IMPAACT P1106: PHARMACOKINETIC CHARACTERISTICS OF ANTIRETROVIRALS AND TUBERCULOSIS MEDICINES IN LOW BIRTH WEIGHT INFANTS

CO-CHAIRS:

MARK COTTON, MMED, DTM&H, PHD

MARK MIROCHNICK, MD

DESIGN AND PRIMARY OBJECTIVE

- **Design** Phase IV prospective pharmacokinetic (PK) study of ARV and TB drugs in low birth weight infants

- **Primary Objective** To describe the pharmacokinetics (PK) and safety of NVP, INH, RIF, and LPV/r in LBW infants receiving the drug(s) as part of clinical care.

SECONDARY OBJECTIVES

1. To describe the PK and safety of TMP-SMX, ZDV, d4T, ABC and 3TC in LBW infants receiving the drug(s) as part of clinical care.

2. To develop population PK models of ARVs, TB drugs and TMP-SMX in LBW infants.

3. To describe the impact of CYP 2B6 genetic variants on NVP metabolism and NAT2 genetic variants on INH metabolism in LBW infants.

4. To describe the association of PK parameters and drug exposures with birth weight, gestational age, postnatal age, HIV/TB infection status and other clinical variables.

5. To use population PK models to perform Monte Carlo simulations of current and alternative dosing regimens for ARVs, TB drugs and TMP-SMX.

POPULATION

- Low birth weight (LBW) infants (≤2500 grams at birth) who are receiving or will be receiving as part of clinical care:
    1. Nevirapine (NVP) prophylaxis
    2. Tuberculosis (TB) prophylaxis or treatment

    and/or

    3. Combination antiretroviral (ARV) treatment containing lopinavir/ritonavir (LPV/r)

GENERAL DESIGN

Phase IV prospective pharmacokinetic study to evaluate the PK and safety of currently prescribed HIV and TB drugs in low birth weight infants (≤2500 grams at birth) with 6 arms:

1. Receiving HIV prophylaxis with NVP (no TB prophylaxis/treatment)
2. Receiving HIV prophylaxis with NVP and TB prophylaxis with INH (no RIF)
3. Receiving HIV prophylaxis with NVP and TB prophylaxis/treatment with INH plus RIF
4. Not receiving any HIV drugs but receiving TB prophylaxis/treatment with INH alone or INH plus RIF
5. Infants initiating treatment with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)
6. Infants initiating treatment with LPV/R plus 2 NRTIs, and receiving RIF (and may be receiving INH)

ELIGIBILITY CRITERIA

Arms 1, 2 and 3 – NVP prophylaxis for HIV

- Breastfeeding infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP
- Age 7 to 14 days
- Birth weight ≤ 2500 grams
- Receiving or will be receiving prophylaxis as prescribed by clinical care provider as follows: NVP (Arm 1), NVP plus INH (Arm 2), NVP plus INH plus RIF (Arm 3)
- Parent or legal guardian able and willing to provide written informed consent.

ELIGIBILITY CRITERIA

Arm 4 – TB prophylaxis (no NVP)

- Age 7 to 14 days
- Birth weight ≤ 2500 grams
- Receiving prophylaxis with INH alone or INH plus RIF as prescribed by clinical care provider
- Not receiving any therapy for HIV prophylaxis or treatment
- Parent or legal guardian able and willing to provide written informed consent.

ELIGIBILITY CRITERIA

Arms 5 and 6 (HIV-infected infants)

- Documentation of HIV-1 infection defined as positive HIV DNA PCR done as part of clinical care. An HIV RNA confirmatory test must be done at study entry but results may be pending at time of enrollment.
- Birth weight ≤ 2500 grams
- Age ≤12 weeks (defined as 84 days)
- Intention by clinical care provider to prescribe LPV/r plus 2 NRTIs and no RIF (Arm 5) or LPV/r plus 2 NRTIs plus RIF (Arm 6)
- Parent or legally acceptable representative able and willing to provide written informed consent

EXCLUSION CRITERIA FOR ALL ARMS

- Any severe congenital malformation or other medical condition incompatible with life or that would interfere with study participation or interpretation, as judged by the examining clinician.

Arm	Infant Study Treatment	Infant Feeding	Infant Age at Entry	Sample Size (evaluable subjects, total and per weight band)	Infant Entry Weight Bands	Maternal HIV Status	Infant TB Status	Maternal ART
1	NVP	Breastfeeding	7-14 days	N=40 N=12 N=12 N=16	Total <1400gm 1400 - <1800gm 1800 - <2500gm	HIV-infected	TB not exposed	No NVP
2	NVP + INH	Breastfeeding	7-14 days	N=18 N=6 N=6 N=6	Total <1400gm 1400 - <1800gm 1800 - <2500gm	HIV-infected	TB exposed	No NVP
3	NVP + INH + RIF	Breastfeeding	7-14 days	N=28 N=8 N=8 N=12	Total <1400gm 1400 - <1800gm 1800 - <2500gm	HIV-infected	TB exposed	No NVP
4	INH or INH + RIF	Breastfeeding or formula feeding	7-14 days	N=18-36 N=6-12 N=6-12 N=6-12	Total <1400gm 1400 - <1800gm 1800 - <2500gm	HIV-uninfected	TB exposed	No
5	LPV/r + 2NRTIs ± INH	Breastfeeding or formula feeding	≤12 weeks	N=24	≤2500gm	HIV-infected	± TB exposed	±
6	LPV/r + 2NRTIs +RIF ± INH	Breast feeding or formula feeding	≤12 weeks	N=12	≤2500gm	HIV-infected	TB exposed or treated	±

SOE FOR ARMS 1, 2, 3 AND 4

EVALUATION	Screening within 0-14 days of life	Entry within 7-14 days of life	Week 4 of life	Week 6 of life	Week 10 of life	Week 16 of life	Week 24 of life	On study/off drug
STUDY VISIT WEEKS ARE BASED ON TIME ELAPSED FROM BIRTH								
ARM 1 (NVP), ARM 2 (NVP PLUS INH), ARM 3 (NVP PLUS INH PLUS RIF), ARM 4 (INH ALONE OR INH PLUS RIF)								
Visit Windows	-	-				±14days		±7days
CLINICAL								
Informed Consent	X							
History	X	X	X	X	X	X	X	X
Physical Exam[1]	X	X	X	X	X	X	X	X
LABORATORY								
Hematology (Hct)					0.5mL		0.5mL	
Chemistries (ALT, Cr, GGT)		0.5mL[2]		0.5mL[2]				
PHARMACOLOGY[9]								
PK sampling for Arm 1 (NVP)[8]		0.4mL[3]	0.2mL[4]	0.2mL[4]	0.2mL[4]	0.2mL[4]	0.2mL[4]	
PK sampling for: Arm 2 (NVP plus INH)[8] Arm 3 (NVP plus INH plus RIF)[8]		0.4mL[5]	0.6mL[6]	0.4mL[5]	0.4mL[5]	0.4mL[5]	0.4mL[5]	
PK sampling for: Arm 4 (INH alone or INH plus RIF)[8]		0.4mL[5]	0.4mL[5]	0.4mL[5]	0.4mL[5]	0.4mL[5,7]	0.4mL[5,7]	
PHARMACOGENETICS[9]								
Genotyping				X[10]				
TOTAL BLOOD VOLUME		0.4-0.9mL	0.2-0.6mL	0.2-0.9mL	0.7-0.9mL	0.2-0.4mL	0.7-0.9mL	

PK SAMPLING SCHEDULE FOR ARMS 1, 2, 3 AND 4

Arm	Subjects (N)	Age Wk2	Age Wk4	Age Wk6	Age Wk10	Age Wk16	Age Wk24	Samples (N/subject)
1	40	Pre, 2h	Pre	Pre	Pre	Pre	Pre	7
2	18	1.5, 4h	Pre, 1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h	13
3	28	1.5, 4h	Pre, 1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h	13
4	18-36	1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h	1.5, 4h*	1.5, 4h*	8-12

*Only for Arm 4 on INH alone (INH plus RIF will only receive 12 weeks of therapy)

<u>Pharmacokinetic sample time collection windows are:</u>

1.5 hours =1 to 2 hours

2 hours =1.5 to 2.5 hours

4 hours =4 to 6 hours

SOE FOR ARMS 5 AND 6

	Entry within 7 days prior to LPV/r initiation	3-5 days after LPV/r initiation	7-9 Days after LPV/r initiation	Week 2 after LPV/r initiation	Week 6 after LPV/r initiation	Week 10 after LPV/r initiation	Week 16 after LPV/r initiation	Week 24 after LPV/r initiation	On study/off drug
ARMS Arm 5 (LPV/r PLUS 2 NRTIs AND NO RIF BUT MAY BE RECEIVING INH) Arm 6 (LPV/r PLUS 2 NRTIs PLUS RIF AND MAY BE RECEIVING INH)									
VISIT WINDOWS	-	-	-	±4 days	±7 days	±7 days	±14 days	±14 days	±7days
CLINICAL									
Informed Consent	X								
History	X	X		X	X	X	X	X	X
Physical Exam[1]	X	X		X	X	X	X	X	X
Electrocardiogram *(See Appendix II)*	X	X	X	X	X				
Echocardiogram (*See Appendix II)*	X		X		X				
LABORATORY									
Hematology (Hct)						0.5mL		0.5mL	
Chemistries (ALT, Cr, potassium, calcium, osmolality)				0.5mL[2]	0.5mL[2]		0.5mL[2]		
VIROLOGY									
HIV RNA PCR	0.5mL[3]								
PHARMACOLOGY[7]									
PK sampling Arm 5 (LPV/r plus 2 NRTIs, no RIF)[6] Arm 6 (LPV/r plus 2 NRTIs plus RIF)[6]				0.6mL[4]	0.2mL[5]	0.6mL[4]	0.2mL[5]	0.6mL[4]	
PHARMACOGENETICS[7]									
Genotyping					X[8]				
TOTAL BLOOD VOLUME	0.5mL			0.6-1.1mL	0.2-0.7mL	1.1mL	0.2-0.7mL	1.1mL	

PK SAMPLING SCHEDULE FOR ARMS 5 AND 6

Arm	Subjects (N)	Study Wk2	Study Wk6	Study Wk10	Study Wk16	Study Wk24	Samples (N/subject)
5	24	Pre, 1.5, 4h	Pre	Pre, 1.5, 4h	Pre	Pre, 1.5, 4h	11
6	12	Pre, 1.5, 4h	Pre	Pre, 1.5, 4h	Pre	Pre, 1.5, 4h	11

<u>Pharmacokinetic sample time collection windows are:</u>
1.5 hours=1 to 2 hours
4 hours=4 to 6 hours

CARDIOLOGY EVALUATIONS FOR ARMS 5 AND 6