18). Refer URGENTLY. Give frequent sips of ORS on the way. Advise when possible.

Fever

Give first dose of ceftriaxone IM (p. 15). Test for low blood sugar, then treat or prevent (p. 16). Give one dose of paracetamol for fever 38°C or above (p. 13). Refer URGENTLY. If Malaria test positive and child older then 12 months, treat for Malaria (p. 11). Treat for SUSPECTED MENINGITIS. Test for low blood sugar, then treat or prevent (p. 16). Give one dose of paracetamol for fever 38°C or above (p. 13). Refer URGENTLY. Give additional dose Vitamin A (p. 19). If clouding of the cornea or pus draining from the eye, apply chloramphenicol eye ointment. Give first dose of amoxicillin (p. 10) unless child is receiving IM ceftriaxone for another reason. REFER URGENTLY. Immunize all close contacts within 72 hours of exposure.

Prescribed treatment
## LYNX Molecular Platform: HIV Viral Load Test

<table>
<thead>
<tr>
<th>Target Specification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal of Test</strong></td>
<td>A quantitative real-time PCR diagnostic test for the measurement of HIV-1 viral load copies per ml of plasma</td>
</tr>
<tr>
<td><strong>Limit of Detection</strong></td>
<td>200-1000 copies / ml of plasma, depending on the volume of sample collected</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>&lt;$12K per instrument; &lt;$10 per cartridge</td>
</tr>
<tr>
<td><strong>Power Source</strong></td>
<td>12V; mains power with UPS for outages</td>
</tr>
<tr>
<td><strong>Connectivity</strong></td>
<td>Internal EDGE/3G modem provided upon request</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>2015</td>
</tr>
</tbody>
</table>
Step 1: Collect whole blood into mini-cartridge

Step 2: Place mini-cartridge into spinner (provided by manufacturer)

Step 3: Remove mini-cartridge from spinner and snap onto cartridge

Step 4: Add Cartridge to Available Slot

Step 5: Wait for Reaction to Complete

Step 6: Remove Cartridge and Read Results

60 minutes
## Goal of Test

A qualitative real-time PCR diagnostic test for the detection of Mycobacterium tuberculosis (TB) complex DNA in sputum.

## Drug resistance screening

Yes, Rifampicin resistance via a separate cartridge.

## TB Screening: Sensitivity / Specificity

~98% sensitive on S+C+
~75-90% sensitive on S-C+
~98% Specificity

## Rifampicin Screening (as compared to drug sensitivity testing for Rifampicin)

~97% sensitive
~98% specific

## Cost

 <$12K per instrument; <$10 per cartridge

## Power Source

12V; mains power with UPS for outages

## Connectivity

Internal EDGE/3G modem provided upon request

## Availability

TB Screening = 2Q, 2015
Rifampicin Screening = 4Q, 2015
Step 1: Collect Sample

- Collect 1-5 mL of sputum
- Add equal parts thinning agent
- Place Sample in heating/mixing device for 10 minutes
- Use disposable pipette to transfer 1 mL of sputum into cartridge

Step 2: Add Cartridge to Available Slot

Step 3: Wait for Reaction to Complete

Step 4: Remove Cartridge and Read Results

60 minutes
Conclusions: New Challenges/Innovative Answers

- New and improved anti-HIV drugs are necessary
  - Could play a role in “cure” approaches
  - Monthly or quarterly treatment could have a large impact
  - Think in terms of cost of goods
  - Promote African or LMIC drug manufacturing

- New diagnostic and treatment devices are essential for improved health and survival
  - Determine what is needed in your country/region
  - Become involved from the ground up
  - Promote African or LMIC manufacturing and distribution
  - Understand and develop growth policies for intellectual property
  - Encourage academic Biomedical Engineering programs
## Drug Use Prediction

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<tr>
<th>Protease Inhibitors</th>
<th>Integrase Inhibitors</th>
<th>Non-Nucleoside RTIs</th>
<th>Nucleoside RTIs</th>
<th>CCR5 inhibitors</th>
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<tr>
<td>dolutegravir</td>
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<tr>
<td>darunavir/r</td>
<td>evitegravir</td>
<td>rilpivirine</td>
<td>3TC, FTC</td>
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<tr>
<td>lopinavir/r</td>
<td>raltegravir</td>
<td>efavirenz</td>
<td>TDF, abacavir</td>
<td>maraviroc</td>
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<tr>
<td>nelfinavir</td>
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<td></td>
<td></td>
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<tr>
<td>indinavir</td>
<td></td>
<td>nevirapine</td>
<td>AZT, ddI, d4T</td>
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</table>
Thank You!

- **SOLTHIS**
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