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Challenges of HIV/AIDS in Africa

New Challenges
New Answers

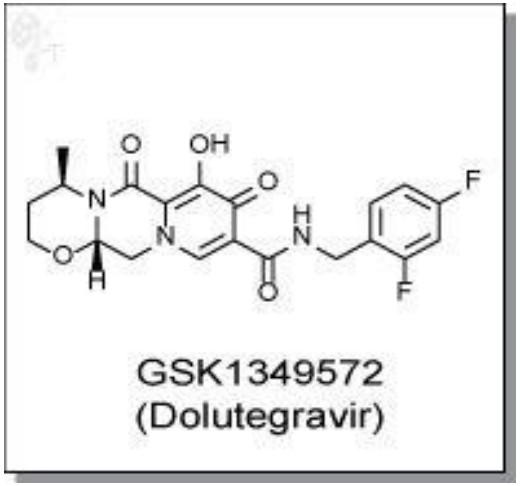



Introduction
What are the pressing HIV/AIDS needs in Africa?

- 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



GSK1349572
(Dolutegravir)

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

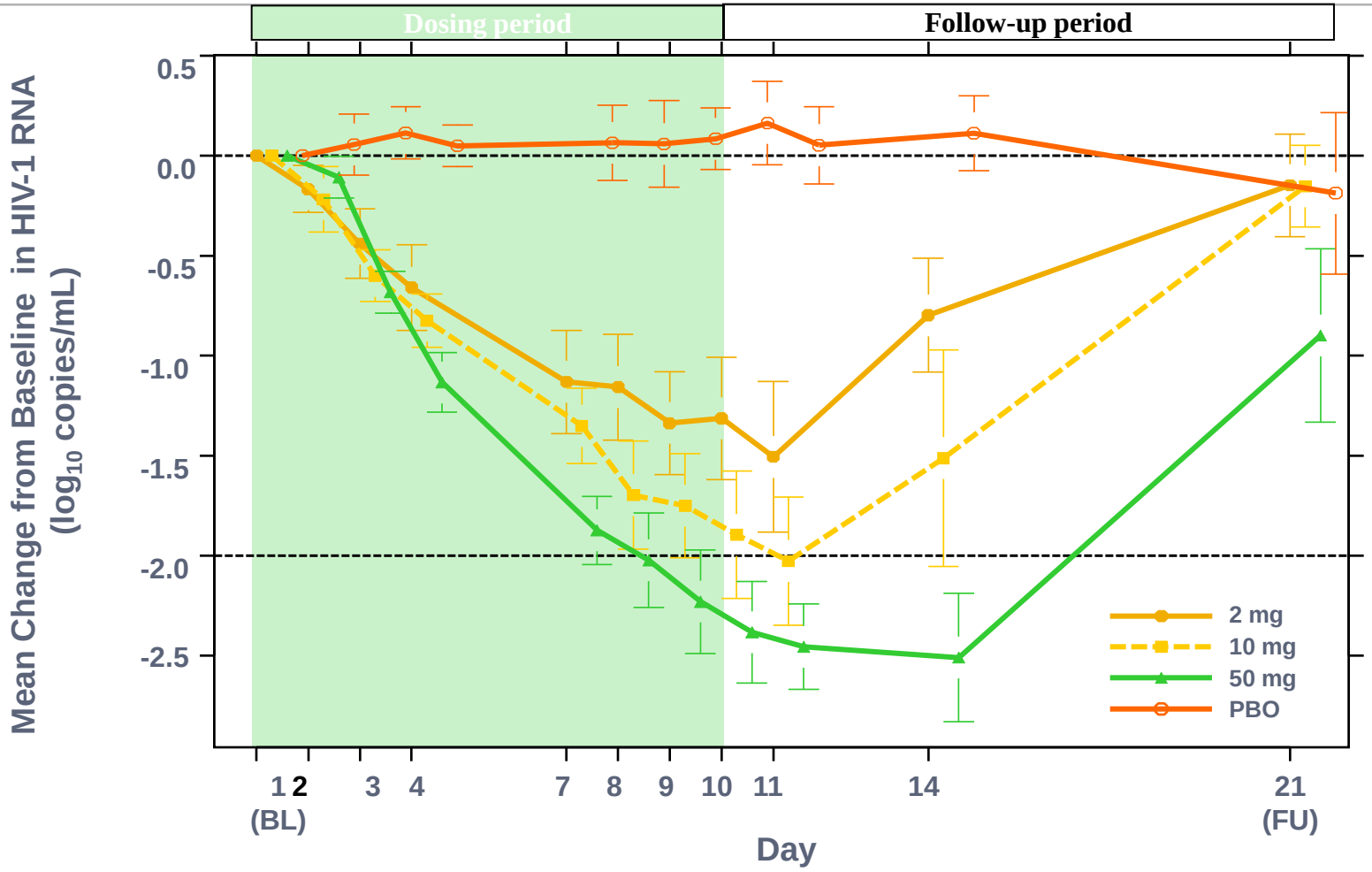
[1] Min S, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA099.

[2] Song I, et al. IAS 2009, Cape Town, Wednesday poster #WEPEB250.

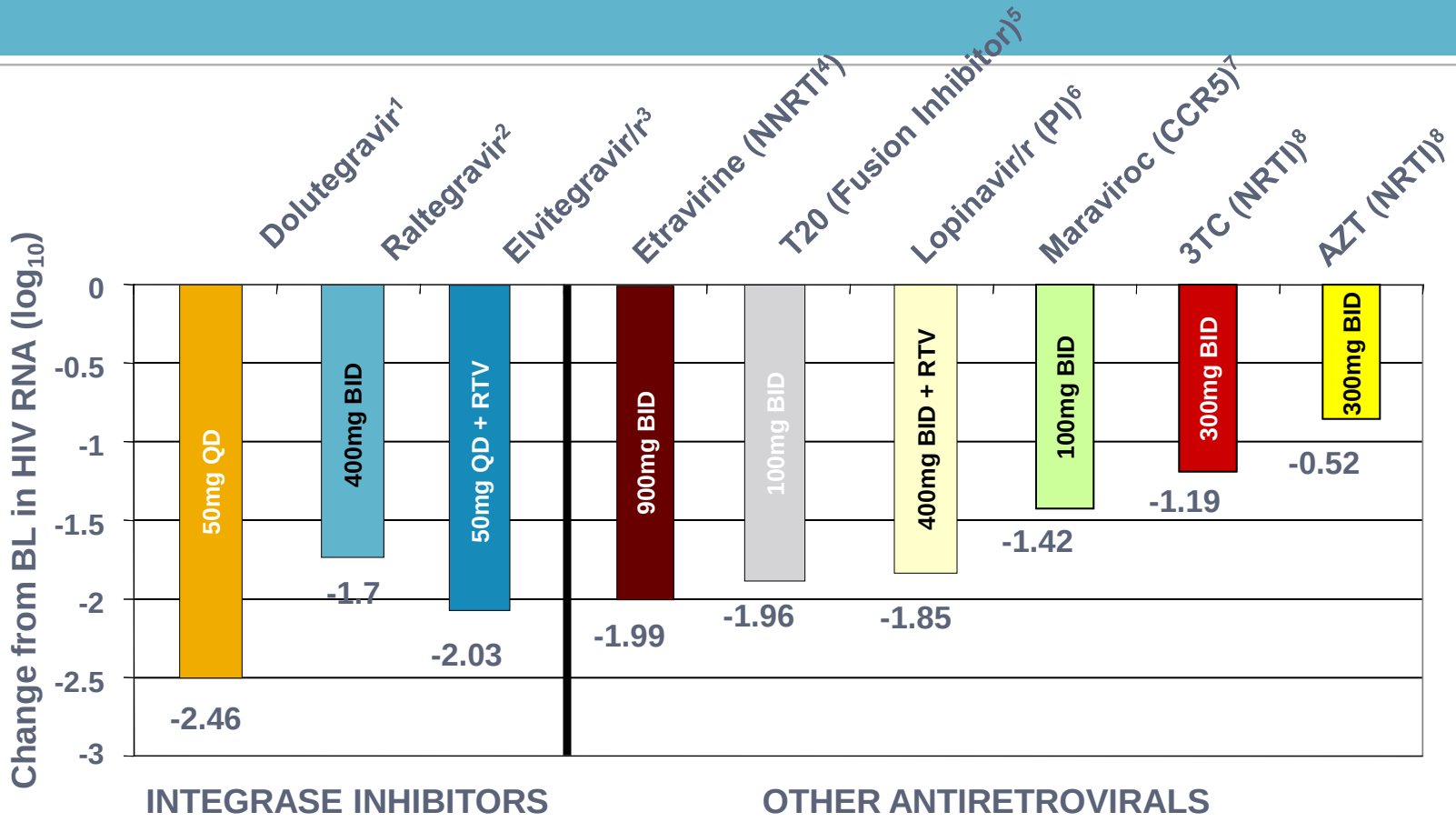
[3] Sato A, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA097.

[4] Underwood M, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA098.

Dolutegravir: Antiviral Activity



Monotherapy Antiviral Activity



1. Lalezari J. 5th *IAS 2009, Cape Town*, abstract TUAB105.
2. DeJesus E. *J Acquir Immune Defic Syndr* 2006 ; 43:1-5.
3. Markowitz et al. *JAIDS* Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. *AIDS* 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy RL. *AIDS* 2001;15:F1-F9.
7. Fätkenheuer G et al. *Nat Med* 2005 Nov; 11:1170-1172.
8. Eron JJ, *N Engl J Med* 1995, 333:1662-1669.

Clinical Summary: Dolutegravir

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

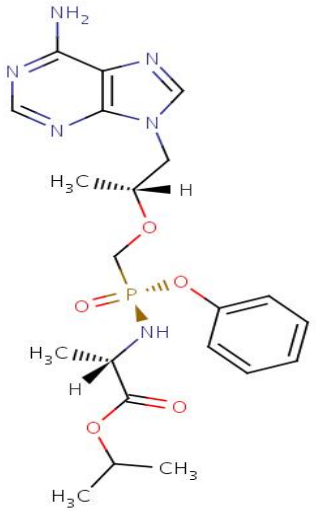
Dolbutegravir Summary
This drug is significantly different

- Potent antiviral activity
  - 2.6 $\log_{10}$ 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

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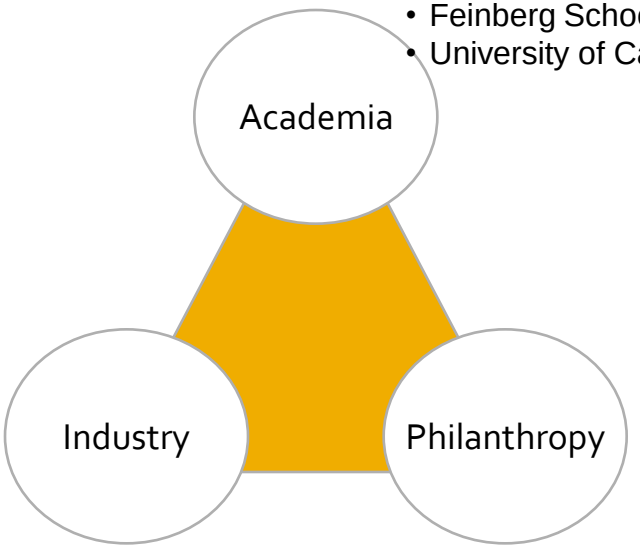
Northwestern University Background

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:

Abbott
A Promise for Life

QUIDEL
CORPORATION

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

Current Partners:

northwestern
GLOBAL HEALTH
foundation

BILL & MELINDA
GATES foundation

NU Background

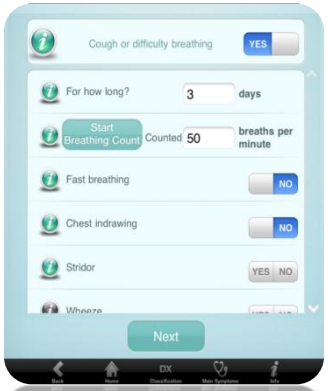
In prior years, >100 MBA students & faculty have conducted medical diagnostics market research in >10 countries

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



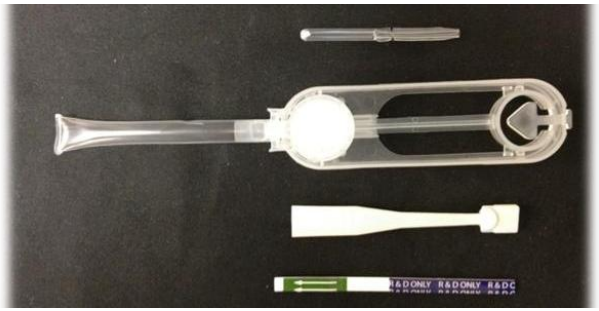
IMCI Tablet

HIV Viral Load Test

TB Diagnostic Test

p24 Infant HIV Test

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

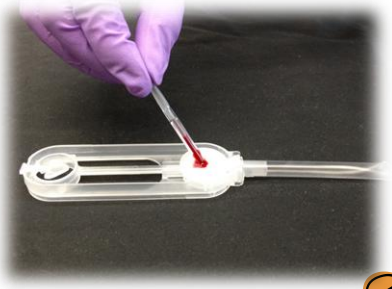


* Assumes minimum manufacturing volumes are achieved across all customers

p24 Infant HIV Test

Step 1: Collect blood

Step 2: Apply blood to LYNX Plasma Separator

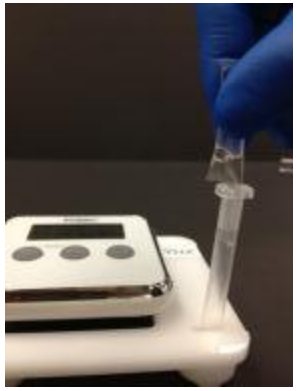


Step 3: Plunge Plasma Collection Pad into the Reaction Tube

Step 4: Separate Reaction Tube from LYNX Plasma Separator

10 minutes

Step 5: Add LYNX Buffer



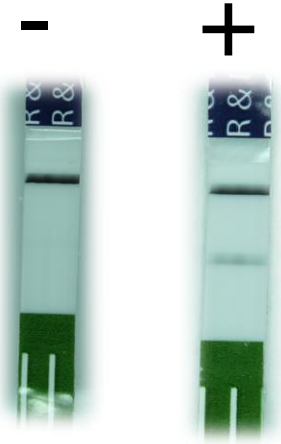
Step 6: Heat

11 minutes

Step 7: Insert LYNX Test Strip

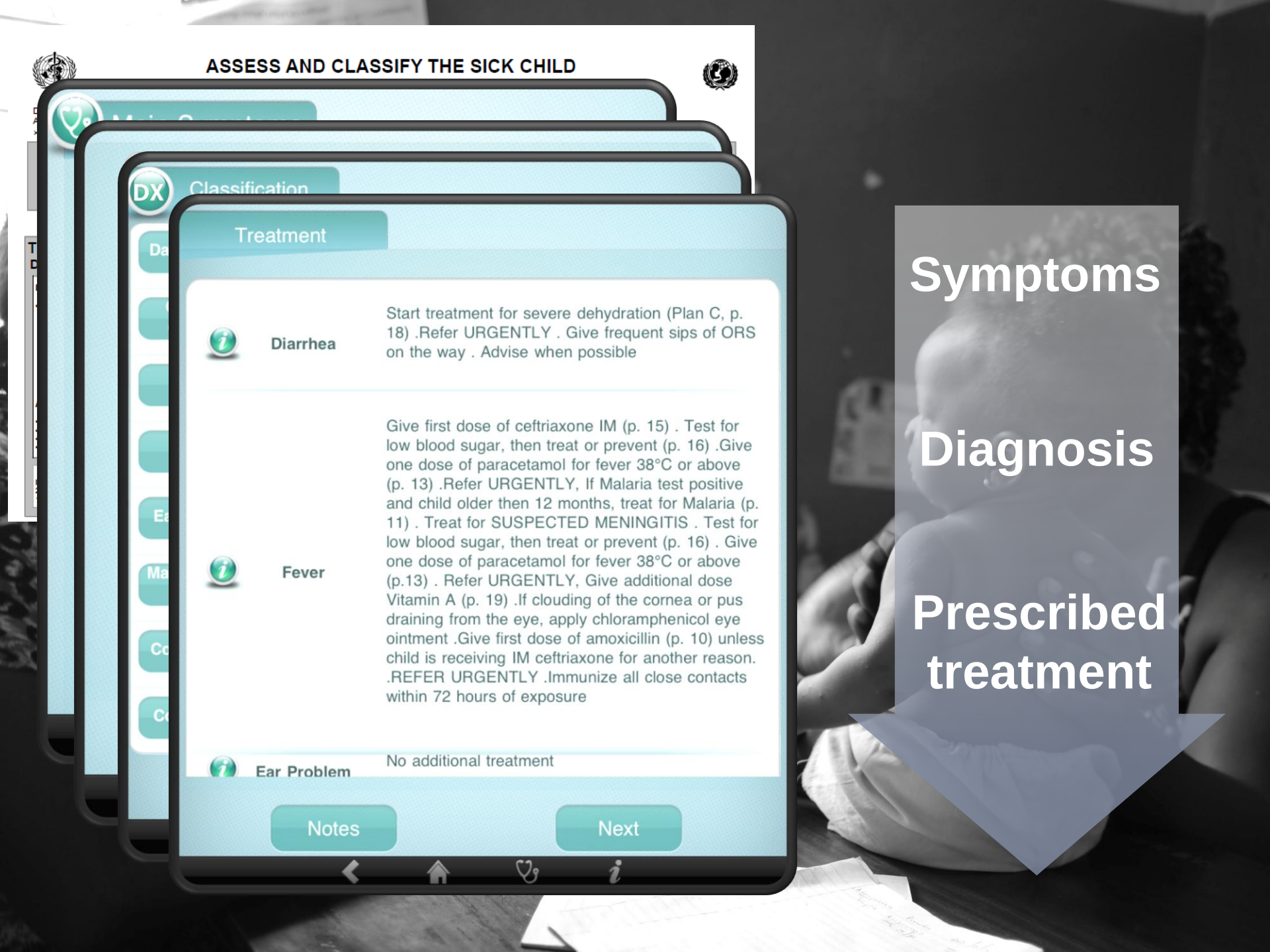
30 minutes

Step 8: Read Test



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

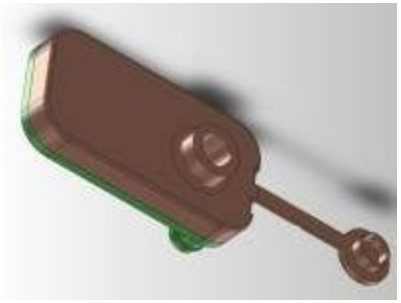
- ❑ Accuracy (diagnosis and/or treatment)
- ❑ Adherence (HC worker and/or patient adherence)
- ❑ Speed (time to diagnose)
- ❑ Throughput (# of patients per day)
- ❑ Supply chain (commodity forecasting)
- ❑ Cost (training, hard and soft costs)


ASSESS AND CLASSIFY THE SICK CHILD
DX
Classification
Treatment
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
Ear Problem
No additional treatment
Notes
Next
Symptoms
Diagnosis
Prescribed treatment

LYNX Molecular Platform: HIV Viral Load Test

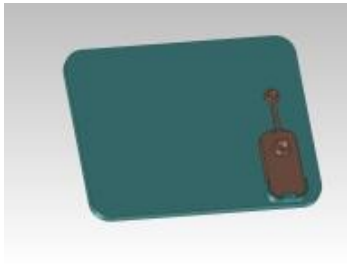
Target Specification	Description
Goal of Test	A quantitative real-time PCR diagnostic test for the measurement of HIV-1 viral load copies per ml of plasma
Limit of Detection	200-1000 copies / ml of plasma, depending on the volume of sample collected
Cost	<$12K per instrument; <$10 per cartridge
Power Source	12V; mains power with UPS for outages
Connectivity	Internal EDGE/3G modem provided upon request
Availability	2015

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

60 minutes

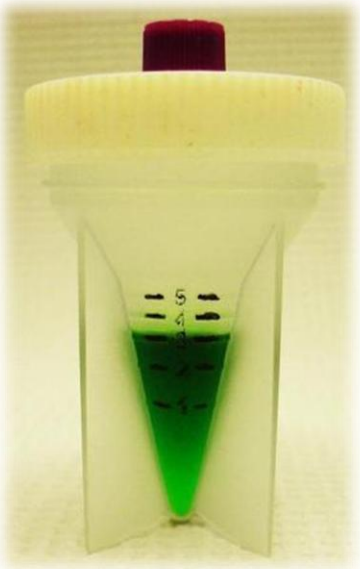
Step 6: Remove Cartridge and Read Results

LYNX Molecular Platform: TB Test

Target Specification	Description
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

60 minutes

Step 4: Remove Cartridge and Read Results

Conclusions: New Challenges/*Innovative* Answers

- New and improved anti-HIV drugs are necessary
  - Could play are 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

ACTIVITY

Protease Inhibitors	Integrase Inhibitors	Non-Nucleoside RTIs	Nucleoside RTIs	CCR5 inhibitors
	dolutegravir		TAF	
darunavir/r	evitegravir	rilpivirine	3TC, FTC	
lopinavir/r	raltegravir	efavirenz	TDF, abacavir	maraviroc
nelfinavir				
indinavir		nevirapine	AZT, ddI, d4T	

Drug Use Prediction

ACTIVITY

Protease Inhibitors	Integrase Inhibitors	Non-Nucleoside RTIs	Nucleoside RTIs	CCR5 inhibitors
	dolutegravir		TAF	
darunavir/r	evitegravir	rilpivirine	3TC, FTC	
lopinavir/r	raltegravir	efavirenz	TDF, abacavir	maraviroc
nelfinavir				
indinavir		nevirapine	AZT, ddI, d4T	

Thank You!

- SOLTHIS
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  - Jonathan Blackburn
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  - Bill and Melinda Gates Foundation
  - Northwestern Global Health Foundation
- University of Lagos
  - Niyi Osuntoki
  - Sade Ogunsola
- University of Ibadan
  - Akinwale Coker
  - Issac Adewale
- Industry
  - John Pottage (ViiV)
  - John Martin (Gilead)
  - Quidel