TB Prevention Drugs for Infant and Children Living with HIV: Challenges, Prospects and Key Research Gaps

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TB Burden in Children and Adolescents is HUGE and UNDER RECOGNIZED

7.5 million children (0–14) infected with TB each year (Dodd et al, 2014)

1 million children (0–14 years) developed TB in 2017
52% <5 year olds

727 000 adolescents (10–19 year-olds) developed TB in 2012 (Snow et al, 2018)

1.6 million TB deaths in 2017

233 000 children (0–14) TB deaths in 2017
80% in children <5 years
96% of deaths in children who did not access TB treatment

39 000 (17%) deaths among children living with HIV

Childhood TB Roadmap 2018
Young Children and Adolescents are at High Risk for Progression to TB Disease
TB Preventive Therapy is Poorly Implemented among Household Contacts

1.3 Million household contacts < 5 years
27% initiated on TPT in 2018
Link Between TB & HIV in Children: Well-known, Not Acted Upon

• TB is the **most common** opportunistic infection among CALHIV

• Children with severe immune suppression have a **5-fold higher risk** of TB

• CALHIV contribute to 17% of TB-associated child mortality

• ART is strongly protective against TB in CALHIV (HR 0.30, 95%CI: 0.21-0.39)
  • Only about **half of eligible children** access ART

• TB Preventive Therapy (TPT) **reduces TB incidence** and mortality in PLHIV

• TPT is **not fully implemented** as part of a comprehensive HIV care package for CALHIV

Childhood TB Roadmap 2018, UNAIDS 2018, Dodd et al 2017
Despite Strong Recommendation, TPT is Poorly Implemented among PLHIV

- **1.8 million** TPT initiations among PLHIV in 65 countries
- **49%** of PLHIV newly enrolled in care were initiated on TPT in 16 of 38 high TB or TB/HIV burden countries
- No disaggregated data on CALHIV
WHO End TB Strategy Prioritizes TPT as a critical tool for TB Elimination
IPT provides a durable survival benefit in adults living with HIV.
37% reduction in the risk of death that was independent of ART over an average of 4.9 years of follow up.
INH Prophylaxis for CLHIV

IPT has an early survival benefit and reduces TB incidence in CLHIV

IPT does not improve TB-disease-free survival among infants living with HIV


Madhi, et al. NEJM 2011
REALITY Trial

Enhanced antimicrobial prophylaxis + ART results in reduced mortality rates at 24 and 48 weeks in children >5 years and adults living with HIV

Hakim, et al. NEJM 2017
WHO Recommendations for TB Preventive Treatment in PLHIV, 2018

• **Adults and adolescents** with an unknown or positive TST who are unlikely to have active TB, irrespective of the degree of immunosuppression, ART, previous TB treatment, and pregnancy.
  
  *Strong recommendation, high-quality evidence*

• **Infants aged < 12 months** who are in contact with TB case if the investigation shows no TB disease.
  
  *Strong recommendation, moderate-quality evidence*

• **Children aged ≥ 12 months** unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB if they live in a high TB prevalence setting.
  
  *Strong recommendation, low-quality evidence*
The recommendation that HIV+ children below 12 months of age only receive TB prevention therapy for confirmed post exposure prevention is based on conflicting data from 2 prospective studies, one showing benefit and the other not.

Serious consideration should be given to extending pre-emptive TB prevention therapy to HIV+ infants below 12 months of age for the following reasons:

a) the highest risk for TB infection to progress to disease is below 12 months old
b) a source case is only identified in half of children
c) caregivers often only identify a source case when their own children are suspected of having TB

Mark Cotton 2020
Community Transmission and Pediatric TB Disease in High TB Burden Settings

The population-attributable fraction of *M. tuberculosis* transmission to children due to household exposures estimated between 10% - 30%

New TPT Options for CALHIV
3HP in Adults and PLHIV

All study participants, mostly HIV negative

HIV+ participants with supplemental enrollment

Sterling et al., NEJM 2011,365:2155-66

Sterling et al., AIDS 2016,30:1607-15
Bioavailability of crushed RPT tablets provides similar exposures in children 2 years and older compared to adults.

3HP is non-inferior to 9H in children 2 years and older.
IMPAACT4TB
Scaling up 3HP for TB Prevention

Low income countries
Zimbabwe, Tanzania, Mozambique, Ethiopia, Malawi

Low Middle Income Countries
Indonesia, Kenya, Ghana, India, Cambodia

High Middle Income Countries
South Africa, Brazil

Consortium Partners

THE AURUM INSTITUTE
JOHNS HOPKINS UNIVERSITY
STOP TB PARTNERSHIP
GLOBAL DRUG FACILITY
KNCC TUBERCULOSIS FOUNDATION
CLINTON HEALTH ACCESS INITIATIVE
TAG Treatment Action Group

To eliminate TB
TBTC Study 35

• Dosing of child-friendly formulation in children 0-12 years with and without HIV
  • This includes children 0-2 years
• Mango-flavored, water-dispersible, fixed dose combination of INH and RPT
• Allows CALHIV on EFV and DTG to enroll
  • No specific sample size to study DDI
• Recruitment Ongoing
  • Age de-escalation
  • First interim analysis anticipated in June 2020
# 3HP and ARV Interactions in Children

<table>
<thead>
<tr>
<th>ARV</th>
<th>Weekly RPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>Not studied in adults or children</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Anticipated interaction, no plans to evaluate</td>
</tr>
<tr>
<td>EFV</td>
<td>No clinically significant reduction in C\textsubscript{T}; no dose adjustment needed in adults Children: TBTC S35</td>
</tr>
</tbody>
</table>
| DTG   | **DOLPHIN Study:** Well tolerated, DTG troughs > IC90. VL remains suppressed. No dose adjustment

**NOT YET STUDIED IN CHILDREN, ?IMPAACT4TB**

Farenc, et al. CROI 2014; Dooley, et al. CROI 2019
Summary of Knowledge Gaps in 3HP among Children Living with HIV

• Few CALHIV in pediatric efficacy trials

• No dedicated DDI studies for 3HP with pediatric ART
  • Anticipated DDI with LPV/r, NVP and DTG

• No data on 3HP and DTG in children < 15 years
  • IMPAACT4TB?

• No data on 3HP in children < 2 years (TBTC S35)
  • TBTC Study 35
3RH in Children

- Meta-analysis: 3RH equivalent to 6-12H for efficacy, side effects and mortality

- Safe & efficacious in children < 15 years with LTBI
  - no TB events in either 3-4RH or 9H arms

- Many pediatric ART interactions: LPV/r, NVP, DTG

Issues:
*Can the duration of therapy be shortened with higher doses?*
*Availability of child-friendly formulations worldwide*
*Rifampicin and drug interactions for CALHIV*


## RIF and ARVs in children

<table>
<thead>
<tr>
<th>RIF +</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>Single study in children &lt;3yrs (n=21): 57% subopt. Cmin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| LPV/r | Double-dose LPV/r → sub-optimal LPV levels<sup>2</sup>  
Boosted LPV/r → optimal Cmin<sup>3</sup> and good VL outcomes<sup>4</sup>  
No PK data on infants <7m |
| DRV/r | Double dosing may overcome RIF effect based on PK population modelling study. Confirmatory studies in humans required<sup>5</sup> |
| EFV   | Not recommended for children < 3 years of age |
| INSTI | Raltegravir – conflicting adult data<sup>7</sup>, double dosing may benefit, P1101  
Dolutegravir – double dosing can overcome RIF effect<sup>8</sup> |
| 3NRTI | 3NRTI immunologically+clinically similar to NNRTI-ART<sup>9</sup>  
Valuable in children co-treated for TB with controlled HIV |
| TAF   | Double dosing can overcome RIF effect<sup>10</sup> |

1. Oudijk 2012  
2. McIleron 2011  
3. Ren 2008  
4. Frohoff 2011  
5. Dickinson 2016  
6. Bertz 2013  
7. Grinstejn 2013  
8. Dooley 2013  
9. ARROW 2013  
10. Custodio 2017

Courtesy Diana Gibbs
Pharmacokinetics DTG BID+RIF in children

**Parameter** | DTG 25mg BID + RIF (n=5) | DTG 50mg BID + RIF (n=7) | Adult reference DTG 50mg QD\(^1\) (N=16)
---|---|---|---
\(C_{\text{trough}}\) (mg/L) | GM (CV\%) | 0.90 (16) | 1.11 (99) | 0.83 (26)
\(AUC_{0-24h}\) (h\(\cdot\)mg/L) | GM (CV\%) | 53.4 (21) | 60.3 (63) | 43.4 (20)
\(C_{\text{max}}\) (mg/L) | GM (CV\%) | 3.62 (24) | 4.50 (47) | 3.3 (16)

1. Min et al. AIDS. 2011;25(14):1737-45
IMPAACT P2024

- In protocol development
- PK and Safety of 1HP
- Children < 15 years with and without HIV
- Evaluate PK of DTG (double dosed)
- Sanofi’s dispersible tablet

# 3HP, 1HP and ARV Interactions in children

<table>
<thead>
<tr>
<th>ARV</th>
<th>Weekly RPT</th>
<th>Daily RPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>Not studied in adults or children</td>
<td>1HP resulted in significantly reduced nevirapine (NVP) trough concentrations</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Anticipated interaction, no plans to evaluate</td>
<td>Anticipated interaction, no plans to evaluate</td>
</tr>
<tr>
<td>EFV</td>
<td>No clinically significant reduction in C&lt;sub&gt;T&lt;/sub&gt;; no dose adjustment needed in adults</td>
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</tr>
<tr>
<td></td>
<td>Children: TBTC S35</td>
<td>Children: IMPAACT P2024</td>
</tr>
<tr>
<td>DTG</td>
<td><strong>DOLPHIN Study</strong>: Well tolerated, DTG troughs &gt; IC90. VL remains suppressed. No dose adjustment</td>
<td><strong>ACTG 5372</strong>: evaluating BID +/- OD DTG with 1HP</td>
</tr>
<tr>
<td></td>
<td><strong>NOT YET STUDIED IN CHILDREN, ?IMPAACT4TB</strong></td>
<td><strong>IMPAACT P2024</strong>: evaluating BID DTG with 1HP</td>
</tr>
</tbody>
</table>

INH-CTX-B6 Fixed-dose Combination

- Made by CIPLA, India
- On WHO EOI List
- WHO prequalification
- First used in REALITY
  - Adults - 1 tablet daily
  - Children 5-12yr: 1/2 tablet daily

- Need a half-dose scored tablet for children < 5 yr

Cotrimoxazole 960mg
Isoniazid 300mg
Vitamin B6 25mg

Courtesy Diana Gibbs
TB Risk and Prevention in HIV Exposed and Uninfected Children
**Infant Tuberculosis Prevention Study (iTIPS)**

Non-blinded RCT of INH efficacy to prevent primary Mtb infection
- HEU infants 6 weeks of age without known TB exposure
- Randomized to 12 months of daily INH vs. No INH

**Primary Outcome: Mtb infection 12 months post randomization**

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>No INH</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=132</td>
<td>N=133</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Mtb infection</td>
<td>7.0/100PY</td>
<td>13.4/100PY</td>
<td>0.53 (0.24-1.14)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Although approximately half as many children in the INH arm had Mtb infection, our trial did not demonstrate a significant protective INH effect.
3RH For HIV Exposed Infants on NVP Prophylaxis

- RIF reduces NVP concentration
- NVP levels required to prevent MTCT unknown
- Prudent to avoid RIF-based TPT regimen while on NVP prophylaxis
- Weekly or daily RPT effects are unknown and require study
# Summary TPT Options in CALHIV

<table>
<thead>
<tr>
<th>TPT Regimen</th>
<th>Ages</th>
<th>Pediatric-Friendly Formulation</th>
<th>DDI – LPV/r</th>
<th>DDI – NVP*</th>
<th>DDI – EFV</th>
<th>DDI—DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>6H</td>
<td>0-15 years</td>
<td>YES</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3RH</td>
<td>0-15 years</td>
<td>YES*</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Double dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Only for &lt;25kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3HP</td>
<td>2-12 years</td>
<td>Next 3-5 years</td>
<td>+</td>
<td>+</td>
<td>S35</td>
<td>IMPAACT4TB?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBTC S35, Sanofi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4R</td>
<td>0-15 years</td>
<td>No**</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Double dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**Capsules can be opened for &gt;7kg; not available thru GDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1HP</td>
<td>&gt; 12 years</td>
<td>Not yet, Sanofi</td>
<td>+</td>
<td>+</td>
<td>P2024</td>
<td>P2024</td>
</tr>
</tbody>
</table>

6H will still be needed for the highest risk children for some time:
1. CALHIV on DTG, LPV/r and NVP
2. HIV-exposed infants on NVP prophylaxis* maternal TB or exposure early in life