LANDSCAPE ANALYSIS OF INTERACTIONS BETWEEN MALNUTRITION & DRUG EFFECTIVENESS

REPORT ON: HIV, TB, & MALARIA

Produced by: Lokken E, Dietrich C, Duerr A
Meeting Agenda

- Project Background and Objectives
- Methods
- Results
- Limitations and Opportunities
- Next Steps
Background

- Under-nutrition is a major underlying cause of more than one-third of deaths in children under 5 years old, particularly in South Asia and sub-Saharan Africa.
- There are several known changes in drug kinetics in the presence of malnutrition, yet there is limited data on the effectiveness of many drugs in the presence of malnutrition in young children.
- There is insufficient evidence to suggest whether the dosages of current drugs in use should be changed in patients with malnutrition.

Objectives

- Identify and review evidence from studies that aimed to evaluate the nutrient-drug interactions for Malaria, HIV, TB, EDD, pneumonia, and NTDs.
- Identify evidence suggesting changes in dosing/treatment regimen for malnourished kids
- Summarize the existing pharmacokinetic and clinical data and highlight the knowledge gaps and opportunities.
Phases of work

- **Phase 1**
  - Focus on pediatric first-line drugs for Malaria, HIV, and TB

- **Phase 2 (TBD)**
  - Pneumonia (amoxicillin and other drugs)
  - Select specific diseases within the Enteric & Diarrheal Disease and Neglected Tropical Disease divisions for literature review
# Proposed Timeline and Work Plan

## Scoping
- Confirm work plan and scope
- Strategize approach

## Phase 1
- Review relevant literature & extract data
- Relay initial findings & finalize results

## Phase 2?
- Agree on goals of Phase 2
- Review relevant literature & extract data
- Finalize results

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= Check-In Point
Meeting Agenda

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Search strategy

- Step 1: Independent systematic literature review for HIV, TB, and Malaria using Medline and EMBASE databases
- Step 2: Reference review of papers included from literature review to identify any additional pharmacokinetic papers
Diseases and Drugs of Interest

- **HIV**
  - Nevirapine, lopinavir, efavirenz, tenofovir, emtricitabine, zidovudine, lamivudine, abacavir, stavudine*

- **TB**
  - Isoniazid, rifampicin, ethambutol, pyrazinamide

- **Malaria**
  - Artemether, artesunate, lumefantrine, mefloquine, amodiaquine, dihydroartemisinin, piperaquine, sulfadoxine–pyrimethamine

*Not a current first-line drug
Search terms for Medline and EMBASE

- **DISEASE OF INTEREST**

- AND (pharmacokinetics OR pharmacodynamics OR "plasma concentration" OR "weight* band" OR bioavailability OR absorption OR metabolism OR distribution OR toxicity OR "side effect" OR **DRUGS OF INTEREST**)

- AND (malnutrition OR malnourish* OR undernutrition OR under-nutrition OR underweight OR under-weight OR stunting OR wasting) AND (child* OR pediatric OR infant)
Inclusion/Exclusion Criteria

**Inclusion Criteria**

- Study population
  - Includes children < 18 years old
  - Protein-calorie malnourished (must be defined, but no restriction on definition)
  - Conducted in an African or Asian country
- Drug of interest (see prior slide)
- Outcomes
  - Pharmacokinetic (ex: $C_{\text{max}}$, AUC)
  - Clinical (with drug dosing) such as mortality, TB treatment failure, malaria recrudescence, CD4 count, and HIV viral load
- Published 1995-present
- English language only

**Exclusion Criteria**

- Study population
  - Adults
  - Includes only non-malnourished individuals
  - Does not include an unexposed population
  - Focused on micronutrient deficiencies rather than protein-calorie related malnutrition
  - Not conducted in an African or Asian country
- Not drug of interest
- Outcomes
  - Clinical outcomes without drug dosing
- Published before 1995
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## Literature review search results

<table>
<thead>
<tr>
<th>Disease</th>
<th># of manuscripts*</th>
<th>Included from literature search</th>
<th>Included from reference reviews^</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>773</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>TB</td>
<td>318</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Malaria</td>
<td>413</td>
<td>4</td>
<td>0</td>
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*From Medline and EMBASE; de-duplicated

^Reference reviews for clinical outcomes were not conducted
Summary of HIV Findings

- The START team identified 7 pharmacokinetic studies + 2 studies reporting clinical outcomes only.
- 5/7 of the PK studies measured Nevirapine concentrations.
- No clear pattern between PK parameters and malnutrition, either in general or by specific malnutrition definition.

Limitations:
- Varying regimen backbones and formulations
- Possibility that under-dosing could reduce sensitivity in some studies
  - Some evidence that under-dosing is associated with younger age through dosing practices or biologically faster clearance. Exception is AZT in Fillekes 2014.
- Sparse reporting of clinical outcomes, particularly stratified by nutritional status
- Only one study conducted in Asia
# HIV Study Details

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<tr>
<th>Drug(s)</th>
<th>Malnutrition Results</th>
<th>Author, Year</th>
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<tr>
<td>EFV, LPV, NVP</td>
<td>HAZ, WAZ, and/or BAZ ≤ -2 SD - F1*, no significant difference EFV, a trend for lower F1 in LPV (p=0.114), higher NVP exposure (p = 0.046)</td>
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<td>AZT</td>
<td>HAZ - No independent effect on any measures, WAZ – Each unit increase, lower AUC (p=0.001), higher clearance (p=0.005)</td>
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<td>HAZ &amp; WAZ – No association with AUC_{0-24hr} (p=0.20)</td>
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<td>NVP</td>
<td>WAZ – no association; Total Body Water % - no meaningful association</td>
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<td>NVP</td>
<td>Wt/Ht (Malawi ref)^ - No significant difference between malnourished and normal children for total AUC (p=0.17) or unbound AUC (p=0.22)</td>
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<td>HAZ – One unit higher, higher concentration (p=0.05), BAZ – One unit lower, higher concentration (p=0.03)</td>
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*F1=measure of bioavailability  
^Weight for height ≤85% of Malawian standard
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*F1 = measure of bioavailability

<sup>^</sup>Weight for height ≤ 85% of Malawian standard
The START team identified 0 studies assessing the PK parameters of anti-malarials in malnourished children, but did identify 4 studies assessing the effect of nutritional status on clinical outcomes such as parasite density and clearance, recrudescence, and incidence of uncomplicated malaria.

While the drugs, malnutrition definition, and clinical outcomes were different across the studies, each study identified worse outcomes among malnourished children.

Limitations:
- Small number of studies
- High study heterogeneity
- No PK outcomes-what do these results tell us about drug efficacy?
## Results

### Malaria Study Details

#### Study and Drug

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<tr>
<td>Single dose of SP (Wolday 1995)</td>
<td>Malnourished children (weight for height &lt;80% or edema) had a higher parasite density at baseline and slower parasite clearance than non-malnourished children.</td>
</tr>
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<td>Randomized to DP or AL (Verrett 2011)</td>
<td><strong>DP</strong>: Among children not on TS prophylaxis*, decreasing HAZ was associated with an increased risk of recrudescence. <strong>AL</strong>: No association between malnutrition and time to parasite clearance or recrudescence.</td>
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<td>AL meta-analysis (WWARN 2015)</td>
<td>Among children 1-3 years old, children who had WAZ &lt; -2 had a 56% higher risk of recrudescence compared to those who were not underweight (HR: 1.56, 95%CI: 1.04-2.43).</td>
</tr>
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<td>Intermittent prevention using SP (Danquah 2009)</td>
<td>No association between malnutrition (any WAZ, HAZ, WHZ) and incidence of asymptomatic parasitemia or uncomplicated malaria. Decrease in malarial episodes was smaller among malnourished children (malnourished: 9.5% decrease vs non-malnourished: 18.4%^)</td>
</tr>
</tbody>
</table>

*Trimethoprim-sulfamethoxazole

^No statistical test for comparison.
Among 8 studies reporting PK outcomes and their association with malnutrition, only one found an association between malnutrition and lower pharmacokinetic parameters for isoniazid, rifampicin, and pyrazinamide.

Limitations:
- High study heterogeneity
  - Range of dosing (mg/kg) and regimens (daily vs. intermittent)
  - Single and steady state studies
  - Variety of malnutrition definitions including kwashiorkor, Wellcome Classification of % of expected weight for age, weight for age z-scores, and weight for height/length < 70% of expected
- Likely confounding by HIV status
- Some papers do not report PK parameter values stratified by nutritional status, but rather assess nutritional status as covariates
- Isoniazid: acetylator status assessed in only a couple of studies
TB Study Details

Drug under PK study
- Isoniazid (n=6)
- Rifampicin (n=3)
- Pyrazinamide (n=5)
- Ethambutol (n=2)

Single or steady state
- Isoniazid: Single (n=2), Steady (n=4)
- Rifampicin: Steady (n=3)
- Pyrazinamide: Single (n=2), Steady (n=3)
- Ethambutol: Single (n=1), Steady (n=1)

Results
One steady state study found a significant association between stunting and underweight and a lower $C_{\text{max}}$ and $AUC_{8\text{hours}}$ for isoniazid, rifampicin, and pyrazinamide.¹

No significant associations in remaining 7 studies.

¹ Ramachandran, 2013. Age, nutritional status and INH acetylator status affect pharmacokinetics of anti-tuberculosis drugs in children
Meeting Agenda

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Study Design:
To what extent, can we discern whether nutritional status affects drug efficacy?

Limitations & Opportunities

Outcomes Measured

- PK
- Clinical

Study Category 1
- IDEAL
  - Links PK & clinical outcomes

Study Category 2
- ACCEPTABLE
  - PK parameters as a proxy for drug efficacy

Study Category 3
- UNCLEAR
  - Causality unclear; high potential for confounding
Study Design:
To what extent, can we discern whether nutritional status affects drug efficacy?

Limitations & Opportunities

Outcomes Measured

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<tr>
<td>Study Category 3</td>
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IDEAL
Links PK & clinical outcomes

ACCEPTABLE
PK parameters as a proxy for drug efficacy

UNCLEAR
Causality unclear; high potential for confounding
PK Study Quality Considerations and Limitations of Existing Studies

- High study heterogeneity >>> low comparability
  - Formulations
  - Malnutrition definition
  - Single vs steady state
  - Co-infections
  - Gender distribution

- Between person heterogeneity
  - Micronutrients at time of blood draws
  - Host factor genetics influencing drug absorption, metabolism, and excretion

- Methods:
  - Number of blood draws (implications for accuracy of AUC calculation)
  - Small sample sizes

- Ethics of PK studies in malnourished kids (i.e., multiple blood draws in children)
Study Design:
To what extent, can we discern whether nutritional status affects drug efficacy?

Limitations & Opportunities

Study Category 1
- **PK**: ✔
- **Clinical**: ✔
- **IDEAL**: Links PK & clinical outcomes

Study Category 2
- **PK**: ✔
- **Clinical**: ✗
- **ACCEPTABLE**: PK parameters as a proxy for drug efficacy

Study Category 3
- **PK**: ✗
- **Clinical**: ✔
- **UNCLEAR**: Causality unclear; high potential for confounding
Clinical Outcome Quality Considerations and Limitations of Existing Studies

- From a study that only includes clinical outcomes, how can we tell if worse outcomes among malnourished children are due to drugs ineffectiveness vs other implications of their malnutrition?
  - In addition, nutritional status improves with treatment for TB and/or HIV.

- Hard to define drug exposure
  - Regimen and formulations might change over the course of HIV and/or TB treatment
  - Unmeasured and/or poor adherence to drugs

- Heterogeneity across studies >>> low comparability
  - Malnutrition definition
  - Outcomes of interest vary (ex: CD4, viral load, side effects)
  - Drug(s) under study and indication for use (ex: malaria treatment vs prophylaxis)
There were also some limitations of the START literature review strategy.

- The systematic literature search was optimized to identify papers with PK, not clinical, outcomes so the clinical outcome results might not be exhaustive.

- The number of possible adverse events associated with drugs, especially HIV, made title/abstract reviews challenging and time intensive so the START team de-prioritized inclusion of studies assessing drug side effects.

- 50% of the included TB PK studies were identified via the reference review, suggesting the search terms were not adequate.
Nonetheless, the START team identified some potential opportunities.

- Additional PK studies are in progress (see details in Appendix 2).

- Some of the papers excluded by the START team included anthropometric measures (e.g., weight, height), but did not assess the role of malnutrition on PK and/or clinical parameters. BMGF could coordinate access to and re-analysis of these datasets.

- Blood spot is an increasingly popular PK method especially among pediatric populations.
  - Methods for re-dissolving the spots might be an area of investment.
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- Limitations, Gaps, and Opportunities
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The START team proposes the following next steps:

- Incorporate discussion from today’s conversation and write brief report of findings to accompany slide deck and data extraction tool.

- In addition to report:
  - Continue with Phase 1?
    - Synthesize list of pediatric PK studies with height/weight raw data to pursue for re-analysis
    - More thorough review for clinical outcomes utilizing optimized search terms
  - Define and proceed to Phase 2 work?
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Scoping

= Check-In Point

Phase 1

Phase 2?
References for Included Studies: HIV


References for Included Studies: Malaria


- WWARN. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a pooled analysis of individual patient data. The Lancet. Published online March 16, 2015.
References for Included Studies: TB


Ongoing Pediatric PK studies:

- Steady state PK in malnourished HIV-infected children (IMPAACT Network protocol P1092, not yet recruiting)
  - Drugs: ZDV+3TC+LPV/r
  - PI: Drs. Maxensia Owor and Philippa Musoke
  - Location: Malawi, Tanzania, Uganda, and Zimbabwe

- Optimal dosing of 1st Line Anti-tuberculosis and Antiretroviral Drugs in Children (DATiC) (recruiting)
  - Drugs: 8 hourly LPV/r during TB treatment, Nevirapine, Lopinavir/Ritonavir, HZRE for TB
  - PI: Dr. Helen McIlneron
  - Location: South Africa and Malawi