Tuberculosis Trials Consortium Study 31
AIDS Clinical Trials Group A5349

Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial

INTERTB Meeting
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Relevant Disclosures

- Funding from Centers for Disease Control and Prevention, TB Trials Consortium
- Funding from NIH/NIAID TB for biomarker discovery and qualification

S31/A5349 Primary Objectives

- Evaluate efficacy of a high dose rifapentine-containing regimen to determine whether the single substitution of RPT for RIF makes it possible to reduce to 4 months (17 weeks) the duration of treatment

  2**P**HZE/2**P**H

- Evaluate efficacy of a 4 month (17 weeks) regimen that substitutes a) high dose RPT for RIF and b) MOX for EMB to determine whether reduction to 4 months (17 weeks) duration is possible *(optimized regimen using existing drugs)*

  2**P**HZ**M**/2**P**H**M**

S31/A5349 Phase 3 Design

- International, multicenter
- 3 arms, randomized 1:1:1
- Open-label
- Non-inferiority design
- N = 2500
- Several secondary objectives and substudies, including PK/PD and biomarker studies
- FDA registration level quality controls
- DSMB review annually and as needed
- Registration of ClinicalTrials.gov: NCT02410772

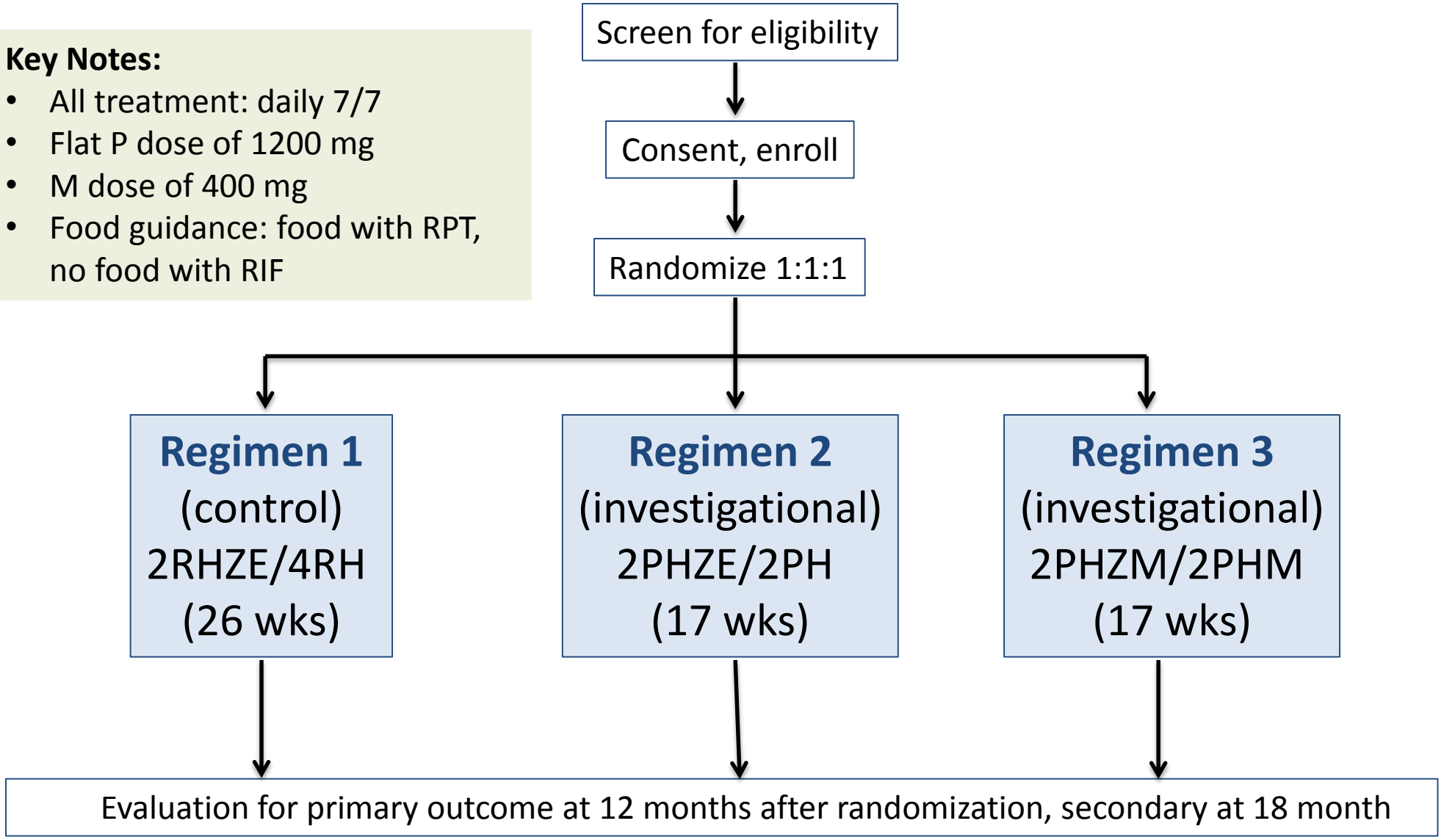
S31/A5349, Selected eligibility criteria

- Inclusion
  - Positive sputum smear for AFB or positive *Xpert MTB* with medium or high result
  - Age >= 12
  - If HIV (+), CD4 T cell count >= 100 cells/mm^3
    - Initially enrolling only “EFV1” group, stable on efavirenz-based ART, for drug interaction PK and viral load testing
- Exclusion
  - > 5 days TB treatment within previous 6 months
  - > 5 days treatment with anti-TB drugs within previous 30 days
  - TB of CNS, bones or joints, miliary, pericardial
  - Weight < 40 kg

S31/A5349 Schema

Key Notes:

- All treatment: daily 7/7
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF



SECONDARY: Evaluate safety and tolerability of the regimens, extensive PK of ALL TB drugs and EFV, biobanking

TBTC Study 31/ACTG A5349 Sites

	Site Locations	ACTG	TBTC
	Brazil	**2**	
✓	Hospital Conceição Porto Alegre	1	
✓	Institute de Pesquica Evandro Chagas, Rio	1	
	China		**1**
✓	TB and Chest Service of Hong Kong		1
	Haiti	**2**	
✓	GHESKIO Institute of Infectious Diseases and Reproductive Health (GHESKIO - IMIS)	1	
✓	Les Centres GHESKIO-INLR	1	
	India	**2**	
✓	BJ Medical College Clinical Research Site, Pune	1	
	Chennai Antiviral Research and Treatment	1	
	Kenya	**3**	
	KEMRI Walter Reed Project, Kericho	1	
✓	Kenya Medical Research Institute/ CDC	1	
✓	Moi University Clinical Research Centre	1	

	Site Locations	ACTG	TBTC
	Malawi	**2**	
✓	Blantyre Clinical Research site	1	
✓	Lilongwe	1	
	Peru	**2**	**1**
✓	Asociación Civil IMPACTA Salud y Educación (Barranco) Lima	1	
✓	San Miguel Clinic - IMPACTAPERU, Putumayo	1	
✓	Universidad Peruana Cayetano Heredia, Lima, Peru		1
	South Africa	**7**	**1**
✓	Durban International Clinical Research Site	1	
✓	FAMCRU- University of Stellenbosch	1	
✓	South African Tuberculosis Vaccine Initiative	1	
✓	Soweto ACTG Clincial Research Site	1	
✓	TASK Stellenbosch	1	
✓	University of Cape Town Lung Institute	1	
✓	WITS CRS	1	
✓	Wits Health Consortium		1

	Site Locations	ACTG	TBTC
	Thailand	**2**	
✓	Chiang Mai University HIV Treatment	1	
✓	Thai Red Cross AIDS Research Centre, Bangkok	1	
	Uganda	**1**	**1**
	Joint Clinical Research Centre, Kampala	1	
✓	Kampala, Uganda-Case Western Reserve University		1
	US	**5**	**5**
✓	Baylor College of Medicine		1
✓	Columbia University		1
✓	San Antonio VA Medical Center		1
	South Texas Consortium		1
✓	U of North TX Health Sciences Center		1
	UCSD San Diego	1	
✓	UCSF CRS San Francisco	1	
	Viet Nam		**1**
✓	Vietnam NTP/UCSF Research Collaboration		1
	Zimbabwe	**1**	
✓	Parirenyatwa Clinical Research Site	1	

Study 31 / ACTG A5349 Site start-up - Gantt Chart

Nov 2017

TBTC Site #	ACTG Site #	Name	Network	Country	City	Monthly Est. Enroll	Monthly Average (Aug, Sep, Oct)	Est. Start Quarter	Est.or Opened to Enroll	opened to enroll	first enrollment	Total Enrolled	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	######	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17
30		Kampala, Uganda-Case	TBTC	Uganda	Kampala	12	15			01/19/16	01/25/16	343																							
37		Vietnam NTP/UCSF Research	TBTC	Viet Nam	Hanoi	4	8			02/29/16	03/04/16	122																							
36		TB and Chest Service of Hong	TBTC	China	Hong	2	2			03/10/16	04/08/16	19																							
34		Wits Health Consortium	TBTC	South Africa	Johannesb	2	6			04/20/16	06/28/16	74																							
45	30022	Les Centres GHESKIO-INLR	ACTG	Haiti	Port au	12	5			05/10/16	05/19/16	112																							
20		U of North TX Health Sciences	TBTC	US	Fort	1	0			05/11/16	06/06/16	6																							
10	31718	TASK Stellenbosch	ACTG	South Africa	Cape	8	11			06/03/16	06/14/16	116																							
09	31792	University of Cape Town Lung	ACTG	South Africa	Cape	4	5			06/06/16	06/14/16	134																							
07	11101	WITS CRS	ACTG	South Africa	Johannesb	6	5			06/07/16	07/22/16	67																							
08	31793	South African Tuberculosis	ACTG	South Africa	Worcester	8	5			06/08/16	08/05/16	92																							
67	31730	GHESKIO Institute of Infectious	ACTG	Haiti	Port au	12	5			06/21/16	06/21/16	74																							
39	31460	Kenya Medical Research	ACTG	Kenya	Kisumu	3	1			07/07/16	07/27/16	33																							
63		San Antonio VA Medical Center	TBTC	US	San	1	0			07/12/16	07/22/16	9																							
62		Baylor College of Medicine	TBTC	US	Houston	1	0			08/01/16	12/22/16	1																							
91	12101	Institute de Pesquica Evandro	ACTG	Brazil	Rio de	5	1			08/11/16	09/30/16	13																							
49	12301	Soweto ACTG CRS	ACTG	South Africa	Soweto	2	3			08/30/16	11/08/16	28																							
24		Columbia University	TBTC	US	New York	1	0			10/17/16	06/22/17	2																							
01	8950	FAMCRU- University of	ACTG	South Africa	Parow	1	2			10/25/16	11/15/16	21																							
06	11201	Durban International Clinical	ACTG	South Africa	Durban	4	1			10/28/16	01/16/17	6																							
41	30313	Parirenyatwa Clinical Research	ACTG	Zimbabwe	Harare	8	9			11/09/16	12/07/16	76																							
94	12201	Hospital Conceição Porto	ACTG	Brazil	Porto	2	0			03/09/17	05/03/17	2																							
43	31441	BJ Medical College Clinical	ACTG	India	Pune	8	4			06/01/17	06/09/17	20																							
42	31802	The Thai Red Cross AIDS	ACTG	Thailand	Bangkok	2	1			07/07/17	08/08/17	3																							
69	31784	Chiang Mai University HIV	ACTG	Thailand	Chiang	5	1			08/03/17	08/28/17	2																							
93	11302	San Miguel Clinic -	ACTG	Peru	Putumayo	12	3			08/07/17	08/11/17	8																							
82	801	UCSF CRS San Francisco	ACTG	US	San	1	0			08/10/17		0																							
90	11301	Asociación Civil IMPACTA Salud	ACTG	Peru	Lima	12	2			08/11/17	08/16/17	6																							
38		Universidad Peruana Cayetano	TBTC	Peru	Lima		2			08/21/17	08/24/17	6																							
03	12601	Moi University Clinical	ACTG	Kenya	Eldoret	8	0			08/21/17	11/02/17	0																							
05	12001	Lilongwe, Malawi	ACTG	Malawi	Lilongwe	5	3			09/19/17	09/28/17	8																							
04	30301	Blantyre Clinical Research site,	ACTG	Malawi	Blantyre	5	0			10/30/17		0																							
02	12501	KEMRI Walter Reed Project,	ACTG	Kenya	Kericho	5		Q4 2017	Nov-2017			0																							
11	12401	Joint Clinical Research Centre,	ACTG	Uganda	Kampala	5		Q4 2017	Nov-2017			0																							
85	701	UCSD San Diego	ACTG	US	San Diego	1		Q4 2017	Nov-2017			0																							
46		Austin	TBTC	US	Austin	1		Q4 2017	Dec-2017			0																							

First enrollment
25 January, 2016

Monthly enrollment rate needed to finish by December, 2018: 100

Enrolled Last Month (Oct 2017): 130

Enrolled in Last 30 Days: 120

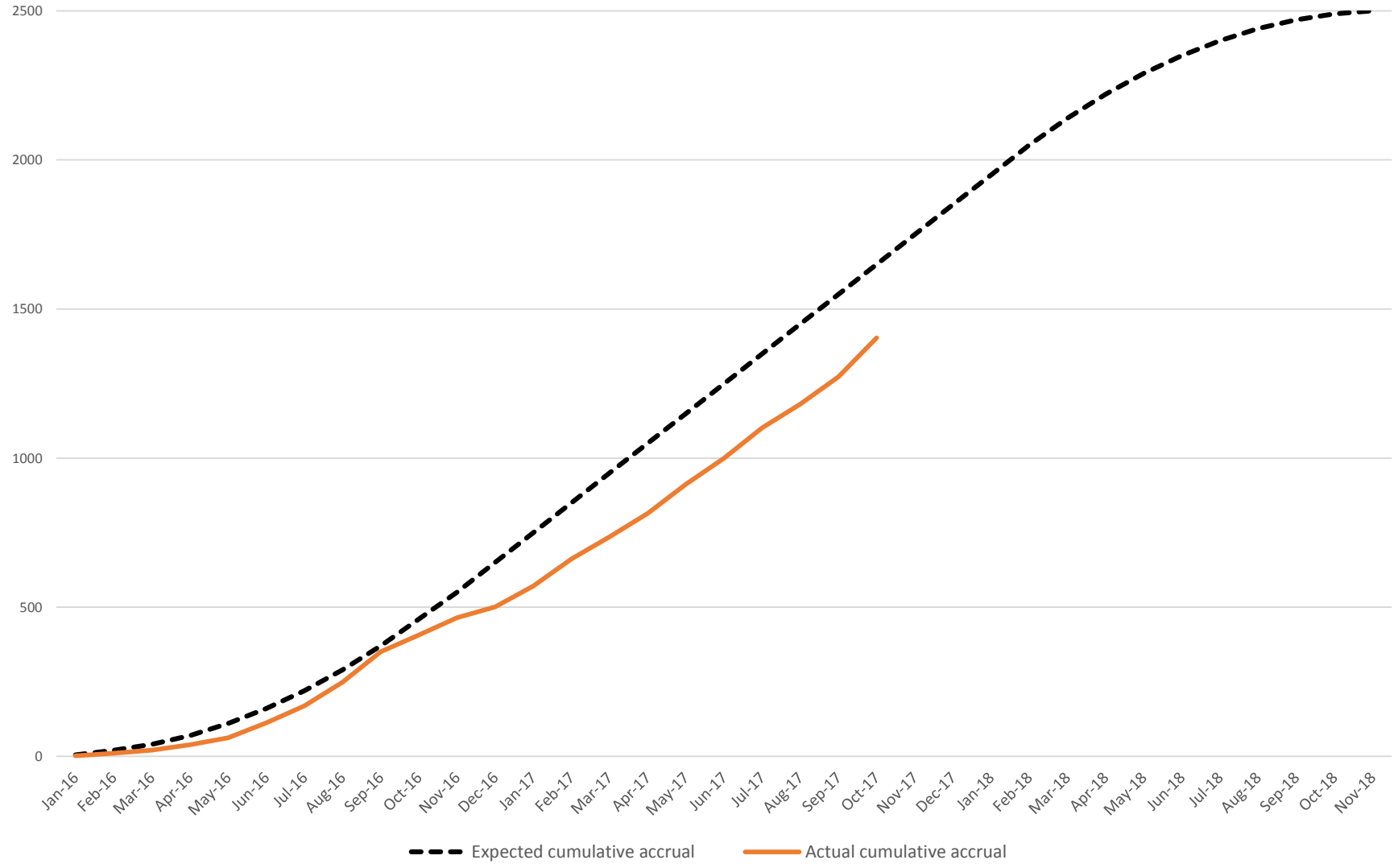
1448 enrollments
(as of 14Nov2017)

58% of target enrollment

Anticipated completion
December 2018

Cumulative Enrollments by Month

(as of 14 November 2017)



Safety Monitoring

- By site teams
- Central (TBTC Data Center)
- Data Safety Monitoring Board
  - 2nd annual meeting held May 2017: no safety concerns raised by DSMB

HIV: EFV1 and EFV2

HIV+ test at enrollment	81
HIV+ test at enrollment & randomized to RPT regimen	56
EFV1 group	
HIV+ test at enrollment	41
HIV+ test at enrollment & randomized to RPT regimen	41
HIV+ test at BL, randomized to RPT regimen, eligible & submitted at least one EPK form	38
EFV2 group	
HIV+ test at enrollment	10
HIV+ test at enrollment & randomized to RPT regimen	10
HIV+ test at BL, randomized to RPT regimen, eligible & submitted at least one EPK form	0

EFV-TB tx drug-drug interaction study: *EFV1 results to date*

Item	Value
# Complete EFV Profiles @ UNMC Lab	25
#PIDs unevaluable (BL < 1000 ng/mL)	2
#PIDs evaluable as of 01-OCT-2017	23
PIDs Passing EFV1 Criteria	21/23 (91%)
Baseline HIV < 200 copies/mL	23/23 (100%) of evaluable EFV PIDs
Week 8 Viral Load <200 copies/mL (collected for 16 of 23 evaluable PIDs)	16/16
# PIDs with Incr. EFV Conc. Wk 0 to Wk 8	17/23 (74%)
# PIDs with Decr. EFV Conc. Wk 0 to Wk 8	6/23 (26%)

EFV1 PK results to date

	Median EFV mg/L (IQR)	EFV Concentration ≥ 1 mg/L (n, %)
Week 0 (baseline)	2.54 (1.81-3.96)	23/23 (100%)
Week 4	3.34 (1.95-7.14)	22/23 (96%)
Week 8	2.63 (2.09-7.23)	21/23 (91%)
	Median EFV CL/F (L/hr) (IQR)	
Pre RPT/H	8.02 (5.79-10.57)	
On RPT/H	7.17 (3.38-9.53)	

EFV-TB tx drug-drug interaction study: *next steps*

- EFV1
  - **Ongoing**; continue to enroll & collect specimens from eligible participants
    - On EFV for ≥ 30 days at time of enrollment AND HIV VL < 200 copies/mL at or within 30 days prior to study entry
  - Data from 90 EFV1 participants will be analyzed
- EFV2
  - **Ongoing**; enroll & collect specimens from eligible participants
    - (HIV pos) not on ART at enrollment (with plan to start EFV-based ART before/around study week 8)
    - Timing of specimen collection depends on when EFV-based ART started
  - Data from 31 EFV2 participants will be analyzed followed by decision-making

Adolescents (<18 yrs) n=42, 3% of Total Enrolled

Site	Total Enrolled	<18years old		
	n	n	Col %	Row %
Total enrolled	**1448**	**42**		**3**
Enrolled at sites enrolling adolescents	820	42		5
Site 01/8950 FAMCRU, ZA	21	1	2	5
Site 05/12001 Lilongwe, MW	11	1	2	9
Site 08/31793 SATVI, ZA	94	5	12	5
Site 09/31792 UCTLI, ZA	139	5	12	4
Site 10/31718 TASK, ZA	120	11	26	9
Site 30 Kampala, UG	354	13	31	4
Site 36 Hong Kong, CN	19	1	2	5
Site 37 Hanoi, VN	123	5	12	4

Ages	n	%
13	1	3
14	4	10
15	14	33
16	9	21
17	14	33

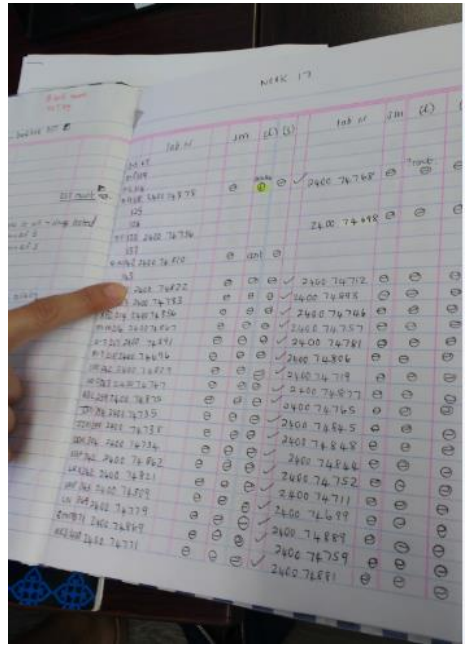
Site Reported Barriers to Enrolling Adolescents

- Little or no access to participants <18 years old
- Parents live away from child due to work
- Parents/guardians are resistant to allowing their children to enroll
- Regulatory restrictions
- School/Boarding School
- Waiting for IRB approval to enroll adolescents
- Weight requirement is prohibitive
- Eligibility of <5 days of TB therapy is prohibitive

Evaluation of Possible Poor Treatment Response

“Possible Poor Treatment Response” process

- Open-label trial – risk of ascertainment bias
- PPTR is an evaluation approach intended to reduce the frequency of subjective outcomes (through protocol-specified, systematic, standardized collection of objective data/specimens regardless of assigned study regimen
- Acknowledges the importance of (and facilitating when appropriate) individual participant-specific management by the treating clinician



- Through the PPTR process we enhance likelihood that the study can ascribe a clear study outcome to each participant with confidence, accuracy, and on the basis of objective data

The occurrence of any one or more of the following triggers the PPTR process:

1. A positive culture confirmed as Mtb from a sputum specimen collected at or after week 17
2. A positive smear from a sputum specimen collected at or after week 17
3. Worsening signs and/or symptoms consistent with TB at or after week 17
4. Radiographic worsening consistent with TB at or after week 17
5. The site investigator is considering extension of TB treatment beyond that of the participant's assigned regimen
6. The site investigator is considering retreatment with any TB therapy after the participant has completed assigned study treatment
7. For a participant on assigned study treatment, the site investigator is considering a change in treatment for efficacy reasons (this does not apply to changes in treatment for pregnancy, temporary drug challenge, or toxicity)

"The following should be performed as soon as feasible when a PPTR is suspected, and ideally **prior to a change or restart of treatment** (if such a change or restart is considered warranted by the site investigator) if the participant's clinical condition permits:"

- **Obtain at least 3 sputum specimens**
- Contact the central study clinician via TBTCStudy31@CDC.gov
  - Put in the email subject line: "**Possible Poor Treatment Response, Site ##, PID 31-xx-xxxxx ATTN: Central Study Clinician**"
- Review participant's contact information
- Symptom assessment
- Review interval medical history/ adverse event assessment
- Concomitant medication assessment
- Measure weight
- Obtain chest radiograph
- Complete and submit the PR form
- Get biomarker specimens (consenting participants)

Quality Assurance & Monitoring

Study 31/ACTG 5349 Key Elements of Mycobacteriology Laboratory Procedures

Table 1: Key Elements of Mycobacteriology Laboratory Procedures

	Laboratory Procedure	Key Element in Procedure	Potential Affect/Impact
1	Sputum Collection & Transport	Participant is to rinse mouth with boiled/sterile/bottled or distilled water prior to sputum collection	Quality of specimen
2	Sputum Collection & Transport	Collect at least 3 to 5 mL of sputum. If larger volumes cannot be obtained, a minimum of 1 mL is acceptable[a]	Quality of specimen
3	Sputum Collection & Transport	Transport sputum specimen to the laboratory in a cool box as soon as possible after collection. Store sputum in a refrigerator or cool box (2-8°C) if not received by to the laboratory within 1 hour of collection[b]	Integrity of specimen
4	Sputum Receipt & Storage	Store sputum specimen in a refrigerator or cool box (2-8 °C) if not processed within 1 hour of receipt at the laboratory	Integrity of specimen
5	Sputum Processing	Decontaminate sputum specimen with a final sodium hydroxide (NaOH) concentration of 1.0 to 1.5% for 15 to 20 minutes prior to adding phosphate buffered saline (PBS) (pH 6.8)	Isolation of MTB
6	Sputum Processing	Centrifuge specimen with a relative centrifugal force (RCF) of 3000x*g*, for at least 15 minutes[c]	Isolation of MTB
7	Sputum Processing	Resuspend the digested decontaminated specimen to final volume of 1.5 to 2.0 mL with PBS (pH 6.8)[d]	Comparability of results
8	Sputum Processing	Include positive controls at least once per week or with each participant batch, and negative controls daily or with each participant batch	Isolation of MTB and Detect Cross-Contamination
9	Smear Microscopy	Positive and negative control slides must be included with every batch of participant slides	Quality of smear results
10	Smear Microscopy	Report results according to WHO/IUATLD grading scale as per the Global Laboratory Initiative (StopTB Partnership) Sputum Microscopy Handbook[e]	Comparability of results
11	Rapid Molecular Testing	Perform rapid molecular test (e.g., GeneXpert) according to the manufacturer's product insert	Comparability of results
12	Rapid Molecular Testing and Smear Microscopy	Report results of screening tests used for subject eligibility to clinic staff within 48 to 72 h of sputum specimen receipt	Turnaround time
13	Solid Media Culture	Inoculate solid media (slant or plate) with 0.2 mL of resuspended sputum sediment[f]	Comparability of results
14	Solid Media Culture	Incubate solid media for at least 6 weeks before reporting a negative result; or at least 8 weeks for drug resistant TB trials	Isolation of MTB
15	Solid Media Culture	Test appropriate controls before media is used, regardless if purchased commercially or prepared in-house[g]	Isolation of MTB
16	MGIT Culture	Inoculate each MGIT tube with 0.5 mL of the resuspended sputum sediment	Comparability of results
17	MGIT Culture	Work up all MGIT cultures (positive and negative) according to the FIND MGIT Manual and MGIT culture algorithms/flow charts included in the study-specific laboratory reference manual[h]	Isolation/Detection of MTB
18	Identification of MTB	Confirm the presence of *M. tuberculosis* complex (MTBC) vs. non-MTBC at each trial time point when culture is positive[i]	Isolation of MTB
19	Identification of MTB	Include positive and negative controls at least once per week or with each batch of participant specimens and with each new lot or shipment of testing kits/reagents	Accuracy of MTB ID
20	Drug Susceptibility Testing (DST)	Include a drug susceptible quality control (QC) strain at least once per week or with each batch of participant specimens	Quality of DST results

Courtesy Dr. Anne Purfield, PhD

Start-Up and Quality Assurance Monitoring

1. TBTC2 Web Application: New Access Requests
2. TBTC2 Web Application: Rules of Behavior
3. TBTC2 Web Application: Member Module Updates (Contact Info & “Function” Assignment)
4. IRB Registration
5. Mycobacteriology Laboratory: Communication & Preparation
6. Pharmacy Plan
7. Drug Shipment
8. Quality Management
9. Community Engagement: Medical & Advocacy
10. Recruitment & Screening plan
11. Delegation of authority log

- Central Monitoring
  - DCC daily data checks and communication with the Sites
- Local Monitoring
  - Sites QA Plans implementation
- On-site Monitoring
  - CROs
  - Westat for TBTC and PPD for ACTG

Study 31 / A5349 Protocol Team (v. 2.0, May 2015)

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***ACTG / **ACTG and TBTC**

*****Joined in 2016**