IMPAACT 2010:
Phase III Study of Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing ART Regimens in HIV-1-Infected Pregnant Women and their Infants

Protocol Team

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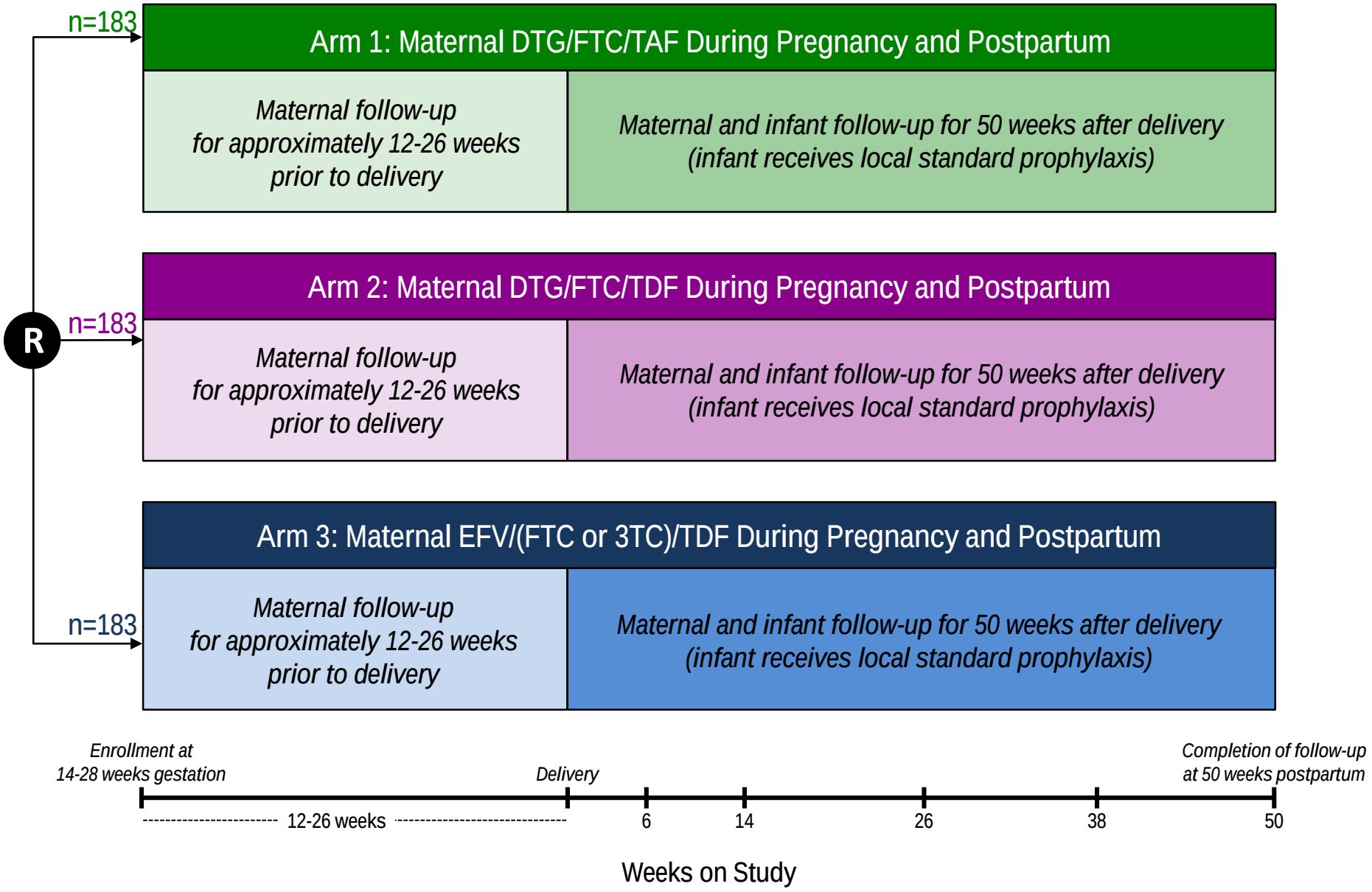
Study 2010 Design

- Randomized 1:1:1 open label 3-arm treatment trial in HIV-infected pregnant women (183/arm, 549 total)
  - DTG/TAF/FTC
  - DTG/TDF/FTC
  - EFV/TDF/XTC
- Women start ART at 14-28 weeks gestation
- Mothers and their children followed through 50 weeks postpartum

Study 2010 Design, Continued



Study 2010 Design, Continued

- Will be preceded by lead-in phase in which up to 25 women will undergo TAF pregnancy PK testing (through co-enrolment in P1026s)
- Study sites: planning communications with the sites shortly

Primary Objectives

- To determine whether a DTG-containing regimen (DTG arms combined) is superior to EFV/(3TC or FTC)/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery
- To determine whether rates of the following safety outcomes differ for any pairwise regimen comparison (between the 3 regimens):
    - Adverse pregnancy outcomes (composite endpoint of spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
    - Maternal grade 3 or higher adverse events through 50 weeks postpartum
    - Infant grade 3 or higher adverse events through 50 weeks postpartum

Secondary & Exploratory Objectives

- Non-inferiority of DTG-containing regimens compared with EFV/(3TC or FTC)/TDF with regard to virologic suppression (<200 cp/mL) at delivery
- Additional comparisons of rates of virologic suppression
    - To <200 cp/mL at 50 weeks postpartum
    - To <50cp/mL at delivery
    - By FDA snapshot algorithm
- Composite adverse pregnancy outcome including congenital anomalies
- Bone: DXA (subset of infants at 26 wks, mothers at 50 wks postpartum)
- Renal toxicity (mothers and infants)
- MTCT, ARV drug resistance (in HIV+ infants, mothers with VF)

- Exploratory objectives:
  - Mother-infant ARV transfer at birth and from breast milk
  - Adherence
  - Postpartum depression
  - Outcomes of new pregnancies occurring on-study
  - Hormonal, inflammatory markers of adverse pregnancy (and maternal health) outcomes

Key Inclusion / Exclusion Criteria

- **Inclusion:**
  - HIV-infected pregnant women with evidence of viable singleton pregnancy
  - Not on ART at entry
    - Prior ARVs during pregnancy, breastfeeding permitted (must have stopped these at least 6 months prior to entry)
    - Up to 10 days of ART during current pregnancy permitted
- **Exclusion:**
  - Taking medication to treat psychiatric illness, active TB, or HCV
  - H/O suicidal ideation or known significant adverse reaction to any of study ARVs
  - Known/suspected major congenital anomaly

Note: fetal ultrasound required during screening or within 14 days of entry, but not required prior to entry

Maternal Antepartum Schedule of Evaluations

			Weeks During Pregnancy				Post	
Study Visit	Screen	Entry	Week 4	Week 8	Week 12	Q4 Weeks[1]	ARV	Early
Visit Window	up to -10 d	Day 0	±2 wks	±2 wks	±2 wks	±2 wks	Switch[2]	D/C[3]
MATERNAL EVALUATIONS								
Informed consent[4]	X							
Maternal medical history	X	X	X	X	X	X	X	X
ARV adherence questionnaire			X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Fetal ultrasound	during screening or within 14 days after entry							
Confirmatory pregnancy testing[5]	0-1 mL							
Confirmatory HIV testing	0-6 mL							
Hepatitis B surface antigen		3 mL						
AST, ALT, creatinine, CrCl	4 mL		4 mL		4 mL	4 mL Wk 24	4 mL	4 mL
Complete blood count	3 mL							
CD4+ cell count		3 mL						
HIV-1 RNA (store residual plasma)		6 mL	6 mL	6 mL	6 mL	6 mL Wk 24	6 mL	6 mL
Perform Only For Phase III Study								
Stored plasma	6 mL							
Stored plasma and cell pellets		10 mL		10 mL				
Stored urine		15 mL						15 mL
Total blood volume: Lead-In	7-13 mL	12 mL	10 mL	6 mL	10 mL	0-10 mL	10 mL	10 mL
Total blood volume: Phase III	13-20 mL	22 mL	10 mL	16 mL	10 mL	0-10 mL	10 mL	10 mL

Maternal Postpartum Schedule of Evaluations

	Delivery	Weeks Postpartum					Post	Confirmation	
Study Visit	up to 14 d New Day 0	6	14	26	38	50	ARV Switch[1]	of Virologic Failure	Early D/C
Visit Window		±2 wks	±6 wks	±6 wks	±6 wks	±6 wks			
MATERNAL EVALUATIONS									
Maternal medical history	X	X	X	X	X	X	X	X	X
ARV adherence questionnaire	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	[X]	X
AST, ALT, creatinine, CrCl	4 mL		4 mL	4 mL		4 mL	4 mL		4 mL
Complete blood count				3 mL		3 mL			
CD4+ cell count				3 mL		3 mL			
HIV-1 RNA (store residual plasma)	6 mL		6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
Perform Only For Phase III Study									
Stored plasma	6 mL	6 mL						6 mL	
Stored plasma and cell pellets	10 mL					10 mL			
Stored breast milk		20 mL							
Stored urine						15 mL			15 mL
Stored hair	X								
DXA scan (at selected sites)						X			
Depression assessment (EPDS)		X				X			
Total blood volume: Lead-In	10 mL	0 mL	10 mL	16 mL	6 mL	16 mL	10 mL	6 mL	10 mL
Total blood volume: Phase III	26 mL	6 mL	10 mL	16 mL	6 mL	26 mL	10 mL	12 mL	10 mL

Infant Schedule of Evaluations

INFANT EVALUATIONS							
	Delivery	Weeks of Age					
Study Visit	up to 14 d	6	14	26	38	50	Early
Visit Window		±2 wks	±6 wks	±6 wks	±6 wks	±6 wks	D/C
Infant medical and feeding history	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
HIV NAT (store residual plasma)	3 mL	4 mL	3 mL	3 mL if BF	3 mL if BF	3 mL	3 mL
ALT and creatinine	1 mL			1 mL if BF			
Complete blood count	1 mL			1 mL if BF			
Perform Only For Phase III Study							
Stored hair	X						
DXA scan (at selected sites)				X			
Total blood volume	5 mL	4 mL	3 mL	0-5 mL	0-3 mL	3 mL	3 mL

Timelines

- Protocol resubmitted on 8 June 2016 to MPRG
- Plan to submit to CSRC this month
- Aiming for final protocol by August 2016
- Anticipate that initial sites would start in first quarter of 2017
- Completion of TAF pregnancy PK lead-in phase 6-12 months
  - Will depend on # of women enrolling in unboosted TAF arm of P1026s prior to 2010; pace (and timing in gestation) of co-enrolment
- Completion of accrual to 2010 anticipated to take 8 months
- Potential challenges with timelines:
  - Completing CTA with Gilead for FTC/TAF (and FTC/TDF)
  - Finalizing purchase or donation of generic EFV/(3TC or FTC)/TDF

Discussion

- Many thanks to Elaine Abrams, Sharon Nachman, James McIntyre, and David Shapiro for guidance and support – and to protocol team