NORTHWEST AIDS EDUCATION AND TRAINING CENTER

CROI 2013: Selected Highlights

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Outline

- OI Management
  - The COAT (Cryptococcal Optimal ART Timing) Study
- Prevention
  - Results of the VOICE PrEP Study
  - Birth Defects in the French Perinatal Cohort
- Hepatitis
  - Is Hepatitis B Re-Immunization Necessary on TDF-FTC?
  - Exciting Hepatitis C Options Coming Soon

OI Management: The COAT Study

COAT: Cryptococcal Optimal ART Timing

- **Background**: optimal timing for ART initiation in cryptococcal meningitis is unclear

	N	Timing	Result
ACTG 5164, Zolopa AR (2009)	282 overall; 35 with cryptococcal meningitis	Within 2 weeks vs. 4-32 weeks	Favored early arm (lower AIDS progression, mortality)
Makadzange AT (2010)	54	Within 72 hours vs. 10 weeks	Favored delayed arm (lower mortality)
Bisson GP (2013)	27	Within 7 days vs. after 28 days	No difference in mortality or CSF clearance; more IRIS in early arm

1. Zolopa AR et al, PlosOne 2009. Makadzange AT et al, CID 2010. Bisson GP et al, CID 2013.

COAT: Cryptococcal Optimal ART Timing

- **Design:**
  - Early ART (<14 days) vs. late (≥4 weeks)
  - Goal: 250 participants in each arm
  - Primary endpoint: 6-month survival
  - Stratified by MS (GCS 15 vs. <15) and CSF WBC (≥ or < 5)
  - Induction: amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg
- **Results:**
  - Halted by DSMB after 177 randomized
  - 6-month survival: early ART- **48/88 (55%),** delayed ART- **62/89 (70%)** [**HR 1.7** (95% CI 1.1-2.8, p=0.03)]

Boulware D et al, CROI 2013, Abstract 144

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COAT: Cryptococcal Optimal ART Timing

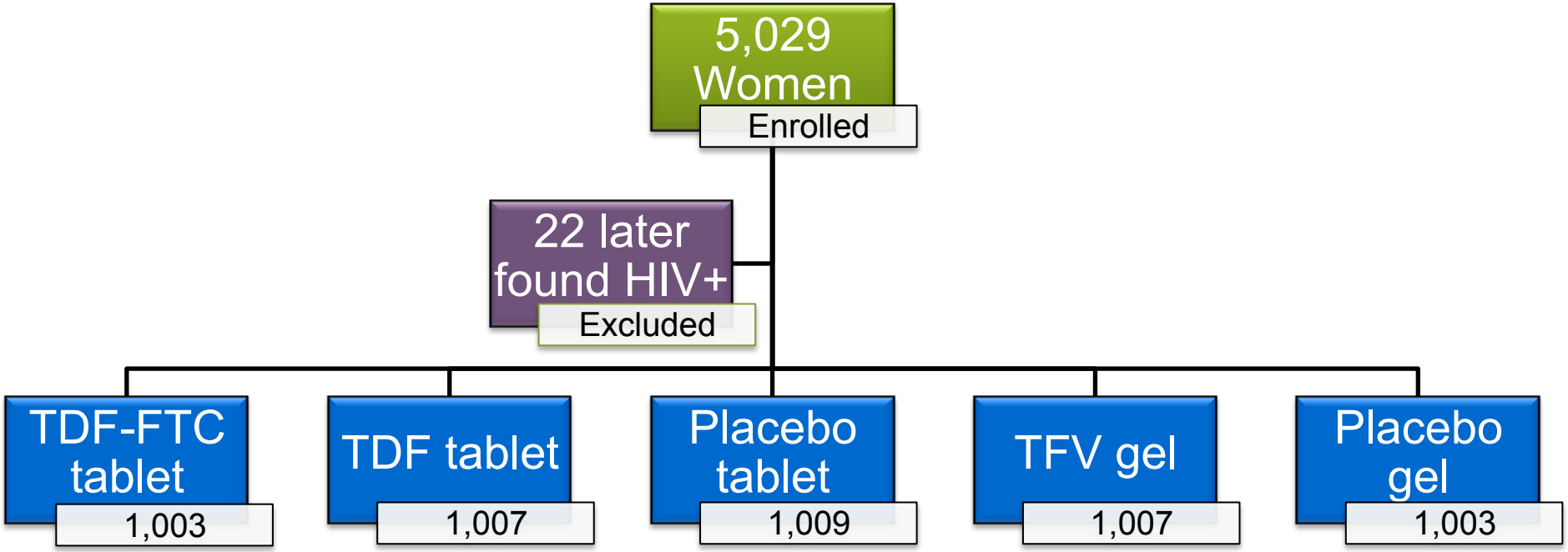
- **Secondary analyses:**
  - Mortality ↑ if AMS at presentation (GCS<15): HR 3.0
  - Mortality ↑ if CSF WBC <5/μL at presentation: HR 5.1
  - Trend toward ↑ IRIS in early group: 13% vs. 10%
- **Recommendations:**
  - Anti-cryptococcal therapy should always come before ART
  - In general, start ART at *4 weeks*
  - Consider delay of ART until *5-6 weeks* if AMS at presentation or if CSF WBC <5/μL

Boulware D et al, CROI 2013, Abstract 144

VOICE PrEP Study

VOICE: Vaginal and Oral Interventions to Control the Epidemic

- Phase 2b randomized, double-blind, placebo-controlled trial



Marrazzo J et al, CROI 2013, Abstract 26LB

VOICE: Results

- Oral TDF arm halted Sept 2011: safe but not effective
- Vaginal TFV gel arm halted Nov 2011: safe but not effective
- **Oral TDF-FTC arm completed Aug 2012**
  - Excellent retention (95% of expected person-years)
  - Product return: 89% adherence
  - Quarterly A-CASI: 90% self-reported adherence

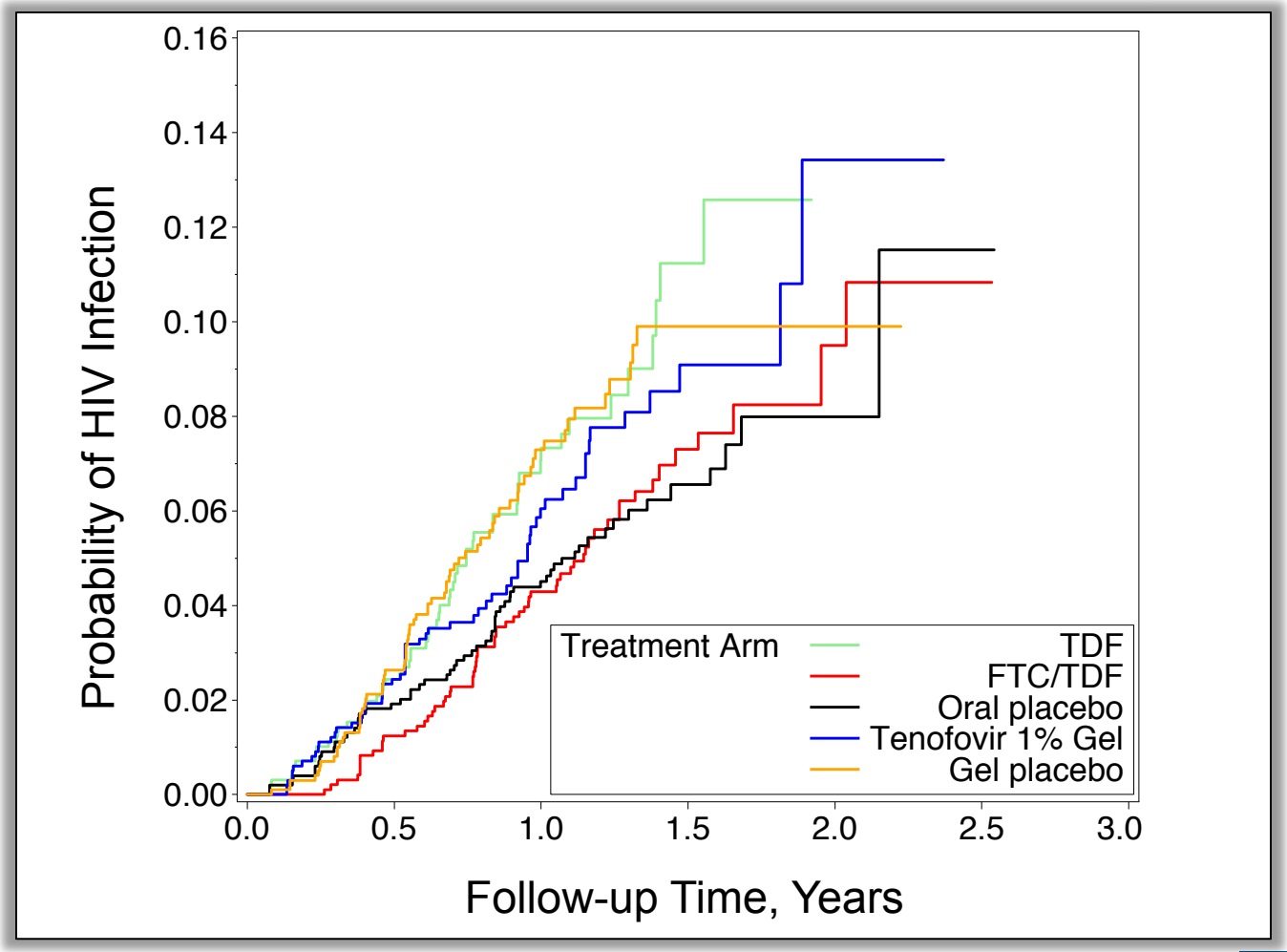
Marrazzo J et al, CROI 2013, Abstract 26LB

VOICE: Results

- 312 HIV acquisition events; overall incidence: **5.7%**
  - Highest incidence in young, unmarried women
- **No difference between oral TDF-FTC and oral placebo**
  - TDF-FTC: 61 events, incidence 4.7/100-person-years
  - Placebo: 60 events, incidence 4.6/100 person-years
- 773 with quarterly blood sampling (3,298 samples):
  - **<40%** had detectable plasma TFV levels
  - More likely detectable: >25 yo, married, male partner >28 yo

Marrazzo J et al, CROI 2013, Abstract 26LB

VOICE: Results



Marrazzo J et al, CROI 2013, Abstract 26LB; slide courtesy of Jeanne Marrazzo

VOICE: Questions Remain

- Why were self-reported adherence and actual adherence so disparate?
- What can we do to better understand adherence, cultural barriers, and perception of risk in this group?
- If a daily medication is not the answer to HIV prevention for women in Africa, where should we be putting our efforts?
- Can the CAPRISA-004 trial be replicated?

Birth Defects in the French Perinatal Cohort

Birth Defects in the French Perinatal Cohort

- **Background:**
  - Cadman J 1998: EFV → neural tube defects in monkeys
  - Brogly SB 2010:
    - EFV exposure in 1st trimester → birth defects
    - AZT → congenital heart defects
  - Ford N 2011: no association b/w EFV and birth defects
  - Knapp KM 2012: EFV exposure in 1st trimester → birth defects
  - Current HHS recommendations:
    - Avoid EFV in women of child-bearing potential
    - Continue if pregnancy discovered while on EFV

Sibiude J et al, CROI 2013, Abstract 81

Birth Defects in the French Perinatal Cohort

- **French Perinatal Cohort**:
  - All HIV+ pregnant women in 90 centers since 1995 (N≈17,000); follows HIV+ infants until age 18, HIV- until age 2
  - AIDS 2008:
    - 1.3% MTC transmission rate overall; 0.4% if VL <50 copies/mL
    - Maternal VL key for transmission risk; early ART essential
    - Called for analysis of risks of prolonged ART use in pregnancy
- Current study: systematic analysis of each type of birth defect for each ARV in each trimester
  - Analyzed 13,124 live births since 1994

Sibiude J et al, CROI 2013, Abstract 81

Birth Defects in the French Perinatal Cohort

Efavirenz (EFV)

- 1st trimester use → increased risk of neurological defects (not neural tube defects) [aOR 3.15]

Zidovudine (AZT)

- Associated with overall increased rate of birth defects (aOR 1.4)
- 1st trimester use → congenital heart defects (aOR 2.5)

Lamivudine (3TC)

- Associated with head and neck malformations (aOR 1.96)
- Associated with musculoskeletal defects (aOR 1.4)

Is hepatitis B re-immunization necessary for vaccine non-responders on TDF-FTC?

Protective Effect of cART against Primary HBV

- **Design:**
  - Retrospective cohort study (N=2,968)
  - Inclusion: HBV serology negative (HBsAg, anti-HBs, anti-HBc) with a second serology available
  - Outcome: anti-HBc seroconversion correlated with RF's (syphilis, MSM) and anti-HBV drug use (TDF, 3TC, FTC)
- **Results:**
  - 530 subjects, 35 infections over median 94-month f/u
  - **Less HBV seroconversion if on HBV-active drug(s) at least 20% of the time (HR 0.17); lowest risk if on TDF**

Heuft M et al, CROI 2013, Abstract 33

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Hepatitis C Therapy: What's Coming…

Hepatitis C: Exciting Results

- 1) **Simeprevir + PEG-Interferon + Ribavirin**
  - HIV-HCV coinfected, genotype 1, tx-naïve and experienced
  - Used response-guided therapy
  - SVR 12 = 75% if tx-naïve, 80% if prior relapse
  - Efavirenz and PI's excluded due to drug interactions
- 2) **Sofosbuvir + Ledispavir + Ribavirin**
  - HCV-infected, genotype 1, tx-naïve and prior nonresponders
  - All treated for total of 12 weeks
  - SVR 12 = 100%

Dieterich D et al, CROI 2013, Abstract 154LB
Gane E et al, CROI 2013, Abstract 41LB