Review of PrEP and Rectal Microbicide Safety Data

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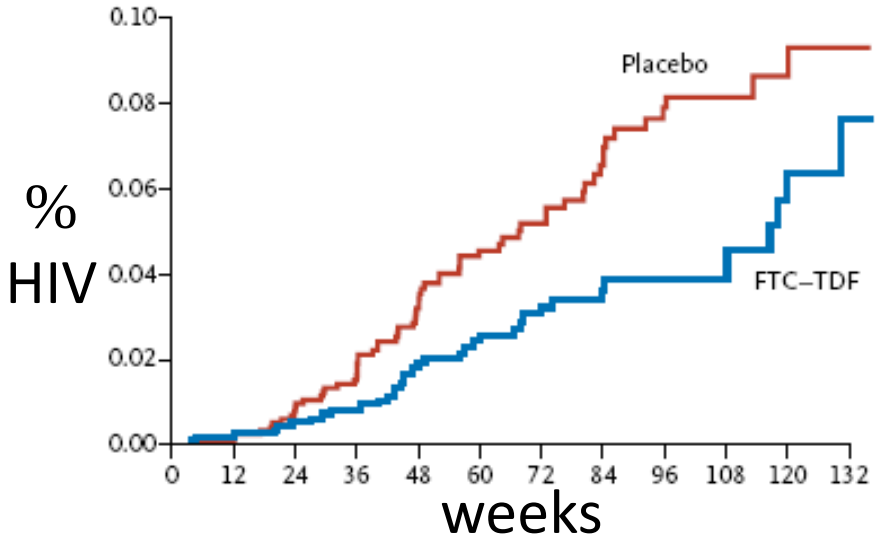
Outline

- iPrEx Study: FTC/TDF
- MTN 007: reduced glycerin 1% tenofovir gel

iPrEx study

- Study: Phase III multicenter trial of 2499 HIV negative MSM or transgender women randomized to receive placebo vs. FTC/TDF
- Median follow up 1.2 years
- Primary Endpoints:
  - AEs
  - HIV seroconversion



Grant NEJM 2010;363:2587

MTN 017 versus iPrEX

- Duration of exposure to FTC/TDF
  - MTN 017: 8 weeks
  - iPrEx: median follow up 1.2 years
- No placebo group in MTN 017
  - May impact adherence (since participants know they will be getting active drug)

iPrEx: Adverse Events

Adverse Event	FTC/TDF (n = 1251)		Placebo (n = 1248)		P Value
	%	Events	%	Events	
Any grade 3/4 event	12	248	13	285	0.51
Death	< 1	1	< 1	4	0.18
Serious adverse event	5	76	5	87	0.57
Elevated creatinine	2	28	1	15	0.08
Creatinine elevation confirmed on next visit	0.4	7.0	0	0	0.06

Grant R, et al. CROI 2011. Abstract 92.

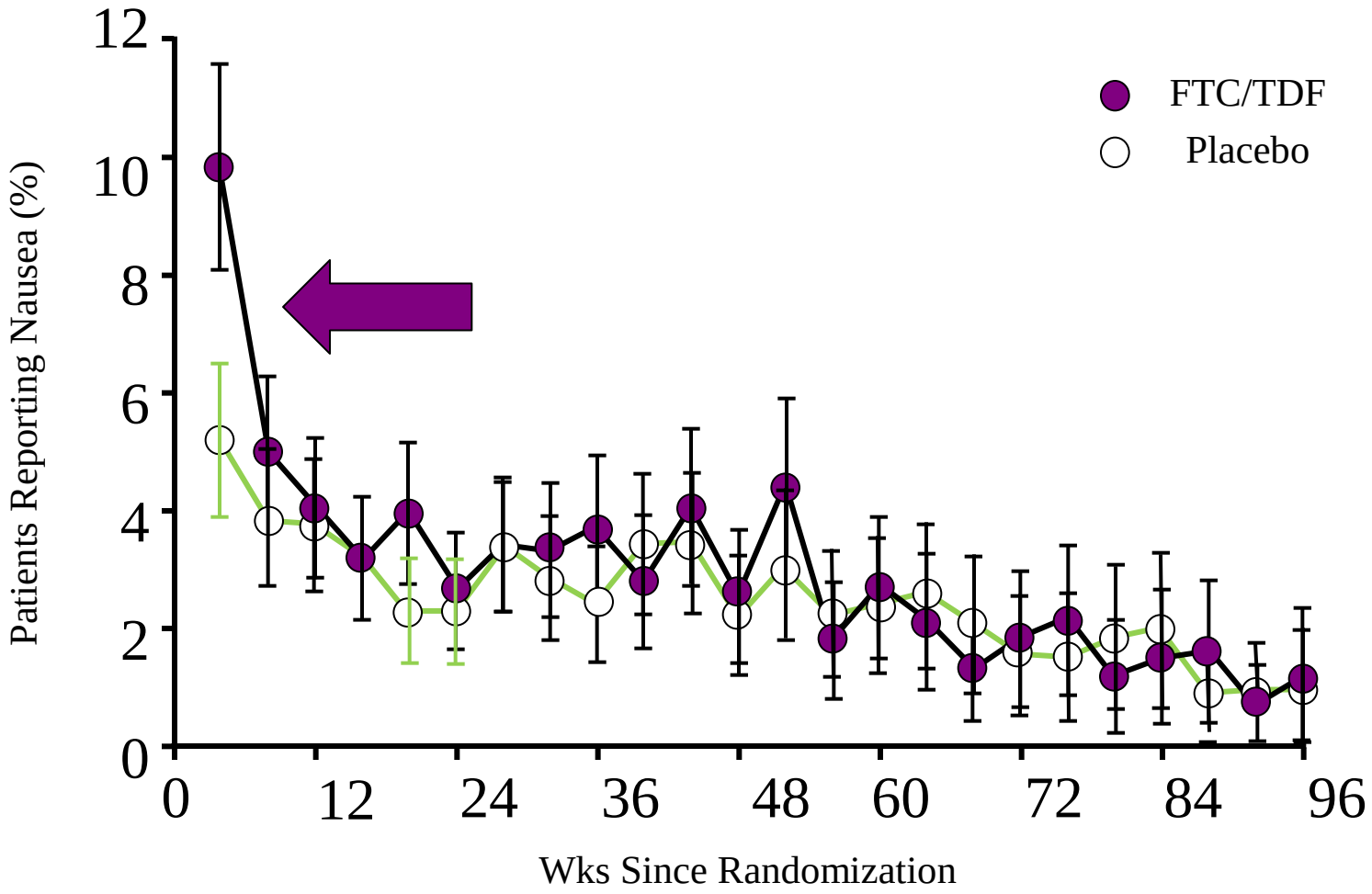
iPrEx: Adverse Events

Adverse Event	FTC/TDF (n = 1251)		Placebo (n = 1248)		P Value
	%	Events	%	Events	
Elevated creatinine*	2	28	1	15	0.08
Headache	4	66	3	55	0.10
Nausea	2	22	<1	10	0.04
Weight decrease	2	34	1	19	0.04

*Creatinine elevation defined as 1.1x upper limit of normal or 1.5x baseline
*36(88%) values were not confirmed on repeat testing

Grant R, et al. NEJM

iPrEx: Nausea on History



Grant RM, et al. N Engl J Med. 2010;363:2587-2599.

Fracture Rates

- BMD changes with TDF or FTC/TDF were small; no evidence of negative effect on health
- No differences in fracture rates between groups[1-3]
- All fractures were trauma related
- Need longer follow-up to evaluate effects on bone density and fracture risk over time

Grohskopf L, et al. AIDS 2010. Abstract FRLBC102. Mulligan K, et al. CROI 2011. Abstract 94LB.
Grant RM, et al. N Engl J Med. 2010;363:2587-2599.

Summary Points

- Overall, FTC/TDC and placebo groups had similar rates of adverse events
- Trend towards creatinine elevation in the FTC/TDF group
- Moderate nausea (Gr 2 and above) and unintentional weight loss seen more in the FTC/TDF group
- Ability to detect safety outcomes potentially compromised by poor adherence

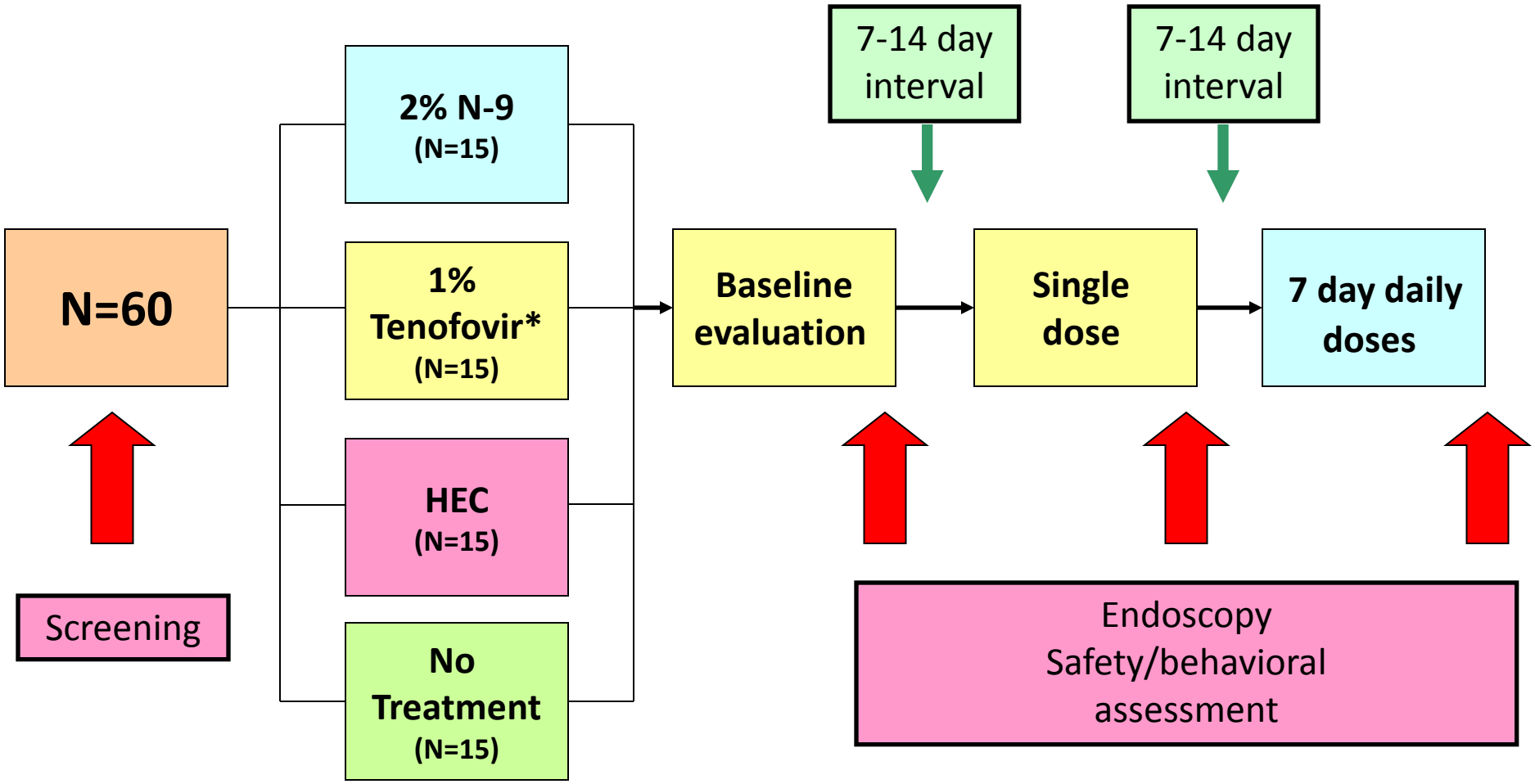
Rationale for MTN-007

- To characterize the safety and acceptability of a reduced glycerin (RG) formulation of TFV 1% gel
  - Original TFV 1% gel: 3111 mOsmol/kg
  - RG TFV 1% gel: 836 mOsmol/kg
  - Iso-osmolar: 290 mOsmol/kg
- Also, to evaluate the utility of a broad range of biomarkers of mucosal safety

MTN 007

- Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel
  - Study population (N=65): receptive anal intercourse-abstinent, HIV uninfected men and women
    - Fenway clinic
    - Pittsburgh
    - Alabama

MTN-007 Study Design



*1% tenofovir reduced glycerin formulation

McGowan PLoS One 2013

MTN 007

- Primary objective
  - To evaluate the safety of tenofovir 1% gel when applied rectally
- Primary endpoint
  - AEs $\geq$ Grade 2 or higher

Baseline Demographics by Arm

	All Arms	TFV Gel	N9 Gel	HEC	No Rx
N	65	16	17	16	16
Mean Age	35.7	35.3	37.0	36.8	33.5
Gender					
• **Male (%)**	45 (69%)	10 (63%)	13 (76%)	12 (75%)	10 (63%)
• **Female (%)**	20 (31%)	6 (38%)	4 (24%)	4 (25%)	6 (38%)
Hispanic	6 (9%)	1 (6%)	2 (12%)	2 (13%)	1 (6%)
Race					
• **Black (%)**	11 (17%)	3 (19%)	2 (12%)	5 (31%)	1 (6%)
• **White (%)**	44 (68%)	10 (63%)	13 (76%)	9 (56%)	12 (75%)
• **Other (%)**	10 (15%)	3 (19%)	2 (12%)	2 (13%)	3 (19%)

MTN 007: Total Number of AEs by Grade and Relationship to Study Product

Severity Grade	NOT Related n (%)	Related n (%)	Total n (%)
Grade I – Mild	82 (66.7%)	41 (33.3%)	123 (80.4%)
Grade 2 – Moderate	21 (77.8%)	6 (22.2%)	27 (17.6%)
Grade 3 – Severe	2 (100.0%)	0 (0.0%)	2 (1.3%)
Grade 4 – Potentially Life Threatening	1 (100.0%)	0 (0.0%)	1 (0.7%)
Grade 5 – Death	0	0	0
TOTAL	106 (69.3%)	47 (30.7%)	153 (100.0%)

Incident Adverse Events by Arm

	All Arms	TFV Gel	N9 Gel	HEC	No Rx
N	65	16	17	16	16
Grade 1	30 (46.2%)	7 (43.8%)	10 (58.8%)	7 (43.8%)	6 (37.5%)
Grade 2	18 (27.7%)	3 (18.8%)	7 (41.2%)	4 (25.0%)	4 (25.0%)
Grade 3	2 (3.1%)	0	0	0	2 (12.5%)
Grade 4	1 (1.5%)	0	0	1 (6.3%)	0
Grade 5	0	0	0	0	0
Total	51 (78.5%)	10 (62.5%)	17 (100.0%)	12 (75.0%)	12 (75.0%)

Gastrointestinal Adverse Events

GI Adverse Events in the Tenofovir Arm	MTN-007 (N = 16) RG Formulation		RMP-02/MTN-006 (N = 12) Original Formulation	
	N	%	N	%
Abdominal pain	3	16%	6	50%
Rectal urgency	0	0%	5	42%
Bloating	0	0%	5	42%
Nausea	0	0%	4	33%
Diarrhea	1	6%	7	58%
Flatulence	6	38%	3	25%
Proctalgia	1	6%	0	0%
Other	4	25%	5	42%
Total	9	56%	12	100%

Acceptability

Product (N)	Intention to Use (%)
RG Tenofovir (15)	87%
HEC Placebo (15)	93%
N-9 (16)	63%

MTN 007: Trends in Summary

- The reduced glycerin formulation of TFV 1% gel was safe and acceptable
- Most adverse events
  - NOT related (69.3%)
  - Gastrointestinal and MILD in nature
    - Flatulence
    - Diarrhea
- Study findings suggest an opportunity to proceed to next phase

Thank You!