

A5300/I2003
PHOENIX Study: Adherence
component

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A5300B/IMPAACT2003B

Protecting Households On Exposure to Newly Diagnosed Index Multidrug- Resistant Tuberculosis Patients (PHOENIX)

ACTG Chairs: GJ Churchyard, S Swindells
IMPAACT Chairs: A Gupta, AC Hesselning



MDR TB in Household Contacts

- Contacts of MDR TB patients who become infected have a high risk of progressing to active TB and possibly death
- The vast majority of MDR TB in children arises from HH transmission
- Currently WHO recommends a watch and monitor approach for contacts



A5300/I2003 PHOENix Study: Aim

PHOENix is a Phase III trial in development by the ACTG and IMPAACT networks to assess the efficacy of 6 months of daily delamanid (novel intervention arm) versus 6 months of isoniazid preventive therapy (control comparison arm) in high-risk household contacts of adult pulmonary MDR TB cases

A5300B/I2003B Study

Hypothesis

- Treating HIV-infected and other child, adolescent and adult household contacts of MDR TB patients, including pre-XDR TB and XDR TB, who are at high risk of developing TB with delamanind (DLM) will **substantially reduce the risk of developing TB**, compared to isoniazid (INH)

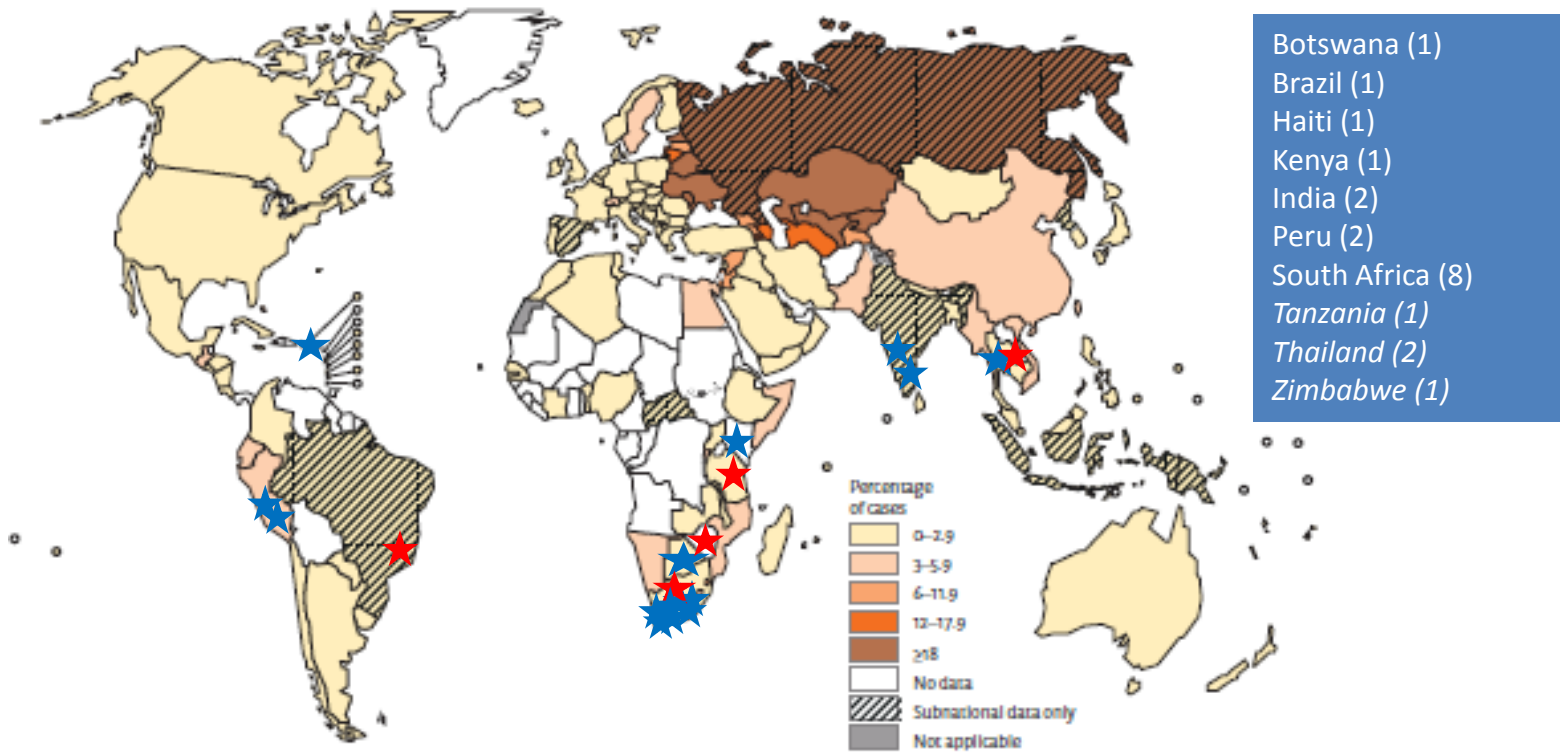
Study Design

Randomization Unit: The household (so high risk contacts within the household will all be allocated to the same study arm)

Sample size & duration

- 3,452 high-risk HH contacts (from 1,726 HH)
- Follow-up: 96 weeks for each participating HH contact
- Total study duration: 304 weeks (5.9 years)

Possible PHOENix Study Sites



Population

Index case:

An adult (18 years and older) with pulmonary MDR TB who has started appropriate treatment within the past six months

- *Confirmed* by phenotypic or genotypic drug resistance testing
- With a *rpoB* mutation detected by GeneXpert *pending* results of *confirmatory DST, or line probe assay* (isoniazid and rifampicin resistance)

Population

Household contact

- A person who lives in the same dwelling unit and shares the same housekeeping arrangements as the index case and who reports exposure within 6 months prior to the index case starting MDR TB treatment

Population

High-risk household contacts

- **Newborns to children <5 years old** regardless of TST/IGRA or HIV status
- **Adults and children ≥ 5 years of age** that are
 - **HIV-infected or non-HIV immunosuppressed** regardless of TST/IGRA status
 - **TST positive ($\geq 5\text{mm}$) and/or IGRA positive** whose HIV status is negative or unknown.

PHOENix Study medications and visits

- If a household is found to be eligible, the household will be randomized to one of the following study regimen:
 - Arm A: Delamanid daily for adults and children, given for 26 weeks
 - Arm B: Isoniazid daily for adults and children, given for 26 weeks. Pyridoxine daily for adults and children, given for 26 weeks.
- Study visits : Monthly during the 26 weeks treatment period.
- A 30-day supply of medication will be dispensed.
- Study treatment will not be given by DOT.

Important issue: Adherence to prophylaxis

- Adherence to study treatments over the prescribed duration of treatment influences the primary study outcome.
 - Scientific Working Group (SWG) recommended that study team give careful consideration to the issue of adherence.
 - PHOENIX adherence working group (AWG) in collaboration with IMPAACT adherence working group did literature review and discussed various options to be considered for measuring adherence in the study.
 - Data on adherence interventions in TB treatment and
- ion are very limited.

Important issue: Adherence to prophylaxis

- Some novel components may need to be adopted from the other studies that are evidence-informed
- PHOENix AWG discussed pros and cons of each method including data to support use in HIV and/or TB treatment, and cost
- Group decided that an electronic dose monitoring tool that provides a more objective, near real-time measure of patterns of adherence would be ideal to have for all participants as validity of this approach has been established in ART and PrEP trials

Adherence to prophylaxis: PHOENix AWG recommendations

Phoenix AWG recommended four electronic medication adherence interventions of many discussed to be potentially considered.

1. Adhere-Tech
2. Wisepill
3. MEMS Caps
4. 99DOTS

Proposed adherence interventions for PHOENIX

AdhereTech 

Smart Pill Bottles to Track &
Improve Adherence in Real-Time



Wisepill Device

- Portable medication dispenser that has a cell phone communication chip which sends a signal (medication event) each time the dispenser is opened
- Adherence records are stored in a Wisepill database

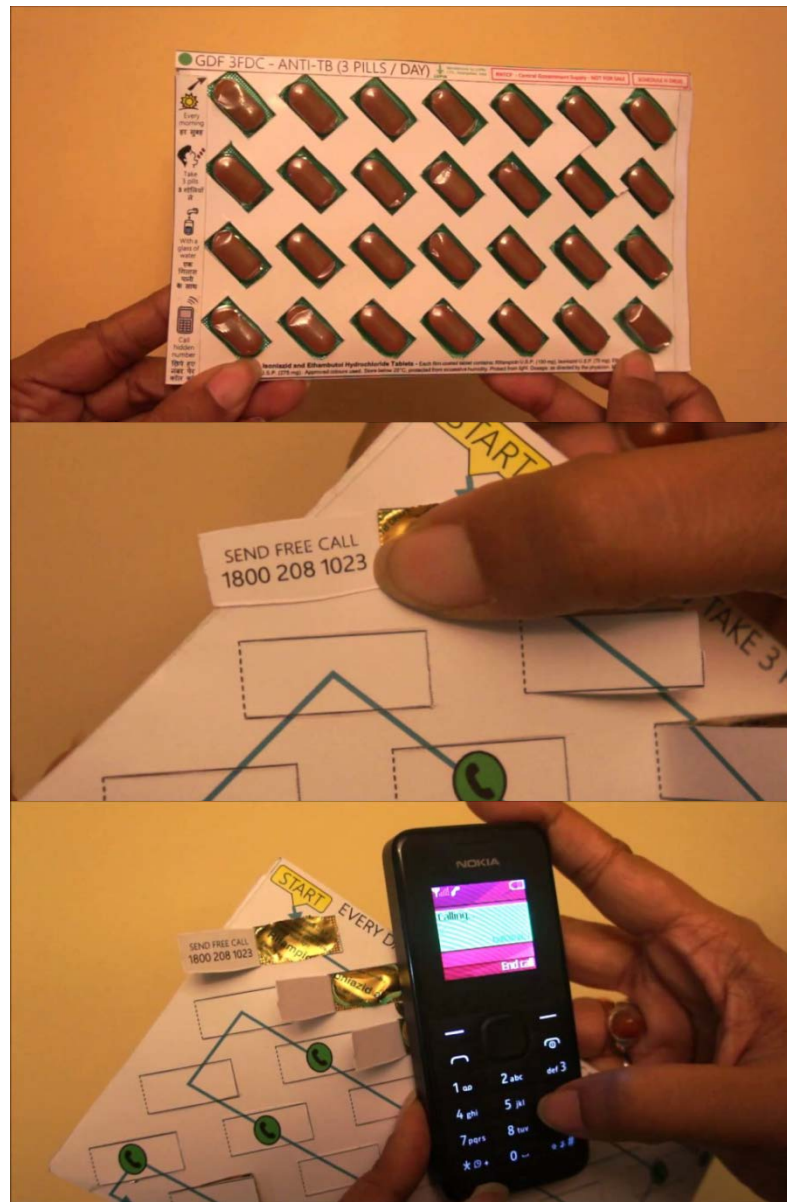


Adhere-Tech and Wisepill

- Both uses cellular technology, Individual gets the feedback and prompt to take medication.
- Does not require participant effort (i.e. passive reporting)
- Each time device is opened, it creates and transfers information to a central server and data are then available to research, clinic, and program personnel via a secure, internet-based interface.

99DOTS

- As a patient take medication, it reveals hidden number . Patient send free call to that number each time medication is taken out.
- 99DOTS promises an effective and low-cost monitoring of cure regimen for tuberculosis patients
- It was launched in India in 2014 and is in Pilot phase with 27 sites in India.
- Currently no data is available on effectiveness of 99DOTS.



Medication Event Monitoring System (MEMS Cap)

- MEMS medication bottles contain a microelectronic chip that registers the date and time of every bottle opening. Assuming that bottle openings represent medication intake, MEMS provides a detailed profile of the patient's adherence behaviour.
- MEMS don't allow for real-time monitoring like Wisepill although costs are comparable.



Recommendation of Wisepill

PHOENIX AWG recommended Wisepill to be considered for PHOENIX trial.

Cost: Wisepill device is \$130 v \$880 for Adhere-Tech

Evidence: Studies are done in resource-limited settings.

Evidence of Wisepill

From the HIV literature:

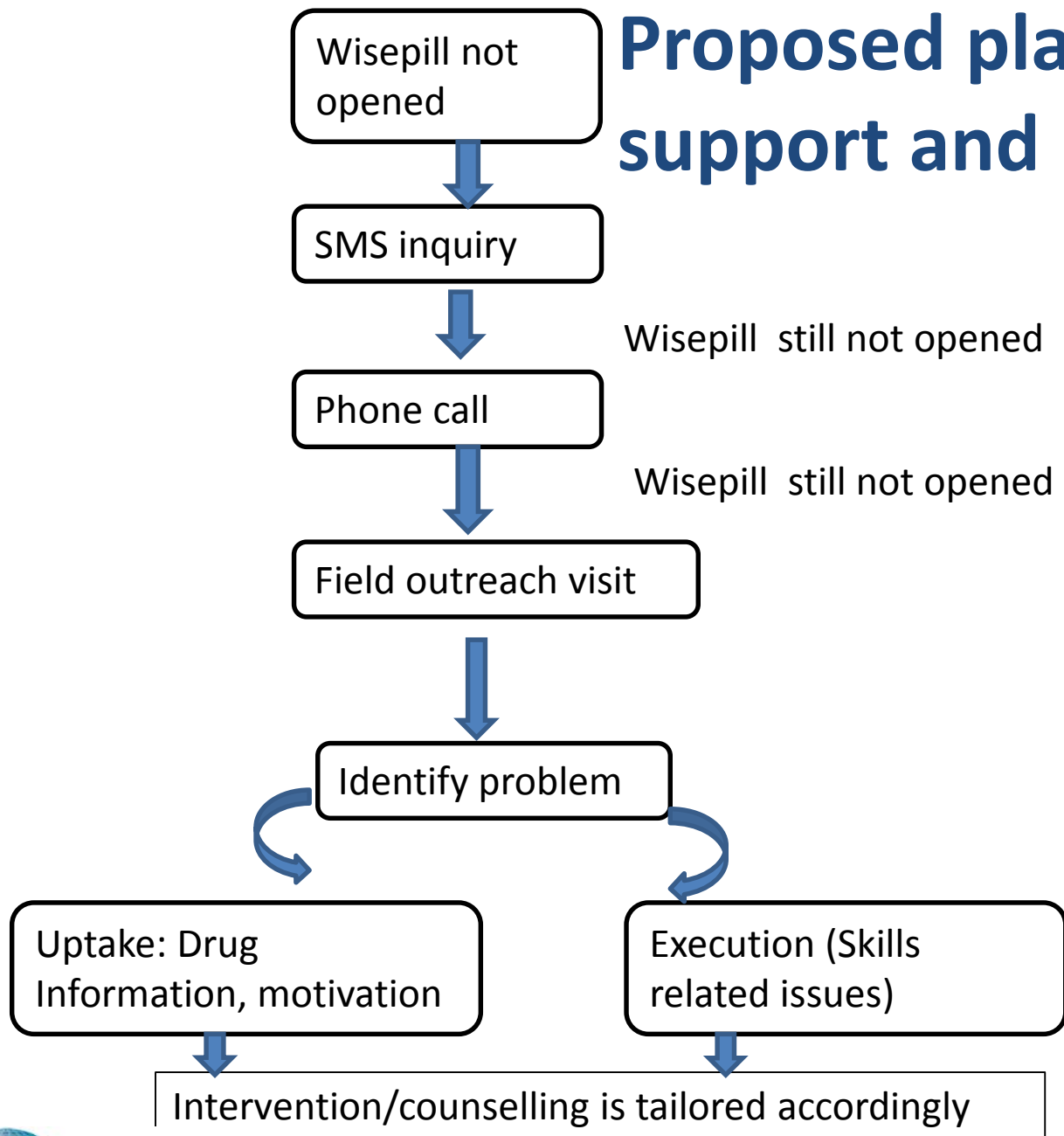
- Average adherence increased with Wisepill + triggered SMS reminders and data-driven counseling (China) (*Sabin, JAIDS, 2015 Aug 15;69(5):551-9*)
- Average adherence did not improve, but treatment interruptions decreased with Wisepill + triggered SMS reminders (South Africa) (*Orrell, JAIDS, 2015 Dec 15;70(5):495-502*)
- Average adherence increased and treatment interruptions decreased with Wisepill + scheduled SMS reminders (Uganda) (*Haberer, AIDS, 2016, Epub*)

Proposed plan:

Adherence support and monitoring

- To provide wisepill for all participants at baseline irrespective of randomisation in intervention or control arm
- A more intensive adherence intervention, including counseling tailored to identify and address barriers (e.g. cognitive behavioral interventions over multiple sessions), should be offered to participants who are identified as having poor adherence based on wisepill monitoring data at each visit
- Adherence will be monitored using self-report, by using stored specimens for PK analysis on blood and urine near real time

Proposed plan: Adherence support and monitoring



Limitations of using electronic adherence devices

Having multiple devices in the home could be very confusing, i.e., looks same, could take others' medicines.

- Color coded device for each person in family would be useful.

Pocket doses (multiple pills removed at a single opening for later dosing)

- point of education and potentially counseling (especially for travel, migratory work, etc).

Curiosity openings (i.e. multiple openings without removing pills).

- Real-time data will require real-time data management and technical monitoring. (It can be managed by site?).

Adherence to prophylaxis: Additional recommendations

All participants should receive a basic education package prior to first dispensation that includes:

- Motivating information and medication planning to maximize self-efficacy. This may be done for an entire family unit together, if appropriate.
- Preparation of material for education that serves as a core package that can be further adapted by sites.
- Material appropriate to children and youth – which may include media and visual arts/drama.

THANK YOU PHOENIX AWG members

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