Best Science for the Most Neglected

Dr. Olaf Valverde Mordt
HAT-r-ACC Project Coordinator

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HNN 2.0 Training "International Cooperation and L&F issues in SC1" (Warsaw, PL)
Summary

• Neglected diseases
• The PDP model
• DNDi
• Human African trypanosomiasis
• DNDi in HAT
• HAT-r-ACC
• R-HAT
• DNDi-FEX-07-HAT
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Neglected diseases affect patients worldwide
Persistence of the fatal imbalance

1975-1999

• **1.1%** of new products for NTDs, malaria and TB
• But **12%** of global disease burden

2000-2011

• 756 products registered (excluding vaccines & biologicals)
• **1%** of 336 new chemical entities approved for NTDs, malaria and TB
• **1%** of 148,445 clinical trials registered for neglected diseases

Sources: Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases, MSF, 2001
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New models to fill the gap in R&D for neglected diseases: Product Development Partnerships (PDPs)

Current PDP landscape working areas include:

- Vaccine R&D
- Diagnostics R&D
- R&D for new or improved treatments
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Origins of DNDi

1999

- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the Drugs for Neglected Diseases Working Group
- JAMA article: ‘Access to essential drugs in poor countries - A Lost Battle?'

July 2003

- Creation of DNDi
- Founding partners:
  - Institut Pasteur, France
  - Indian Council of Medical Research, India
  - Kenya Medical Research Institute, Kenya
  - Médecins Sans Frontières
  - Ministry of Health, Malaysia
  - Oswaldo Cruz Foundation/Fiocruz, Brazil
  - WHO –TDR (Special Programme for Research and Training in Tropical Diseases) as a permanent observer
DNDi’s mission

• To develop new drugs or new formulations of existing drugs for people suffering from neglected diseases.
• To develop drugs for the most neglected diseases (such as sleeping sickness, leishmaniasis, and Chagas disease), while considering engagement in R&D projects for other neglected patients (e.g. malaria, paediatric HIV, filarial infections)
• To strengthen capacities in a sustainable manner, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
• To adopt a dynamic portfolio approach
Responding to the needs of patients suffering from neglected diseases

DNDi’s PRIORITY: Neglected Patients

- Hepatitis C
- Sleeping sickness
- Mycetoma
- Malaria
- Chagas disease
- Paediatric HIV
- Leishmaniasis
- Filarial diseases

...from bench to bedside

+ incubation with WHO of:

Global Antibiotic Research & Development Partnership
Address immediate patient needs & deliver innovative medicines: short- and long-term

New chemical entities (NCEs)

- Long-term projects

New formulations
- New indications for existing drugs

- Medium-term projects

Completing registration dossier
- Geographical extension

- Short-term projects

Research > 5 years

Translation 3-5 years

Development 1-2 years

Implementation
DNDi’s success is only possible through innovative partnerships

CRITERIA FOR SUCCESS
✓ Share the same vision
✓ Mutual understanding
✓ Involvement throughout the whole process

Over 160 partnerships worldwide
Partnering and research capacity building with MoHs and national control programmes

Major role of regional disease platforms:

- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
- Defining patients’ needs and target product profile (TPP)
# DNDi R&D Portfolio December 2018

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>TRANSLATION</th>
<th>DEVELOPMENT</th>
<th>IMPLEMENTATION</th>
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<tr>
<td>Screen</td>
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<td>HAT</td>
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<td>Leish H2L</td>
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<td>Amino pyrazoles</td>
<td>New CL combination</td>
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<td></td>
<td>CGH VL series</td>
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<td>Leish L205 series</td>
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<td>Chagas H2L</td>
<td>Chagas C205 series</td>
<td>Biomarkers</td>
<td>New Benz regimens +/- fosravuconazole</td>
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<td>Fexinidazole</td>
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<td>Daiichi-Sankyo CH2L</td>
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<td>FILARIA</td>
<td>Macro Filaricide 3</td>
<td>Oxfendazole</td>
<td>New VL treatments for PKDL</td>
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<td>MYCETOMA</td>
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<td>Emodepside</td>
<td>MF/Paromomycin combo for Africa</td>
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<td>PAEDIATRIC HIV</td>
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<td>ABBV-4083</td>
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8 new treatments delivered since 2007

2007 **ASAQ**
Malaria
>500 million patients reached

2008 **ASMQ**
Malaria
Used in Africa and Asia

2009 **NECT**
Sleeping sickness
100% of stage-2 patients

2010 **SSG&PM**
Visceral leishmaniasis in E Africa
Now 1st line in all countries

2011 **PAEDIATRIC BENZNIDAZOLE**
Chagas disease
Two sources developed

2011 **NEW VL TREATMENT ASIA**
Visceral leishmaniasis in Asia
Support to disease elimination

2016 **SUPERBOOSTER THERAPY**
Paediatric HIV
Recommended by WHO

2018 **FEXINIDAZOLE**
Sleeping sickness
Approved by European Medicines Agency, first all-oral treatment
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Two phases of human disease

In the classical model HAT is characterized by two phases

Clinical progression varies from patient to patient

Haemolymphatic (early) stage

Neurological (late) stage
HAT elimination: progress

- Number of new cases reported and WHO benchmark

[Graph showing the decline in HAT cases reported and cases expected from 2000 to 2020, with a focus on the T.b.g. (98%) and T.b.r. (2%) benchmarks.]
HAT elimination: progression
Number of rHAT cases reported 2001-2018

<table>
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<tr>
<th>Year</th>
<th>No. Cases</th>
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<td>2017</td>
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</tr>
<tr>
<td>2018</td>
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</tbody>
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The Atlas of human African trypanosomiasis

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO and FAO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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Target product profile:

- Effective in both stages
- Broad spectrum (*T.b. gambiense* and *rhodesiense*)
- Clinical efficacy >90% at 18 month follow up
- Safe for pregnant and breastfeeding women
- Adult and paediatric formulation
- No need to monitor for adverse effects
- Maximum 10 days orally once a day
- Stability in zone 4 during >3 years
- Cidal
- <30€/ treatment* (cost of drug)
Sleeping sickness: two new treatments in development to support sustainable elimination

15 years ago
Melarsoprol: Toxic, resistant
Eflornithine: Not available

Since 2009
NECT
Improved therapy

2018
Fexinidazole
Oral treatment (10 days)

Future objective
Acoziborole
Single-dose, oral treatment
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• To extend the indication of fexinidazole for the treatment of r-HAT (WP1)
• To ensure proper execution of clinical trials through strengthening capacity of treatment and care (WP2)
• To engage the local community to improve treatment access and extend case detection (WP3)
Partners in HAT-r-ACC

**DNDi Project coordination and trial management**

- **Direct intervention**
  - Makerere (Uganda) **Trial lead and Social Sciences**
  - UNHRO (Uganda) and MoH (Malawi) **Trial execution and Community intervention**

- **Training and follow up**
  - IHMT Lisboa **Medical**
  - Swiss TPH **Good Clinical Practice**
  - IRD France **Laboratory**
  - Epicentre France **Data management**
WP4: Drugs for Neglected Diseases Initiative (DNDi)

Project Management Committee (PMC)
Drugs for Neglected Diseases Initiative (DNDi), Institut de Recherche pour le Développement (IRD), Universidade Nova de Lisboa, Makerere University, Malawi Ministry of Health and Population, Uganda National Health Research Organisation (UNHRO), Swiss Tropical and Public Health Institute (Swiss TPH), EPICENTRE

Project Advisory Committee (PAC), EDCTP acting as observer

Consortium Management (HAT-r-ACC)

Clinical Training
- Institut de Recherche pour le Développement (IRD)
- Universidade Nova de Lisboa
- Swiss Tropical and Public Health Institute (Swiss TPH)

Clinical Trial
- Drugs for Neglected Diseases Initiative (DNDi)
- Makerere University

Monitoring
- Drugs for Neglected Diseases Initiative (DNDi)

Data Management and Statistics
- Universidade Nova de Lisboa
- Institut de Recherche pour le Développement (IRD)
- Makerere University

Local Site Management

Logistics and National Level Management
- Uganda National Health Research Organisation (UNHRO)
- Malawi Ministry of Health and Population

Community engagement to increase awareness
- Makerere University
- Uganda National Health Research Organisation (UNHRO)
- Malawi Ministry of Health and Population

Extended laboratory training on case detection

WP1: Drugs for Neglected Disease Initiative (DNDi) (Lead)

WP2: Institut de Recherche pour le Développement (IRD) & Universidade Nova de Lisboa (Lead)

WP3: Makerere University (Lead)

Communication, dissemination and exploitation of results supported by activities including HAT-r-ACC consortium and HAT platform interactions with key stakeholders and target audiences ensuring high level of information exchange
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Cases by country *T. b. rhodesiense*

**2001-2017**
- Uganda, 2977 (58%)
- Tanzania, 1310 (26%)
- Malawi, 645 (13%)
- Zambia, 123 (2%)
- Zimbabwe, 30 (1%)
- Kenya, 25 (0%)
- Mozambique, 2 (0%)

**2013-2017**
- Uganda, 164 (46%)
- Malawi, 139 (39%)
- Zambia, 9 (1%)
- Tanzania, 11 (3%)

5,134 cases declared
356 cases declared
Number of HAT cases (2014-2016) in South-Eastern Uganda

Version: June 2018. Optimised for printing in A3 format
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Clinical Trial

• Protocol Number: DNDi-FEX-07-HAT
• Study title: Efficacy and safety of fexinidazole in patients with human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: A multicentre, open-label clinical trial
• Design: multicentre, open-label, non-randomized
• Recruitment target: 34 evaluable stage-2 r-HAT patients
• Study sites:
  • Lwala Hospital (Uganda)
  • Rumphi District Hospital (Malawi)
  • Patients from neighbouring Health centers: Kaberamaido/Dokolo Districts (Uganda) and Rumphi/Mzimba North District (Malawi) and Chama (Zambia) will be transported to the sites for treatment
Ultimate Objective:

→ To show that fexinidazole offers an alternative over melarsoprol in stage-2 r-HAT patients and over suramin in stage-1 r-HAT patients
• 2 years recruitment and 1-year follow-up
• If the recruitment of 34 evaluable stage-2 patients is shorter than 2 years, the duration of the study can be shortened.
• Each patient’s participation will be 12 to 13 months
Investigators

- **Principal Investigator:**
  - Prof. Dr. Enock Matovu
  - Makerere University

- **Coordinating Investigators:**
  - Uganda: Charles Wamboga: Ministry of Health
  - Malawi: Marshal Lemerani, Ministry of Health

- **Site Investigators:**
  - Lwala (Uganda): Dr Eriatu Anthony
  - Rumphi (Malawi): Dr Westain Nyirenda
DNDi thanks all the HAT donors
Thank you