Is Pediatric HIV a neglected disease?
Role of DNDi in Optimizing HIV treatment in Children.

By
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KASH Conference on
9th February 2017
A little background on DNDi

1999
- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND 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
How we work

With Public and Private Funding

Conducts research with:

Biotechnology & Pharmaceutical Industries

Universities

Public Research Institutions

Ministries of Health

For underprivileged patients

To develop and deliver treatments
Responding to the Needs of Patients Suffering from Neglected Diseases…

Malaria

Leishmaniasis

Paediatric HIV

Sleeping Sickness (HAT)

Chagas Disease

Filaria
Our Journey into Pediatric HIV

2010: DNDi called upon by MSF, UNITAID, WHO to work on pediatric HIV

Dec 2010: DNDi Board approves entry into HIV

April 2011: In-depth consultation with experts advisory group on a target product profile
LPV/r based regimens offer better efficacy and safety: we have known this for years........

P 1060 cohort 1: prior SD NVP


P 1060 cohort 2: no prior NVP

For a long time, this was all we had to treat children
Balancing guidelines with practical issues

- Fixed dose combinations (FDCs) available
- Baby and junior dosing
- Scored tablets
- Can be crushed/dispersed
- Easy dosing

But
- Sub-optimal
- Resistance mutations

NVP + Dual NRTI

- Liquid only currently
- Bitter taste
- Neurotoxic excipients
  - 42% ethanol
  - 15% propylene glycol
- Needs cold chain
- Heavy to carry, hard to hide
- Difficult dosing
- Need for RTV super-boosting in TB/HIV co-infection

LPV/r + Dual NRTI
Question

What is an ideal ARV formulation for young children?
From Idea to reality: The DNDi Pediatric HIV project with CIPLA

- 4 ARVs in one
- Simple to open and use with water, milk, food
- Good taste
- No fridge needed
- Suitable for infants (<2 months - 3 years)
- TB-treatment compatible
- Affordable for governments
What do we have on our hands now to meet the needs of children living with HIV?

- Approved for use from 2 weeks but no dosing for <5kg.
- Currently used with NRTI dispersible tablets in LIVING study.
- Product registration on going in several countries.
Making LPV/r Pellets: Hot melt extrusion


Cipla Limited, Mumbai, India; Sitec Labs, India

Pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>AUC_{24h} (hr·µg/mL)</th>
<th>AUC_{∞} (hr·µg/mL)</th>
<th>C_{max} (µg/L)</th>
<th>T_{max} (hr)</th>
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<tbody>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprinkles</td>
<td>86.98 ± 19.95</td>
<td>92.59 ± 21.96</td>
<td>6.82 ± 1.3</td>
<td>6.29 ± 2.17</td>
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<tr>
<td>Solution</td>
<td>84.57 ± 26.48</td>
<td>89.26 ± 27.83</td>
<td>6.78 ± 1.77</td>
<td>5.99 ± 0.65</td>
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<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprinkles</td>
<td>87.19-120.52</td>
<td>87.76-122.54</td>
<td>91.31-131.02</td>
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</tr>
<tr>
<td>Ratio of Least square means T/R</td>
<td>102.51</td>
<td>103.71</td>
<td>109.38</td>
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<tr>
<td>Ln-transformed</td>
<td>6.69±2.45</td>
<td>6.86±2.51</td>
<td>0.79±0.23</td>
<td>6.08±1.95</td>
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<tr>
<td>Solution</td>
<td>6.23±2.22</td>
<td>6.38±2.24</td>
<td>0.77±0.34</td>
<td>5.72±0.59</td>
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<tr>
<td>Ratio of Least square means T/R</td>
<td>88.23-125.15</td>
<td>88.63-124.5</td>
<td>80.4-135.98</td>
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<tr>
<td>Ln-transformed</td>
<td>105.08</td>
<td>105.09</td>
<td>104.55</td>
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</table>

Fig. 1a. Mean Concentration vs. Time Profile of Lopinavir (Curves)

Fig. 1b. Mean Concentration vs. Time Profile of Ritonavir (Curves)
Chapas-2: comparable exposure and better acceptability of LPV/r sprinkles vs syrup

Figure 1(b): Study-2 (sprinkle vs syrup in infants 3-<12 months)

Figure 1(c): Study-3 (sprinkle vs syrup in children 1-<4 years)

Figure 3(b): Cohort-2 (sprinkle vs syrup in infants 3-<12 months)

Figure 3(c): Cohort-3 (sprinkle vs syrup in children 1-<4 years)
2015: WHO and UNICEF recommend programmatic scale-up of LPV/r pellets

FACT SHEET
ON LOPINAVIR AND RITONAVIR (LPV/R) ORAL PELLETS
40MG/10MG per capsule
bottle pack containing 120 capsules

POLICY BRIEF
SUPPLY PLANNING FOR NEW DOSAGE FORM OF LOPINAVIR AND RITONAVIR ORAL PELLETS
40MG/10MG per capsule, pack of 120 capsules
Prospective study of Lopinavir based ART for HIV Infected children N G lobally (LIVING study)

Study primary objective

To evaluate the effectiveness of LPV/r pellets in addition to AZT/3TC (or ABC/3TC) paediatric fixed dose combination (FDCs) tablet under routine treatment conditions (field conditions) in HIV infected infants and young children who cannot swallow tablets in Africa.
LIVING study – Secondary Objectives

• Document safety of LPV/r pellets in combination with AZT/3TC or ABC/3TC

• Assess population pharmacokinetics of LPV/r and NRTIs when administered as LPV/r pellets plus AZT/3TC or ABC/3TC

• Measure adherence to the new formulation

• Evaluate children acceptability of the LPV/r pellets and associated dual NRTIs as well as ease of use by the care giver.
LIVING study: Primary Efficacy Endpoint

Treatment **effectiveness at 48 weeks** based on a composite endpoint of:

i) virologic response <1000 copies/ml
ii) being alive and
iii) on study drug
LIVING study: Secondary efficacy endpoints

- **Viral load suppression** <1000 copies/ml (as well as <400 & <50 copies/ml) at 48 and 96 weeks after treatment initiation.
- **Clinical failure** at 48 weeks and at the end of follow-up.
- **Immunologic failure**
- **Retention on therapy** (taking into account deaths, lost to follow-up, and treatment discontinuations for any reason)
- **Reduction** of \( \log_{10} \) HIV RNA from baseline through Week 48
- **Change in CD4 cell count** and **CD4%** from baseline through Week 48 and end of follow-up
- **Antiretroviral resistance profiles** of subjects experiencing virologic failure
LIVING study: Safety endpoints

- Rate of severe adverse events (DAIDS grade 3 and above)
- Rate of AE/serious AE leading to treatment discontinuation
- Rates of targeted AEs for lopinavir/ritonavir as well as NRTIs (examples: GI side effects, liver toxicity, ABC-associated hypersensitivity reaction, ZDV-related anaemia and neutropenia...)
LIVING study: Population pharmacokinetics endpoints

LPV/r and NRTIs exposure

AUC, Tmax and C12/Cmin upon population PK modelling upon using sparse sampling
LIVING study: Anthropometry endpoints

- 48 weeks weight/height z-score change from baseline
- 48 weeks height/age z-score change from baseline
- 48 weeks MUAC change from baseline

- Note: Analysis of change in nutritional and immunological status will be controlled for timing of antiretroviral therapy in relation to enrolment (i.e. distinguish children newly initiated who may be having catch up growth or experience immune reconstitution and those already on treatment for some time.)
Questionnaire on Acceptability by caregivers and children of the new LPVr based formulation - taste, ease of swallowing, ease of administration, adherence

Interviews of caregivers to learn their experience using the LPV/r pellets (methods of administration, reaction of the child, type of food used, any incident)

Direct observation of the administration of the medicine at the clinic, or at home if the care giver agrees.
Current status of LIVING study

<table>
<thead>
<tr>
<th>Country</th>
<th>No. enrolled</th>
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<td>Kenya</td>
<td>231</td>
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<tr>
<td>Uganda</td>
<td>175</td>
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</table>

LIVING study Enrolling
Submissions made, awaiting IRB and regulatory approvals
Current status of use of LPV/r Pellets Use in Africa (August 2016)

- LIVING study Enrolling
- Submissions made, Awaiting approvals
- Planned roll-out of LPV/r Pellets following WHO guidance, Placed orders
- Pilot implementation, prior to scale up of LPV/r Pellets.
Acknowledgements

- LIVING Study participants and caregivers.
- All LIVING study investigators in Kenya and Uganda.
- DNDi colleagues in Nairobi and Geneva.
- Partners: CHAI, NEPHAK, CIPLA
- MOH Uganda (Dr Cordelia Katureebe), MOH Kenya (Dr Laura Onyango), MOH Zimbabwe.
- Funder: UNITAID
- Members of the LPV/r Pellets’ working group in PEPFAR
Thank you for your attention