VOICE: The Road to Study Completion

MTN Regional Meeting, October 11, 2011

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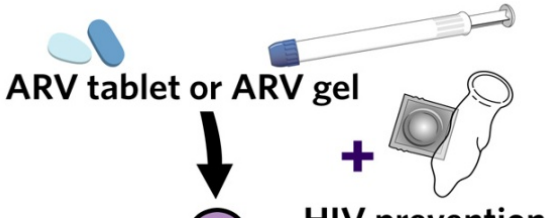
VOICE

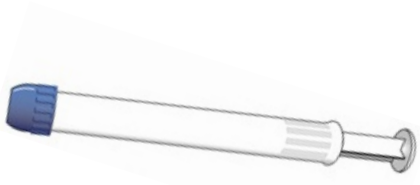
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

Overview

- From implementation to today
  - Accomplishments
    - Accrual, retention, adherence
  - Challenges
    - Retention, adherence, DSMB
- Towards study closure

VOICE 2.0 (MTN 003)





5,000 Women

- Tablet (3,000)
  - Truvada (1,000)
  - Tenofovir (1,000)
  - Placebo Tablet (1,000)
- Vaginal Gel (2,000)
  - Tenofovir Gel (1,000)
  - Placebo Gel (1,000)

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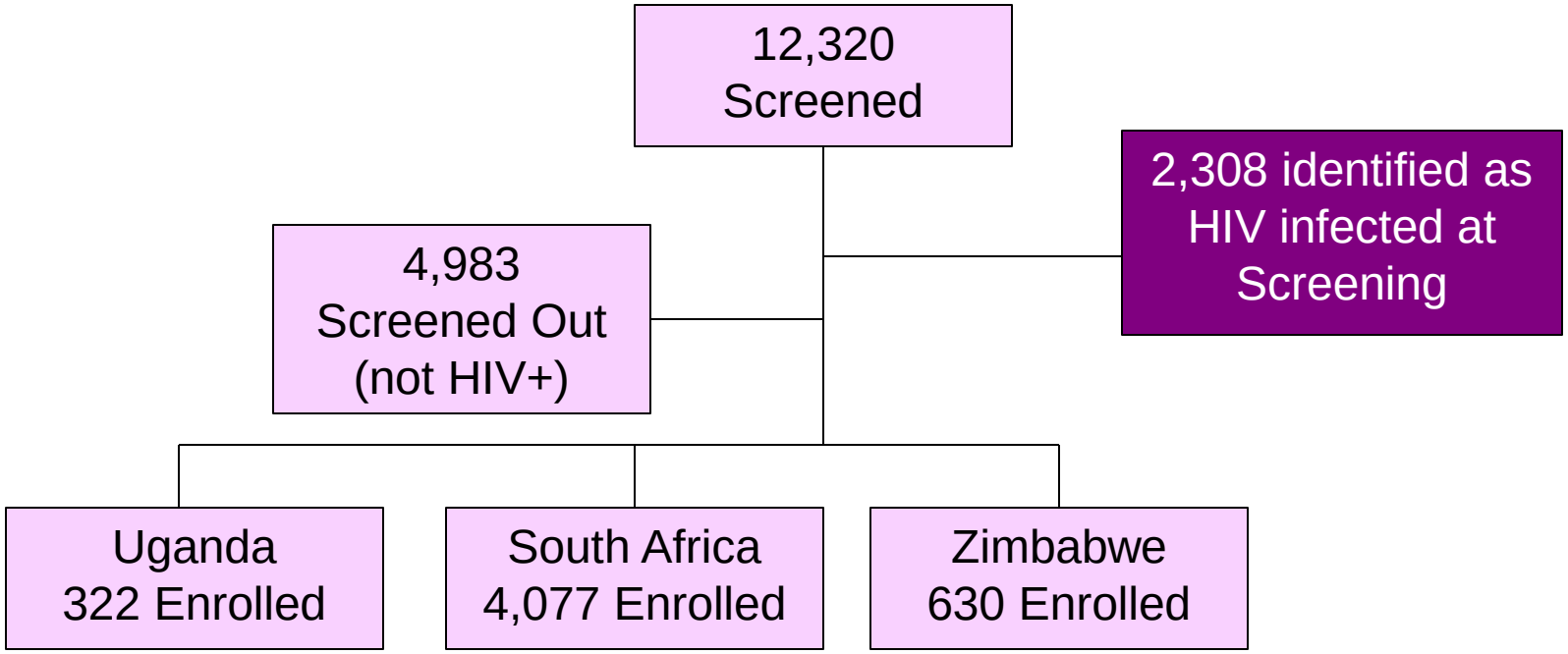
VOICE: Accrual Completed 6/7/11



Total Enrollment = 5,029
Overall Screen to Enroll Ratio = 2.4:1

VOICE: Our Participants*

	SA N = 4077	Uganda N = 322	Zim N = 630
Age	24.7	28.3	28.1
% < 25 y-o	55%	25%	26%
Married	8%	50%	94%
Education (≥ secondary school)	54%	3%	60%
Recent sex with non-primary partner	21%	61%	6%
Condom at last vaginal sex	78%	53%	76%
Anal sex act in the last 3 months (ACASI) - Condom use last act	20% 70%	7% 54%	7% 60%

* Characteristics reported at enrollment

VOICE: Pregnancy Incidence*

	SA N = 3912	Uganda N = 314	Zim N = 619	ALL
PY of follow-up	1898	243	470	2610
No. who became pregnant	112	30	20	162
Incidence rate (per 100 PY)	5.9	12.4	4.3	6.2
95% CI	4.8-7.1	8.3-17.6	2.6-6.6	5.3-7.2

* Through July 1, 2011

Retention Strategies

- Participant-centered approaches
  - Transportation
  - Flexible clinic hours
  - Visit reminders
  - Participant rapport
  - Comfortable clinic environment
  - Male involvement
- Overall Site approaches
  - Peer educators/outreach retention workers
  - Expedited visit flow
  - 2-months product dispensation (per participant needs)
  - Retention committee to review difficult cases

Follow-up Expected & Retained

	*As of 11 March 2011	*As of 1 July 2011
Total Person-Years of Follow-up Retained	92%	92%
Per Woman: Percentage of Expected Follow-up Time Retained		
0%	3%	3%
1-49%	5%	5%
50-74%	5%	3%
75-99%	6%	4%
100%	81%	85%

Adherence in VOICE

- VASP is a strengths-based approach, focusing on participant's *experiences* using the products (what makes it easier/harder), identifying adherence-related needs, and strategies to address these needs
  - Key is to avoid directive "counseling"
- As of 1 June 2011, all sites had implemented VASP
  - Well-received by counselors & participants
  - Sessions reportedly taking less time, participants more open to discussing issues with product use
  - Encouraging trends in self-reported adherence

DSMB, November 16, 2011

- Fifth review of VOICE
- Data through July 1, 2011

What were the recommendations?

"The oral single-drug arm of TDF should be stopped be re is now clear evide better than the placeb pants should be informe se in the TDF arm u treatment and have a active and placebo, discontinued as soon as possible."

Translation:

It is clear tenofovir tablets do not work in VOICE. Tell the VOICE participants as soon as possible. Take the participants off of active tenofovir tablets and placebo for tenofovir tablets as soon as possible.

Recommendation #2

"The DSMB acknowledges and supports the team's pla rticipants in January 20 rd recommen F arm have study soon as possible a y prior to others."

Translation:

Take the participants off of active tenofovir tablets and placebo for tenofovir tablets as soon as possible.

Recommendation #3

"The oral combination of FTC/TDF, and oral FTC/TDF-p active and placebo va ms should be continu The TDF-placebo st discontinue both active and on arms."

Translation:

Continue the other arms in VOICE, except stop the tablets that were the placebo for tenofovir tablets.

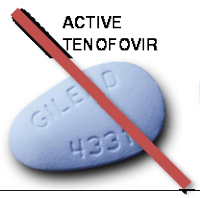
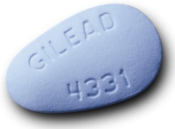
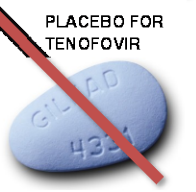
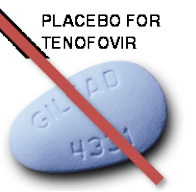
Recommendation #4

"The DSMB has no concerns regarding conduct, s MTN-003B substudy b at those in the TDF st ed from the substudy a

Translation:

Even though there are no safety concerns, or problems with study conduct, stop the tenofovir tablets for participants in VOICE-B, too.

Recommended Changes to Arms

	Before September 2011 DSMB	September 2011 DSMB Recommendation
1% Tenofovir Gel Arm	 ACTIVE TENOFOVIR GEL	 ACTIVE TENOFOVIR GEL
Placebo Gel Arm	 PLACEBO GEL	 PLACEBO GEL
Tenofovir Tablet Arm (TDF Tablet Arm)	ACTIVE TENOFOVIR  PLACEBO FOR TRUVADA 	ACTIVE TENOFOVIR  PLACEBO FOR TRUVADA 
Truvada Tablet Arm (FTC/TDF Tablet Arm)	PLACEBO FOR TENOFOVIR  ACTIVE TRUVADA 	PLACEBO FOR TENOFOVIR  ACTIVE TRUVADA 
Placebo Tablet Arm	PLACEBO FOR TENOFOVIR  PLACEBO FOR TRUVADA 	PLACEBO FOR TENOFOVIR  PLACEBO FOR TRUVADA 

Impact on Study Questions?

Some VOICE/VOICE B Objectives	Impact of DSMB Outcome
Effectiveness of Tenofovir Tablets	Considered Answered – NOT EFFECTIVE IN VOICE POPULATION
Safety of Tenofovir Tablets	Considered at least partially answered, no safety concerns noted
Effectiveness of TDF/FTC Tablets, TFV Gel	Not yet answered
Safety of Other Products	Not yet answered, but no safety concerns thus far
Impact of Tenofovir Tablets on Short-term and Longer-term Outcomes for Bone Density	Ability to answer questions was cut short

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DSMB Outcome Implementation

- October 3:
  - Began unblinding TDF arm
  - Discontinue light blue pill in TDF/FTC arm
  - Ensure that plasma is collected at the product use end visit
  - Schedule for 8-week post-PUEV evaluation

Participants' Reactions: Oral TDF

- Dismay & disappointment at having to exit study early (abandonment)
- Loss of benefits & concern that future study participation could be affected
- Questioning role of adherence in result
- Desire to receive one of the other study products (especially gel)
- Concern about future DSMB
- Questions about infections in active vs placebo
- Effect on future studies in HIV prevention
- Notable concern for VOICE B participants

Potential Effects?

- Adherence to product (especially oral arms)
- Retention
- Reinforcement of fatalism about potential for preventing HIV through chemoprophylaxis
- Social stigma
  - Were women being exited because they acquired HIV in the study?

Planning Ahead for Study Closure

- Team has targeted early January for initiation of end of product visits in women with ≥18 months participation
  - Will continue through end of May when last enrolled participants will come off product
  - All participants will be followed for additional 8 weeks for post-product use seroconversion endpoint assessment
- This plan will facilitate
  - Orderly sequence of closure
  - Distribution/ ease of heavy burden for sites conducting end-of-study visits
  - Compliance with FDA requirements that all be followed on product for ≥12 months
  - Inclusion of maximal number of drug biomarker specimens

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VOICE: Contribution to Evidence Base

- Large number of person-years of follow-up
- Diverse population including
  - Married women: may know partner's HIV status
  - Unmarried women (South Africa)
    - Unlikely to know partner's HIV status
    - Likely impacts motivation to adhere to study product
  - Young women (notable relative to Partners)
  - Probable wider range of adherence given population
- Only trial that includes TFV gel arm
  - If effective, will contribute pivotal data for licensure for HIV & HSV-2 prevention indication

Summary

- VOICE has answered an important question about efficacy of oral TFV as PrEP in women
  - Explanation for these findings will be critical
- Team efforts since September DSMB have been heroic
  - Majority of participants contacted; substantial number of PUEVs completed
  - Complexity of participants' question reflect quality of ongoing informed consent process
- Need sustained effort to ensure contribution of our study of the remaining study products!

THANKS

- To our participants and the amazing VOICE team!!!

- SCHARP & FHI teams
- Pittsburgh MTN core
- Network Lab
- NIH leadership

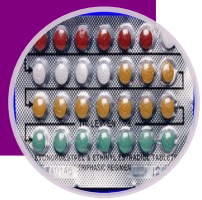
VOICE Exploratory Aims

- Candidate biomarkers – intrinsic and functional immunity

Vaginal Microenvironment

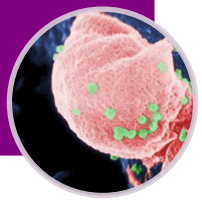
- Potential relationship between BCM, seroconversion, adherence

Contraception



- HSV-1 and HSV-2 seroconversion by type-specific antibody assay

HSV-1 and HSV-2 Seroconversion



PrEP Trials Involving Women

Trial	Population / Active Arm(s)	N (%) Women	P-Y	Efficacy	Comments
FEM-PrEP	Heterosexual women Daily TDF/FTC	1,951	~1,100	0%	Anticipate analyses late 2011
TDF2	Heterosexual men & women Daily TDF/FTC	550 (46)	?	63%	Small no. endpoints; sub-analysis
Partners in Prevention	Serodiscordant couples Daily TDF or TDF/FTC	1,785 (38%)	F: 2,753 M: 4,587	TDF W 68% (CI 29-85) M 55% (CI 4-79) FTC/TDF W 62% (CI 19-82) M 83% (CI 49-94)	Adherence very high; median age of women higher than VOICE (30s); both members of couple consented
VOICE	Heterosexual women Daily TDF or TDF/FTC	5,029 (100)	F:6,500	TDF not effective Other data pending	Only trial to provide data on TFV gel for both HIV and HSV-2 endpoints