Preliminary Analysis of Biomedical Data From the Phase II Clinical Safety Trial of Tenofovir Disoproxil Fumarate (TDF) for HIV-1 Pre-Exposure Prophylaxis (PrEP) Among U.S. Men Who Have Sex With Men (MSM)

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ARCA

FENWAY HEALTH

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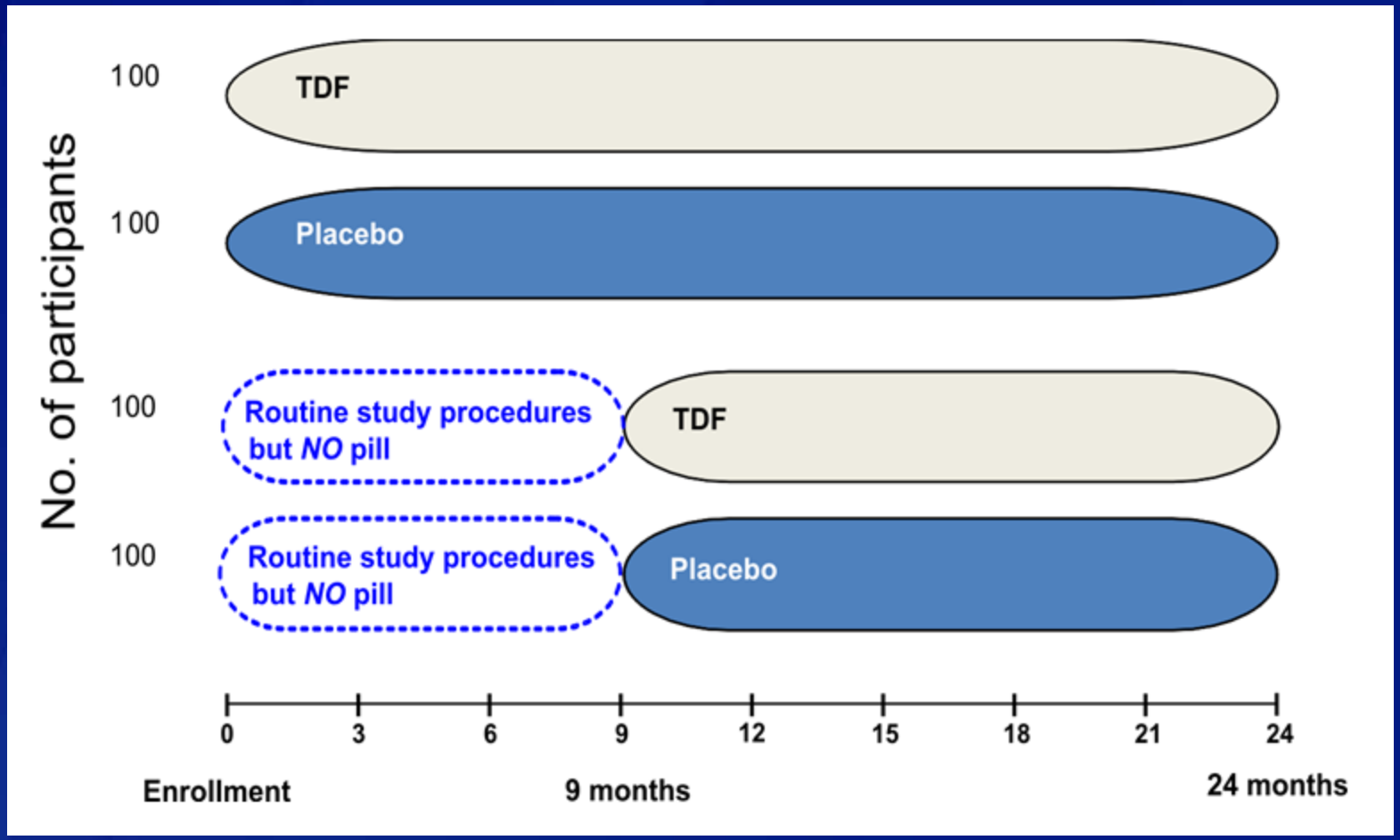
CDC

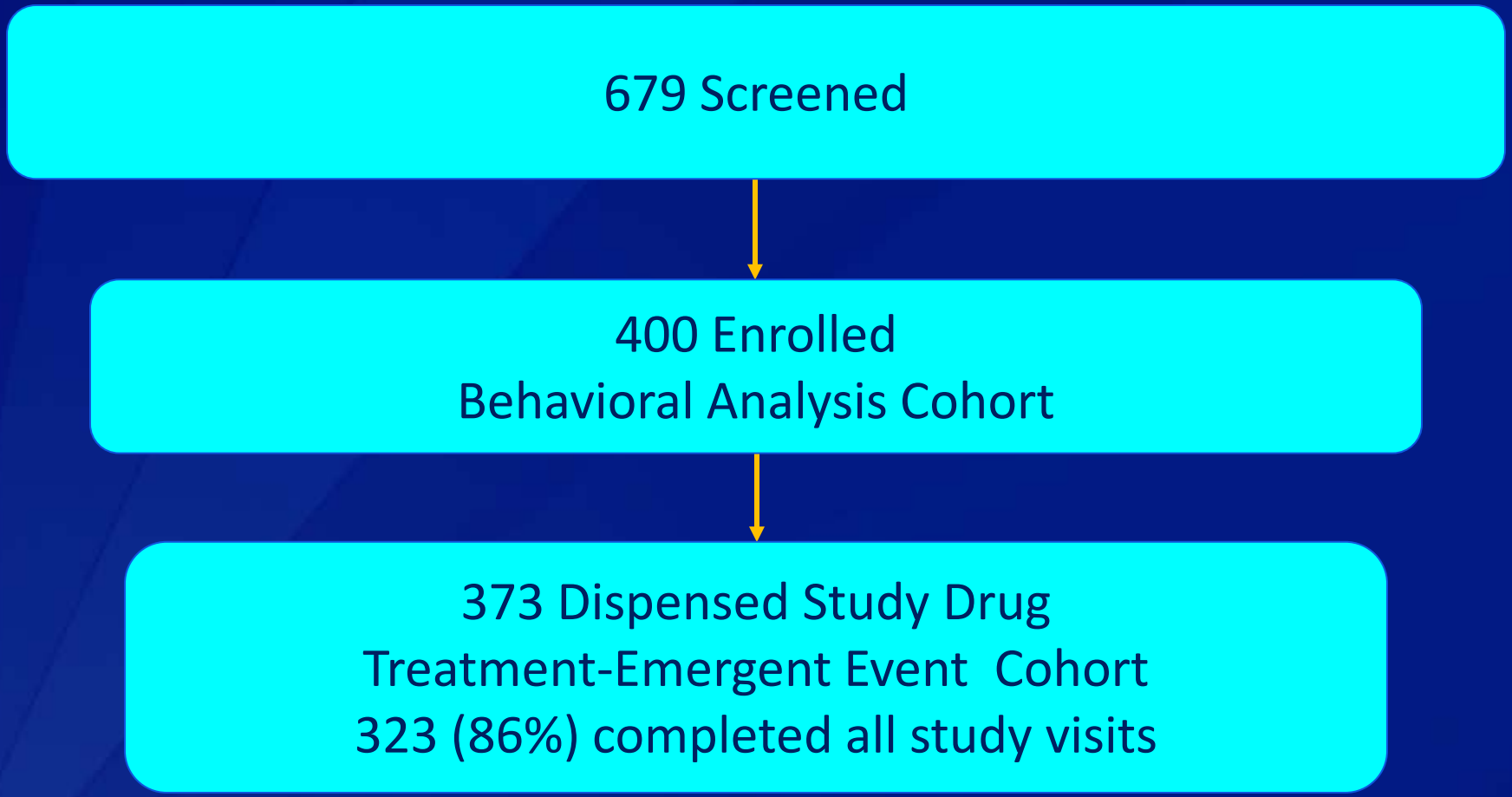
Study Design

- Randomized, double-blind, placebo-controlled safety trial
- Three sites:
  - AIDS Research Consortium of Atlanta (ARCA)
  - San Francisco Department of Public Health (SF)
  - Fenway Health, Boston (FH)
- 400 HIV-uninfected MSM randomized to receive TDF, 300mg/day or placebo
- Visits every 3 months
  - HIV testing
  - Adverse events and laboratory safety parameters
  - Adherence
  - Sexual, sociobehavioral data
  - Risk reduction counseling
- Bone mineral density studies (DEXA)—SF participants

Study Design



Enrollment Overview



Baseline Participant Characteristics

Characteristic	TDF (n=205)	Placebo (n=199)	p
Age in yrs, median (range)	38 (18-60)	37 (18-60)	
Race, n (%)			
White	160 (79.6)	133 (66.8)	0.001
African American	23 (11.4)	37 (18.6)	
Asian/Pacific Islander	10 (5.0)	4 (2.0)	
Other	8 (4)	25 (12.6)	
Hispanic	16 (8.0)	20 (10.1)	
Some College education, n (%)	181 (88.3)	176 (88.4)	
Male partners last 3 mo, median (25-75 %tile)	4 (2-9)	4 (2-7)	
Unprotected receptive anal sex with male last 3 months, n (%)	116 (58)	117 (59)	

Adverse Events Rates per 100 person years

All toxicity grades, Includes recurrent events

Event, n (%)	TDF	Placebo	RR	p
Grade 3 or 4 AE	36 (13.2)	26 (9.9)	1.1	0.7
Diarrhea	42 (15.4)	57 (21.2)	0.7	0.086
Back pain	31 (11.4)	14 (5.3)	1.84	0.07
Headache	27 (9.9)	33 (12.6)	0.82	0.45
Depression	25 (9.2)	32 (12.2)	0.7	0.26
Nausea	27 (9.9)	13 (5)	1.6	0.18
Flatulence	21 (7.7)	22 (8.4)	0.96	0.9
Fatigue	24 (8.8)	17 (6.5)	1.09	0.8
Dizziness	17 (6.2)	9 (3.4)	1.9	0.15
Fracture (any site)	15 (5.5)	5 (1.9)	1.9	0.35
Bone Density Decrease	9 (6.3)	5 (3.7)	1.72	0.32

Grade 3 and 4 Adverse Events

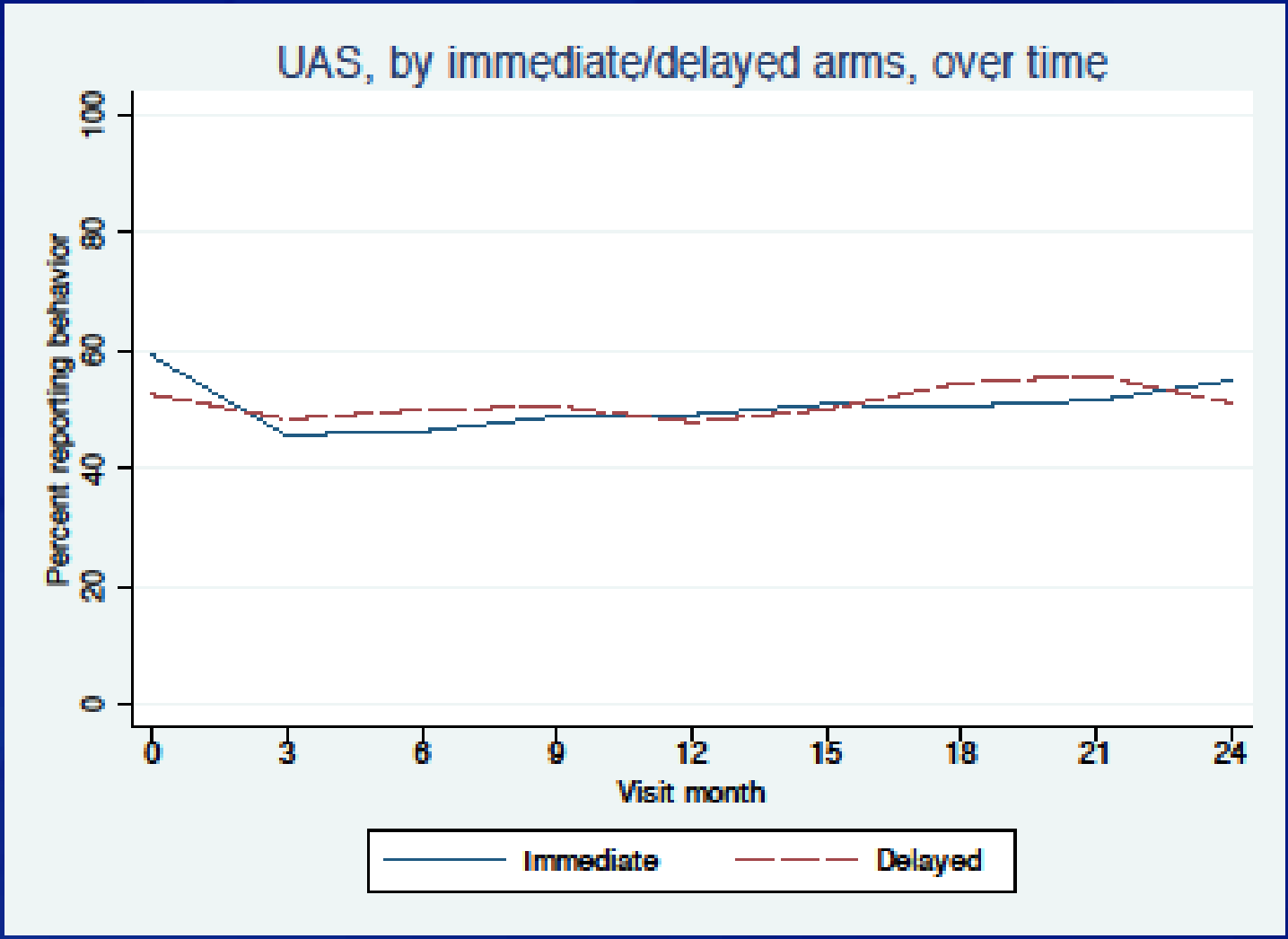
Frequencies (N) and Incidence rates per 100 person-years (IR)

Event, n (%) of participants	TDF N (IR)	Placebo N (IR)
Any grade 3 or 4 event	36 (13.2)	26 (9.9)
Depression	4 (1.5)	2 (0.8)
Hypophosphatemia	0	4 (1.5)
Gastroenteritis	3 (1.1)	0
Appendicitis	2 (0.8)	1 (0.4)
AST increased	1 (0.4)	2 (0.8)
Fracture (any site)	2 (0.8)	0
Diarrhea	1 (1)	1 (1)

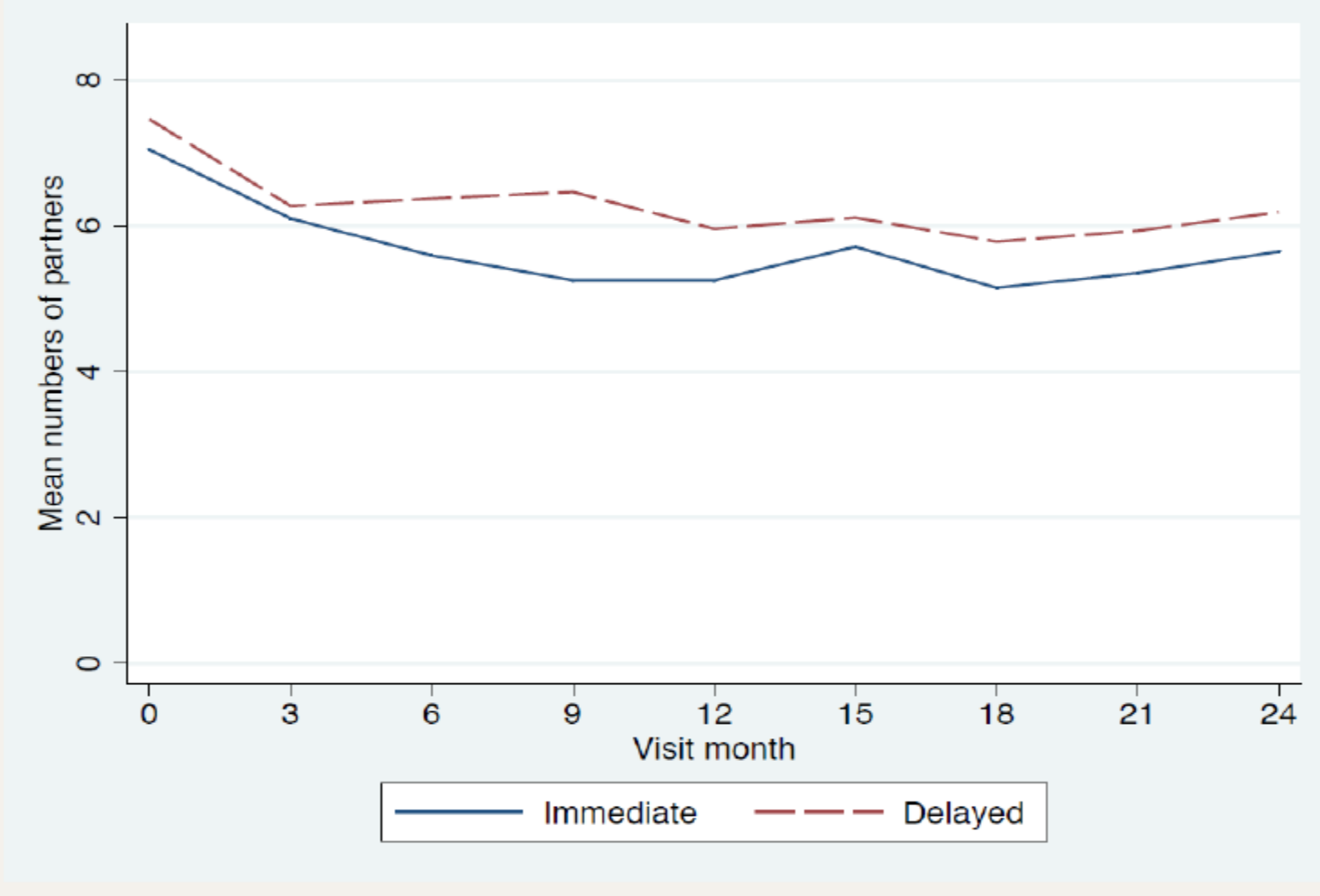
Renal Adverse Events
Creatinine and Phosphorus

Maximum grade, n (%) of participants	TDF (n=186)	Placebo (n=187)	p
Creatinine:			
Grade 1 (>0.5 mg/dL over baseline)	1 (0.5)	0 (0)	1.0
Grade 2 (2.1-3.0 mg/dL)	1 (0.5)	2 (1.1)	0.55
Hypophosphatemia:			
Grade 1 (2.5-LLN)	12 (6.5)	12 (6.4)	0.85
Grade 2 (2.0-2.4 mg/dL)	31 (16.7)	25 (13.4)	0.45
Grade 3 (1.0-1.9 mg/dL)	1 (0.5)	4 (2.1)	0.2
Grade 4 (<1.0 mg/dL)	0	1 (0.5)	1.0

Sexual Behavior: Unprotected Anal Sex Immediate vs. Delayed Arms



Mean Number of Sex Partners Immediate vs Delayed Arms



Seroconversions

- 7 seroconversions among 400 participants
- One HIV antibody negative at screening; positive at one month
  - Viral load on enrollment specimen=1,770 copies/mL
- 3 among delayed arm participants not yet on drug
- 3 among participants on placebo
- No K65R mutations
- No seroconversions among participants on TDF
- No conclusions can be drawn regarding efficacy—distribution could be due to chance

Conclusions

- Daily oral TDF, 300 mg/day, was generally well-tolerated among this cohort of MSM
- Creatinine elevations relatively uncommon, and did not occur more frequently on TDF than placebo; no apparent trend toward decreased renal function over time
- Mild to moderate hypophosphatemia relatively more common, but did not occur more frequently in the TDF arm
- Further analyses are underway regarding
  - Effect on bone mineral density
  - Adherence
  - Behavioral safety

Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study

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TDF2 Methods

- **Study Design:**
  - **Double-blind placebo-controlled randomized clinical trial**
    - **TDF-FTC vs. matching placebo**
  - **≥ 1200 male and female Botswana citizens**
  - **Followed for ≥ 12 months**
  - **Eligibility criteria:**
    - **18-39 years old**
    - **HIV uninfected**
    - **Sexually active within past 3 months**
    - **Healthy**
      - **Normal baseline laboratory tests**
      - **No chronic medical conditions**
      - **Not pregnant or breast feeding**
      - **Willing to use hormonal contraception**

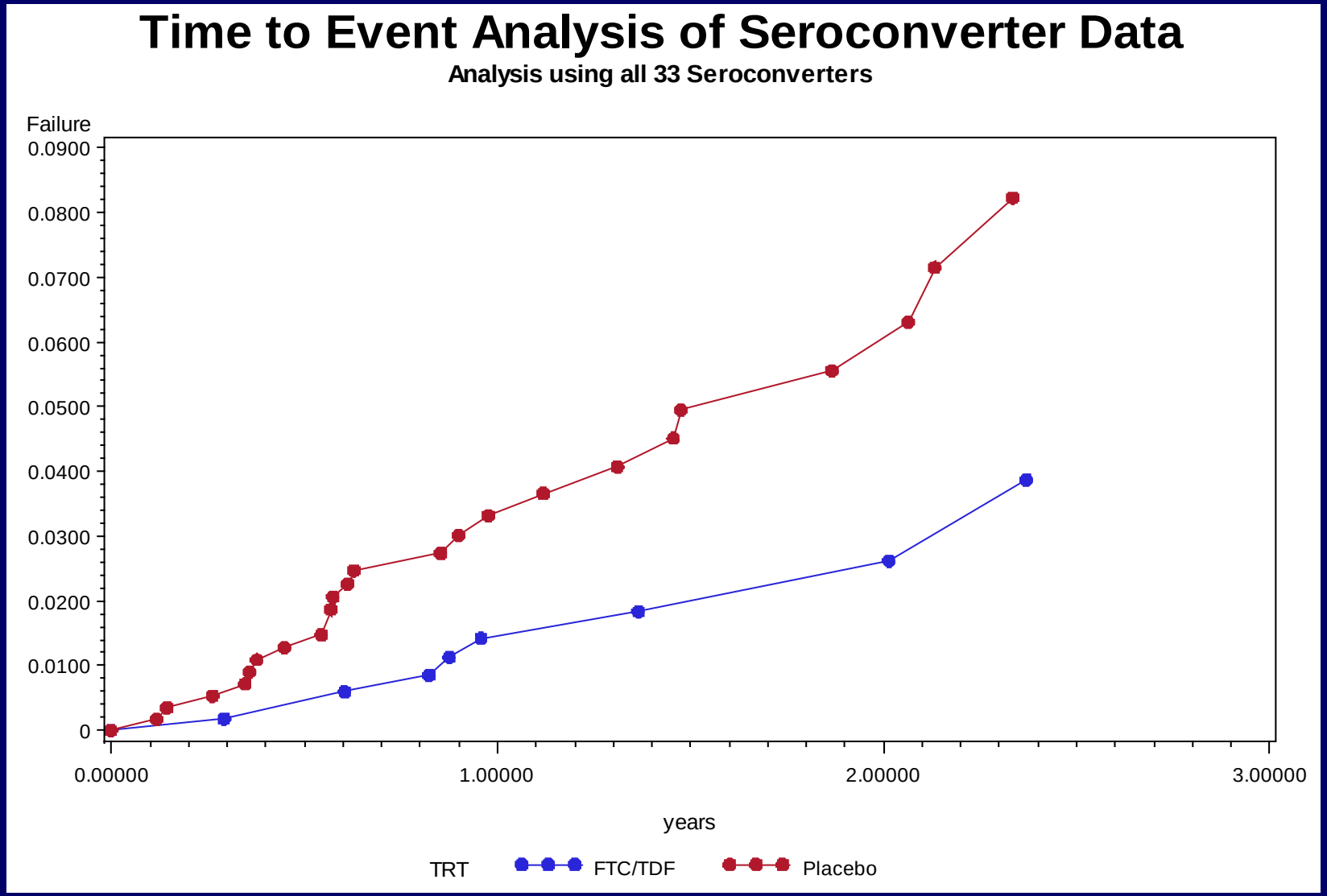
TDF2 Methods (2)

- Study procedures:
  - Tested for HIV infection every month
    - Dual rapid fingerstick tests at screening
    - Monthly oral transudate (Oraquick) thereafter
    - Positives confirmed by additional testing
      - EIA, Plasma viral load, ARV resistance testing
  - Monitored for illness and side effects
  - Lab testing at Month 1 & 2 then every 3 months
  - Individualized HIV risk reduction and medication adherence counseling
  - Assessed adherence using multiple measures
    - Self-report, Pill counts, Drug levels

Baseline Characteristics among TDF2 Study Participants

Demographic Characteristic		TDF-FTC group n=601	Placebo group n=599	P value
Age group:	18-20 years	1.7%	2.5%	0.23
	21-29 years	90.3%	87.3%	
	30-39 years	8.0%	10.2%	
Female Gender		45.6%	45.1%	0.86
Education:	Primary or less	3.0%	3.3%	0.62
	Secondary	73.4%	73.2%	
	Postsecondary	23.6%	23.5%	
Marital status:	Single	94.7%	93.3%	0.45
	Married	5.2%	6.2%	
	Divorced/Widowed	0.1%	0.5%	

Efficacy – Intention-to-Treat Analysis



9 HIV-infected in TDF-FTC group and 24 HIV-infected in placebo group
Overall protective efficacy 62.6% (95% CI 21.5 to 83.4, p=0.0133)

Drug Resistance

- One participant with unrecognized acute wild-type HIV infection at enrollment started on TDF-FTC
  - All mutations emerged to high levels
    - K65R
    - M184V
    - Also A62V conferring cross-NRTI resistance
- One participant in placebo group
  - K65R only in very low levels (<1%)

Safety

Number (%) Participants with Clinical adverse events by treatment group

	TDF-FTC group (n=601)	Placebo group (n=599)	P value
Any adverse event	535 (89.0%)	513 (85.6%)	0.019
Common Cold	229 (38.1%)	239 (39.9%)	0.78
Fatigue	52 (8.7%)	45 (7.5%)	0.44
Headache	227 (37.8%)	224 (37.4%)	0.75
Dizziness	92 (15.3%)	64 (10.7%)	0.019
Abdominal pain	154 (25.6%)	152 (25.4%)	0.69
Nausea	113 (18.8%)	43 (7.2%)	<0.0001
Vomiting	69 (11.5%)	41 (6.8%)	0.005
Diarrhea	76 (12.6%)	65 (10.9%)	0.24
Back Pain	56 (9.3%)	67 (11.2%)	0.35
Rash	39 (6.5%)	41 (6.8%)	0.87
Fracture	5 (0.8%)	4 (0.7%)	0.69
Any serious adverse event	55 (9.2%)	51 (8.5%)	0.58
Death	2 (0.3%)	4 (0.7%)	0.46

Safety (2)

Number Abnormal Laboratory Values by treatment group

	TDF-FTC group	Placebo group	P value
Grade 1-4 events			
Hypophosphatemia	218	240	0.31
Hyperamylasemia	991	1011	0.96
Elevated SGOT	43	39	0.70
Elevated SGPT	48	63	0.43
Hyperbilirubinemia	70	72	0.97
Elevated Creatinine	1	0	-
Grade 3-4 events			
Hypophosphatemia	21	24	0.66
Hyperamylasemia	12	18	0.92

Adherence/Behavioral Data

	TDF-FTC group	Placebo group	P value
Medication adherence by pill count			
Overall	84.1%	83.7%	0.79
Among 33 seroconverters	89.9%	92.9%	0.65
Among 23 seroconverters	85.5%	93.1%	0.33
Sexual behavior			
% with > 1 sexual partner in the prior month	14.2%	14.1%	0.86
% of vaginal episodes with condom use	81.9%	79.7%	0.21

Conclusions

- Daily TDF-FTC effective and safe for prevention of HIV infection among heterosexual men and women overall compared to placebo

- Overall safety and efficacy findings consistent with Partners PrEP data

Next steps

- Other planned analyses include
  - Efficacy among participants with varying levels of self-reported adherence
  - Drug level testing for efficacy and adherence
  - Change in bone mineral density
  - Trends in risk behavior over time
- Open label provision of TDF-FTC for 12 months for all study participants
- CDC & partners will fully review all heterosexual trial data & develop specific guidance for use among heterosexual men and women