MTN 003D Overview: An Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial

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Outline

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   - Study Objectives
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   - Study Objectives
   - Study Sites & Sample
   - Study Design and Data Collection Tools
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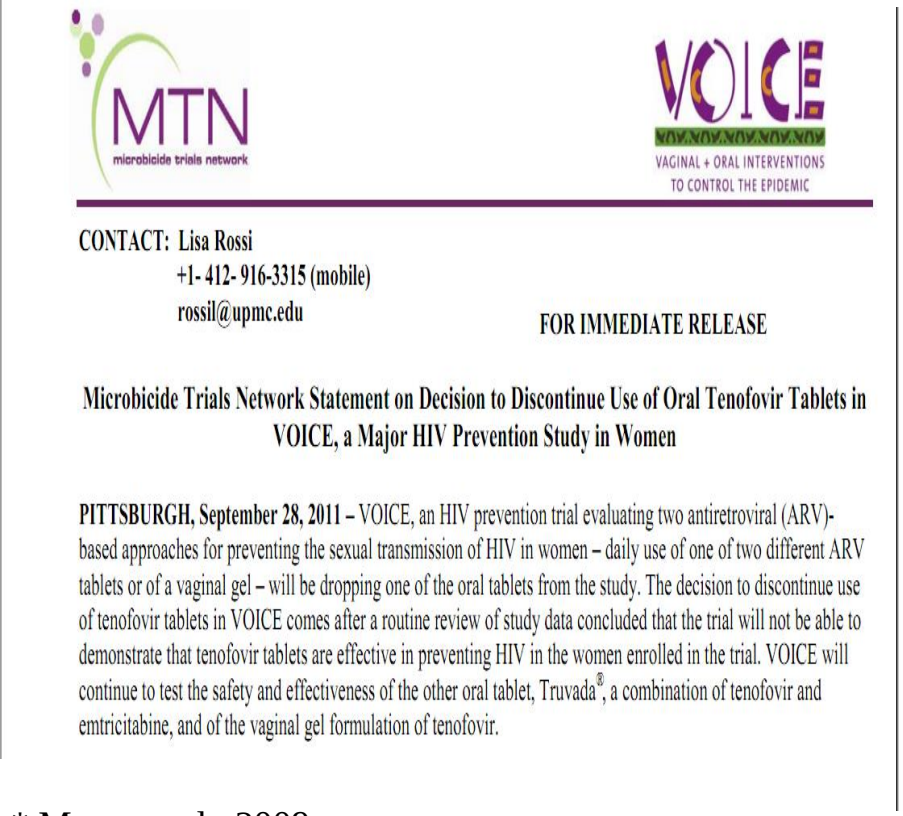
   - Study Team & Key Roles

Stage 1

Background: Dilution of Efficacy*?

- DSMBs futility results:
  tenofovir vaginal gel & oral tablet stopped



MTN microbicide trials network

VOICE VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

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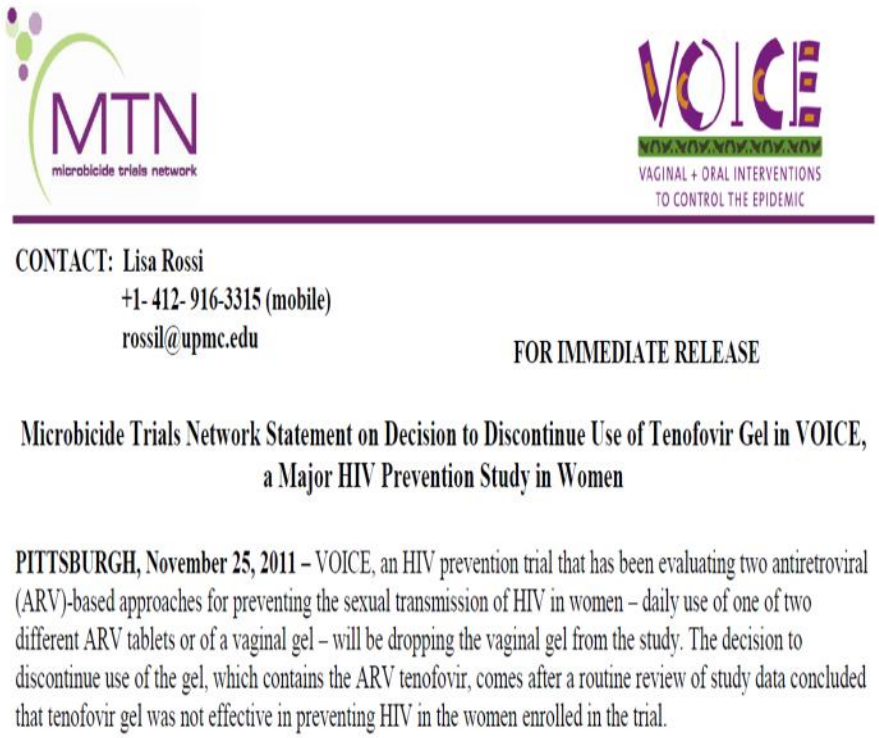
FOR IMMEDIATE RELEASE

Microbicide Trials Network Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women

PITTSBURGH, September 28, 2011 – VOICE, an HIV prevention trial evaluating two antiretroviral (ARV)-based approaches for preventing the sexual transmission of HIV in women – daily use of one of two different ARV tablets or of a vaginal gel – will be dropping one of the oral tablets from the study. The decision to discontinue use of tenofovir tablets in VOICE comes after a routine review of study data concluded that the trial will not be able to demonstrate that tenofovir tablets are effective in preventing HIV in the women enrolled in the trial. VOICE will continue to test the safety and effectiveness of the other oral tablet, Truvada®, a combination of tenofovir and emtricitabine, and of the vaginal gel formulation of tenofovir.



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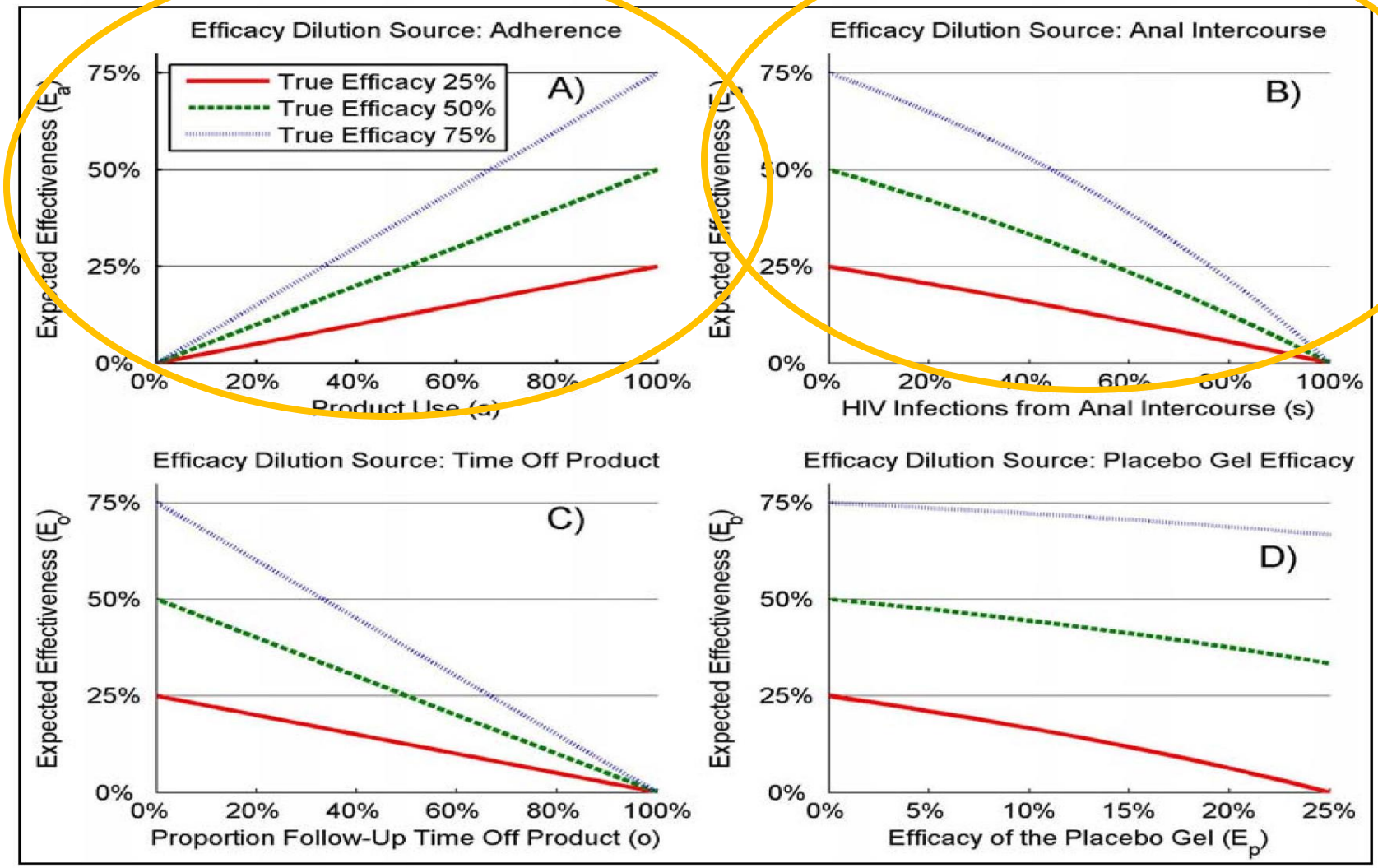
Microbicide Trials Network Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women

PITTSBURGH, November 25, 2011 – VOICE, an HIV prevention trial that has been evaluating two antiretroviral (ARV)-based approaches for preventing the sexual transmission of HIV in women – daily use of one of two different ARV tablets or of a vaginal gel – will be dropping the vaginal gel from the study. The decision to discontinue use of the gel, which contains the ARV tenofovir, comes after a routine review of study data concluded that tenofovir gel was not effective in preventing HIV in the women enrolled in the trial.

* Masse et al., 2009

Sources of Efficacy Dilution



* Masse et al., 2009

Adherence

P24_1G. Please rate your ability, over the **past 4 weeks**, to insert gel exactly as you were instructed.

1. [ ] Very poor
2. [ ] Poor
3. [ ] Fair
4. [ ] Good
5. [ ] Very good
6. [ ] Excellent

We are most **interested in knowing on how many days you inserted gel. So if you cannot remember** which day(s) **exactly you** did insert gel, please guess. We **prefer that** you indicate that you missed **some** days, even if you cannot remember which **exact** days you missed.

NOTE: Q25aG repeats going backwards 7 days starting with yesterday.

25aG. Yesterday (x-day) did you insert gel?

1. Yes
2. No
3. Don't remember

MTN 001 Trial: discrepancy between self report and plasma drug level

- After observed dosing, ALL had detectable plasma TFV
- After 6 weeks of home dosing:

Daily TFV oral tablet

38% of participants:

had TFV plasma levels inconsistent with daily dosing

BUT

reported 100% adherence

Daily TFV vaginal gel

48% of participants:

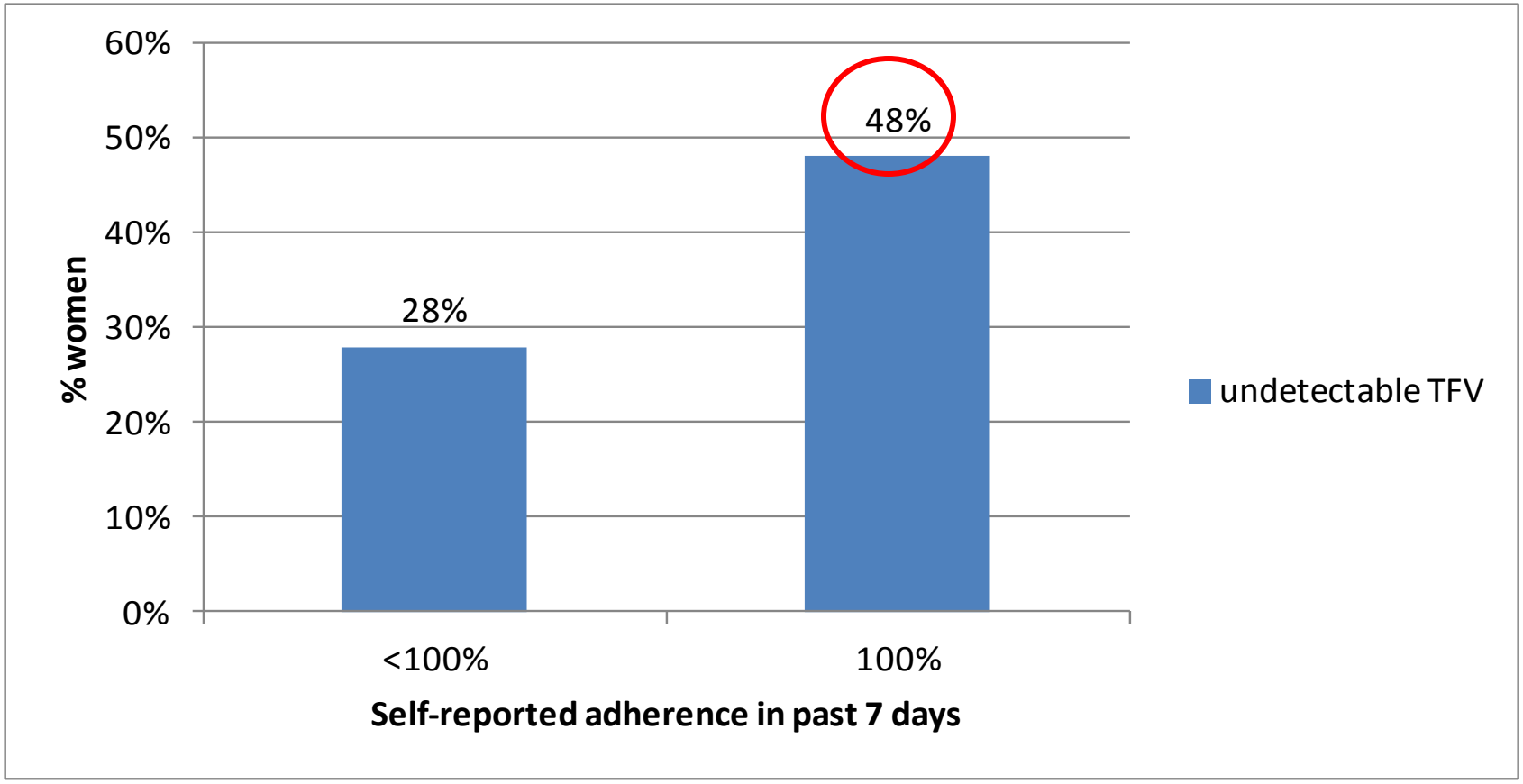
had undetectable TFV plasma levels

BUT

reported 100% adherence

Minnis et al., 2012; van der Straten M2012

MTN-001: Adherence to Vaginal Gel



- Those reporting 100% adherence were **more** likely to have undetectable plasma drug level (p=0.02)

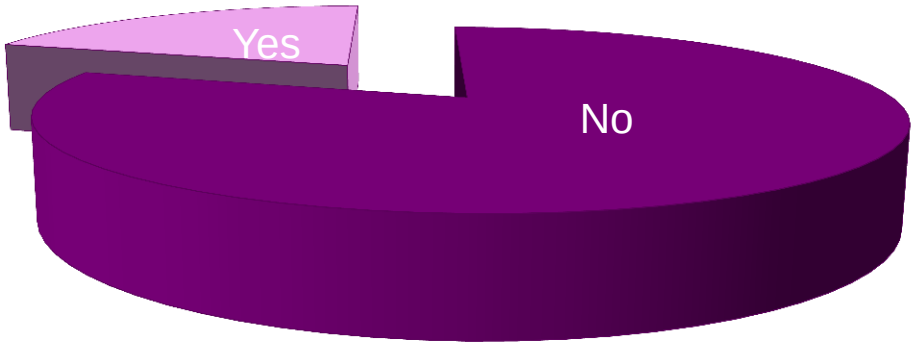
Anal Sex

11. In the **past 3 months** how many times have you had anal sex? By anal sex we mean when a man puts his penis inside your anus.

0 → **Skip to Q12**
1
2
3
4
5
6
7 or more times

Version 5.0 March, 30, 2009

Reported 1 or More Anal Sex Acts in the Past 3 Months?



Study Objectives

- Primary:
  - to explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants' actual and reported product use
  - to explore the reasons, motivations, and context of engaging in receptive anal intercourse (and rectal use of gel among VOICE participants in the gel group)
- Secondary:
  - to explore participants' risk perceptions and motivations to participate in VOICE and the association of these factors with product use or non-use in a prevention trial setting

Study Sites & Sample Size

- Uganda
  - Kampala (MU-JHU, n=22)
- Zimbabwe
  - Chitungwiza (Seke South and Zengeza, n=26)
- South Africa
  - Durban (Isipingo and Overport, n=40)

Overall Stage 1 Sample

- Former VOICE participants

Study group:	Gel Users	Tablet Users	Total
Reported Anal Sex	18 [4]	17 [4]	35 [8]
Sero-converters	5 [4]	5 [4]	10 [8]
All other women	20 [32]	23 [32]	43 [64]
Total	43 [40]	45 [40]	88 [80]

*Target accrual numbers presented in brackets

Relevant Stage 1 Findings

- Participants largely did not admit to non-adherence
- Participants suggested that presenting women with blood test results would encourage honesty in reporting adherence

Stage 2

Final VOICE Results

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FOR IMMEDIATE RELEASE

Daily HIV prevention approaches didn't work for African women in the VOICE Study

Truvada found not an effective strategy in this population
Young, single women were least likely to use tablets or gel, and more likely to get infected at very high rates

ATLANTA, March 4, 2013 – Results of a major HIV prevention trial suggest that daily use of a product – whether a vaginal gel or an oral tablet – does not appear to be the right approach for preventing HIV in young, unmarried African women.

Of the three products tested in the VOICE Study – tenofovir gel, oral tenofovir and oral Truvada® – none proved to be effective among the 5,029 women enrolled in the trial; most participants did not use them daily as recommended. Drug was detected in less than a third of blood samples from women who were assigned to use either Truvada or oral tenofovir and in less than a quarter of samples from women designated to use gel. Moreover, those least likely to use their assigned products, single women under age 25, were also the most likely to acquire HIV. Incidence in these young women approached nearly 10 percent in some of the study sites in South Africa, a

Tenofovir Detection During Study Participation*

	TDF	FTC/TDF	TFV Gel
Percent of *women* with TFV not detected in *any* samples	58%	50%	55%

* At routine quarterly visits among participants in the random sample of active arms

Adherence from 3 Different Measures

	TDF	FTC/TDF	TFV Gel
Total percent of doses reportedly taken*			
Returned Pill or Applicator Counts	87%	92%	86%
Self Report (7 days)	90%	91%	90%
Adherence based on plasma TFV detection			
Percent of *samples* with TFV detected averaged across women (mean)	**30%**	**29%**	**25%**

* Mean across all women's proportion of adherence estimated by these measure

Tenofovir Detection with Plasma Testing:

- Assay is more sensitive for oral (tablets) than vaginal (gel) dosing
- Window of detection is longer for oral (tablets) than vaginal (gel) dosing
- Tablets: TFV detectable for up to ~7 days
- Gel: TFV detectable for up to ~ 3 days

No drug detected=

- **Tablets: no dose taken in past week**
- **Gel : no dose taken in past 3 days**

Study Objectives

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  - to explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants' actual and reported product use
  - ~~to explore the reasons, motivations, and context of engaging in receptive anal intercourse (and rectal use of gel among VOICE participants in the gel group)~~
- Secondary:
  - to explore participants' risk perceptions and motivations to participate in VOICE and the association of these factors with product use or non-use in a prevention trial setting

Study Sites & Sample Size

- Uganda
  - Kampala (MU-JHU, n~=48)
- Zimbabwe
  - Chitungwiza (Seke South and Zengeza, n~=48)
- South Africa
  - Durban (Isipingo and Overport, n~=48)

Overall Stage 2 Sample

- Former VOICE participants (both MTN-003D naïve and experienced)

		~ No. of IDIs/FGDs *			
Drug Detection Level**	**Study Group**	**HIV(+)**	**HIV(-)**	**~Total FGDs/IDIs**	**~Total No. of Participants**
Low drug detection per PK results	Gel	6 IDI	12 IDI 6 FGD⌂	**24**	**54**
	Tablet	6 IDI	12 IDI 6 FGD⌂	**24**	**54**
High drug detection per PK results	Gel	6 IDI	12 IDI	**18**	**18**
	Tablet	6 IDI	12 IDI	**18**	**18**
TOTAL		**24**	**60**	**84**	**144**

Stage 2 Sample per Location

		~ No. of IDIs/FGDs *			
Drug Detection Level**	**Study Group**	**HIV(+)**	**HIV(-)**	**~Total FGDs/IDIs**	**~Total No. of Participants**
Low drug detection per PK results	Gel	2 IDI	4 IDI 2 FGD⌂	**8**	**18**
	Tablet	2 IDI	4 IDI 2 FGD⌂	**8**	**18**
High drug detection per PK results	Gel	2 IDI	4 IDI	**6**	**6**
	Tablet	2 IDI	4 IDI	**6**	**6**
TOTAL		**8**	**20**	**28**	**48**

Stage 2 Design & Data Collection Tools

- Qualitative Exploratory Study
- Instruments:
  - Demographic survey
  - Discussion Guide [IDI & FGD]
- Available Tools:
  - Section A. MTN press release, educational sheet for study results; local press clippings
  - Section B. Timeline tool; PK visuals
  - Section C. Theme identification cards; pictures of prevention products

Study Timeline and Updates

May 012	• Protocol v1.0 approved
July 012	• Qualitative training (Durban)
Sept 012	• Full IRB approval (MRC) • First IRB approval (MUJHU)
1 Oct 012	• Protocol specific training (Cape Town)
Oct 012	• All sites activated • Stage 1 data collection starts
Mar 012	• Stage 1 data collection ENDS
May 013	• Protocol v2.0 approved
Oct 013	• **Stage 2 qualitative training (Durban)** • **Local IRB approvals obtained for Stage 2 and data collection begins**
Dec 013	• **Stage 2 data collection ends**

Study Team and Key Roles

Core/US

- **Chair**: Ariane van der Straten,
- **Co-chairs**: Liz Montgomery, Barbara Mensch
- **Operations (FHI 360)**: Lisa Levy, Kristy Alston
- **Data coordination (RTI/WGHI)**: Miriam Hartmann
- **MTN Core**: Beth Galaska Burzuk
- **DAIDS**: Jeanna Piper

Site Teams

- **UZ-UCSF**: Nyaradzo Mgodi, Petina Musara, Imelda Makhala, Otilia Munaiwa
- **MU-JHU**: Clemensia Nakabiito, Juliane Etima, Teopista Tibaijuka, Josephine Nabukerra
- **MRC**: Sarita Naidoo, Kubashni Woeber, Funeka Mthembu, Nozipho Vilakazi

Behavioral Consultants

- **DTHF:** Zoe Duby, Thola Bennie

QUESTIONS?