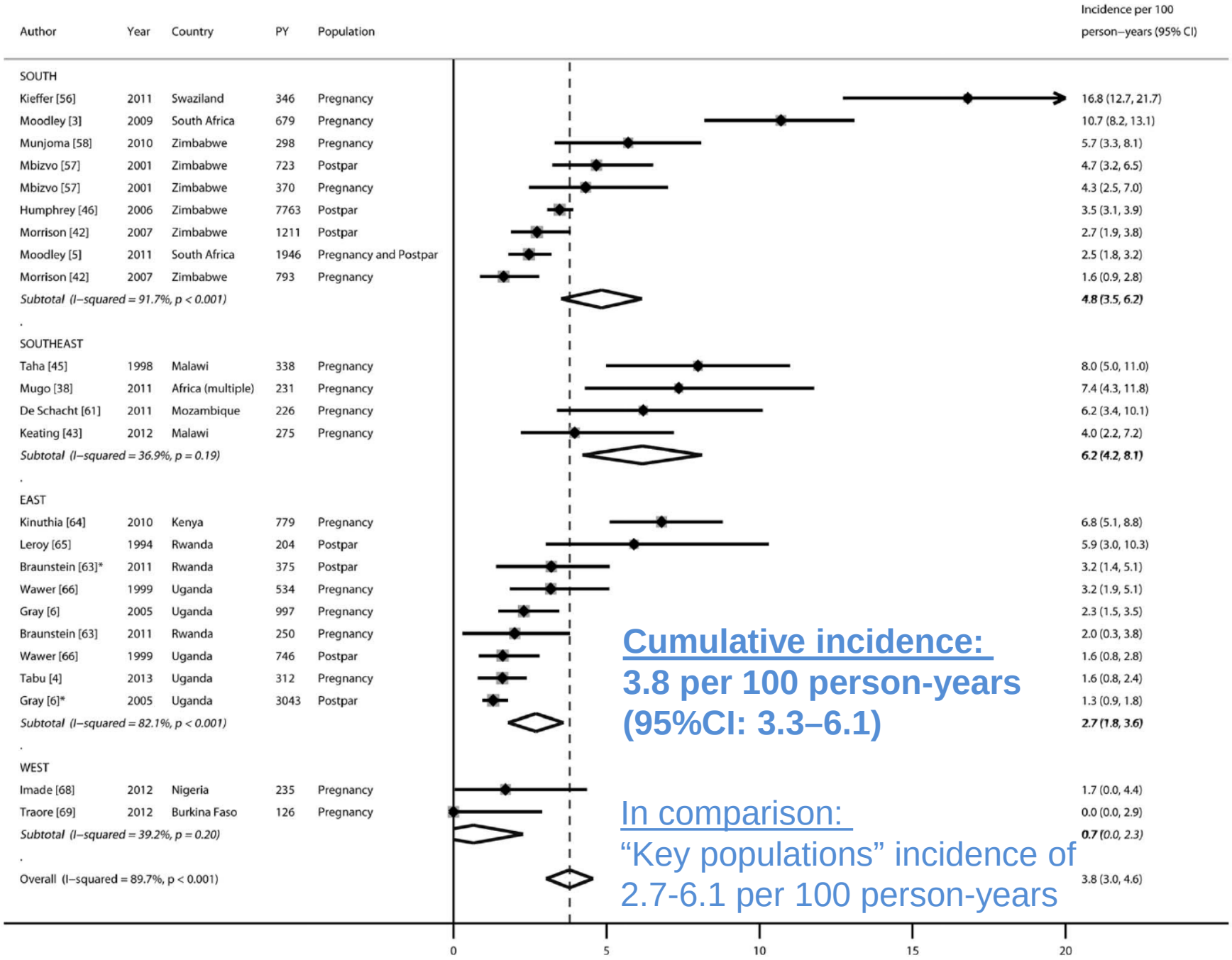
IMPAACT 2009

Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for Primary HIV Prevention during Pregnancy and Breast Feeding in Adolescents and Young Women

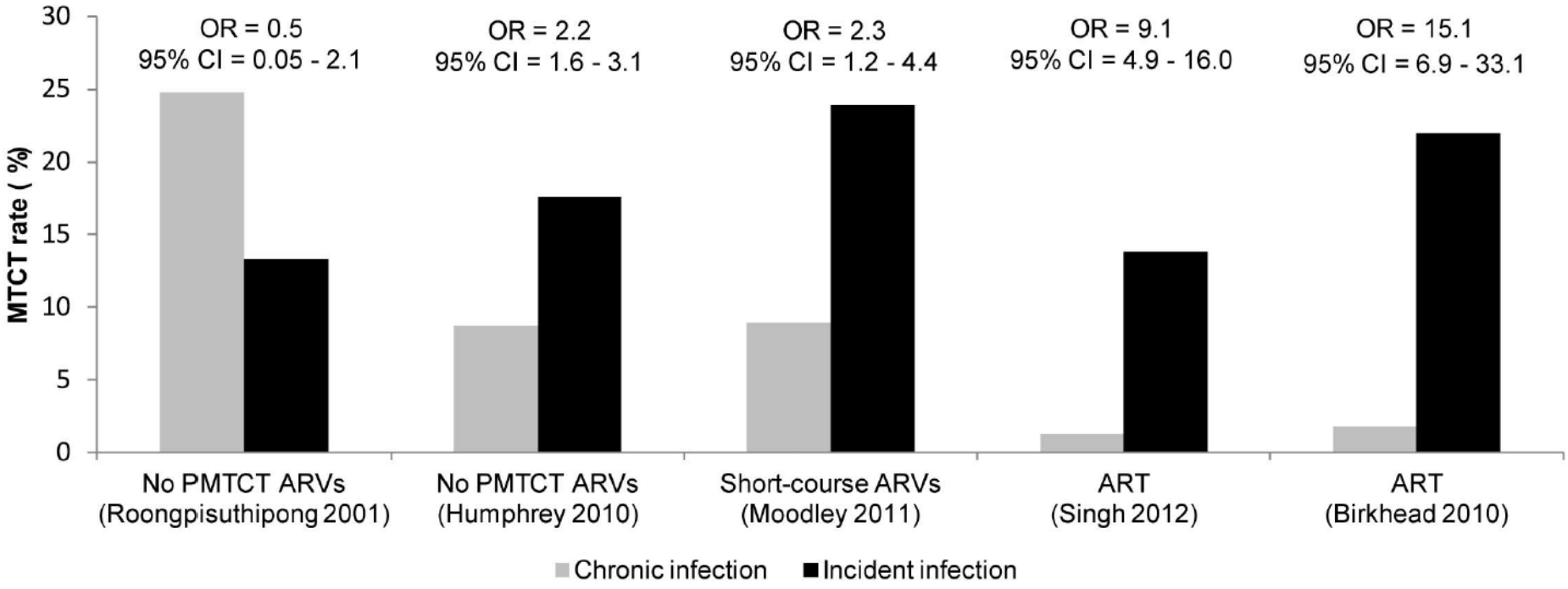


Cumulative incidence:
3.8 per 100 person-years
(95%CI: 3.3–6.1)

In comparison:
"Key populations" incidence of 2.7-6.1 per 100 person-years

Drake, *PLoS Med* 2014

Acute HIV infection associated with greater MTCT risk



Drake, *PLoS Med* 2014

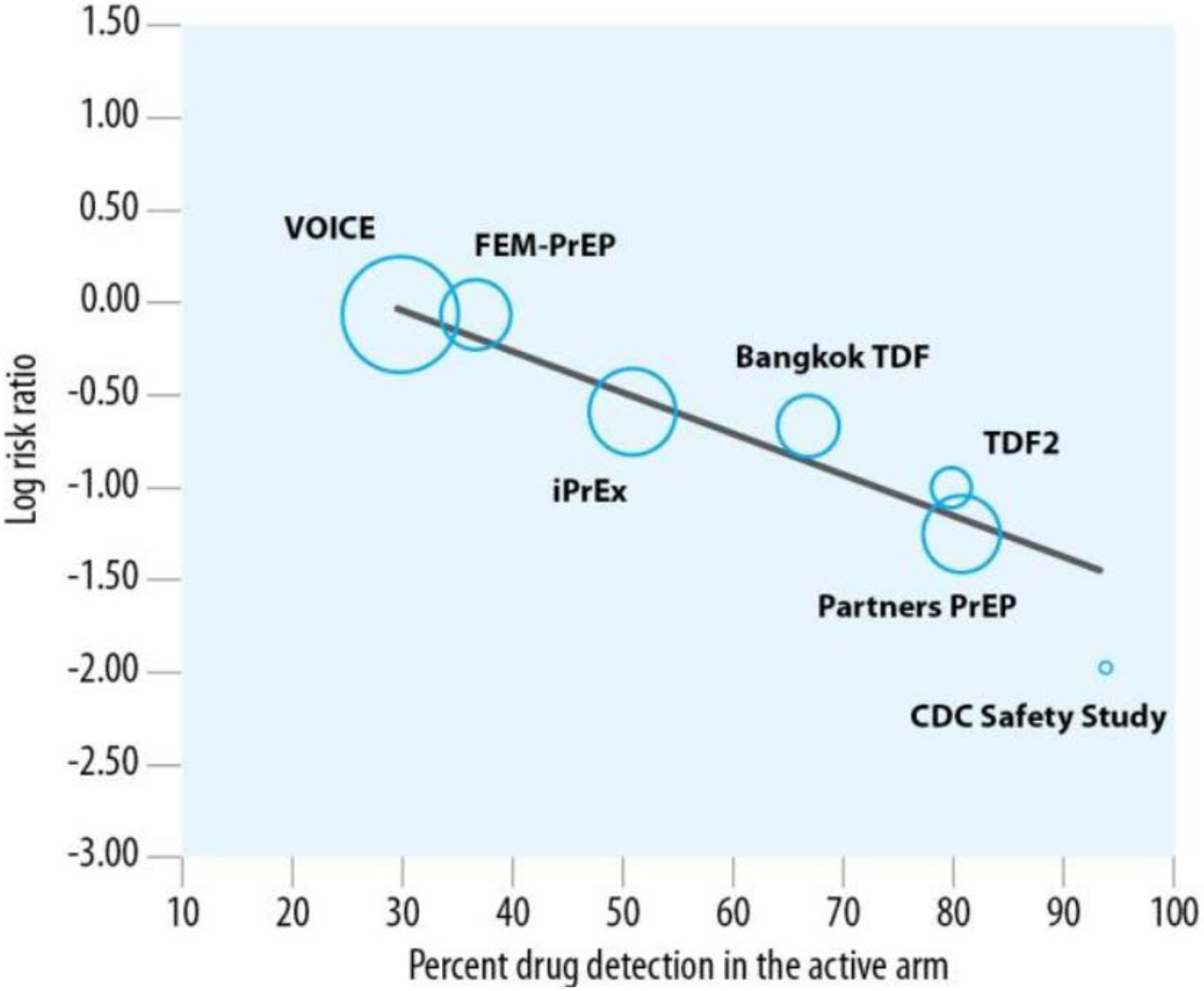
PrEP WHO Guidelines

Antiretroviral drugs for HIV prevention

The updated guidelines include a new recommendation on the use of oral pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV. WHO has expanded its earlier recommendations to offer PrEP to selected key populations. PrEP is now recommended for all populations at substantial risk of acquiring HIV, provisionally defined as an incidence of HIV greater than three per 100 person-years in the absence of PrEP.

3. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION	
3.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV	Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk[2] of HIV infection as part of combination HIV prevention approaches *(strong recommendation, high quality evidence)*.

Key populations:
Sero-discordant couples
Commercial sex workers
Men who have sex with men
Intravenous drug users



Fonner, *AIDS* 2016

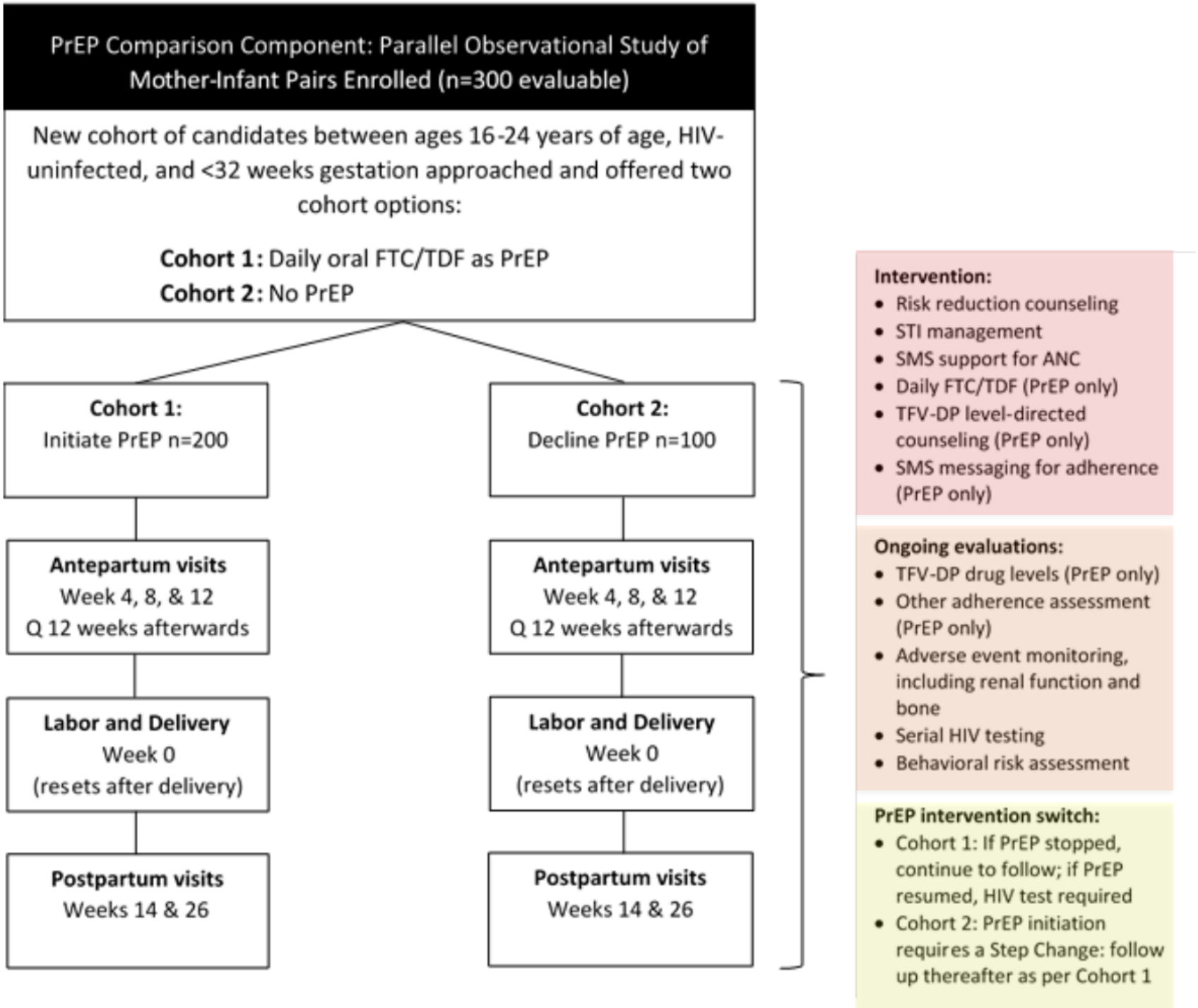
Primary Objectives

- To characterize PrEP adherence among HIV-uninfected women aged 16-24 years who initiate once-daily TDF-FTC in pregnancy

- To compare maternal and infant adverse events (including pregnancy outcomes) between women who initiate PrEP and those who decline PrEP

Secondary Objectives

- To identify individual, social, and structural barriers and facilitators to PrEP uptake during pregnancy
- To compare between the PrEP and non-PrEP cohorts:
  - Reported sexual risk behavior and incidence of STIs
  - HIV incidence
  - HIV drug resistance among HIV-infected mothers and infants


PrEP Comparison Component: Parallel Observational Study of Mother-Infant Pairs Enrolled (n=300 evaluable)
New cohort of candidates between ages 16-24 years of age, HIV-uninfected, and <32 weeks gestation approached and offered two cohort options:
Cohort 1: Daily oral FTC/TDF as PrEP
Cohort 2: No PrEP
Cohort 1: Initiate PrEP n=200
Cohort 2: Decline PrEP n=100
Antepartum visits Week 4, 8, & 12 Q 12 weeks afterwards
Antepartum visits Week 4, 8, & 12 Q 12 weeks afterwards
Labor and Delivery Week 0 (resets after delivery)
Labor and Delivery Week 0 (resets after delivery)
Postpartum visits Weeks 14 & 26
Postpartum visits Weeks 14 & 26
Intervention:
Risk reduction counseling
STI management
SMS support for ANC
Daily FTC/TDF (PrEP only)
TFV-DP level-directed counseling (PrEP only)
SMS messaging for adherence (PrEP only)
Ongoing evaluations:
TFV-DP drug levels (PrEP only)
Other adherence assessment (PrEP only)
Adverse event monitoring, including renal function and bone
Serial HIV testing
Behavioral risk assessment
PrEP intervention switch:
Cohort 1: If PrEP stopped, continue to follow; if PrEP resumed, HIV test required
Cohort 2: PrEP initiation requires a Step Change: follow up thereafter as per Cohort 1

Study population (n=300)

- At least 16 years and less than 25 years
- Confirmed pregnancy at any gestational age
- HIV negative by HIV RNA screening
- No history of chronic disease
- For PrEP cohort:
  - Willingness to take PrEP through pregnancy to 26 weeks postpartum
  - Access to cell phone to receive SMS messages

Study endpoints (1)

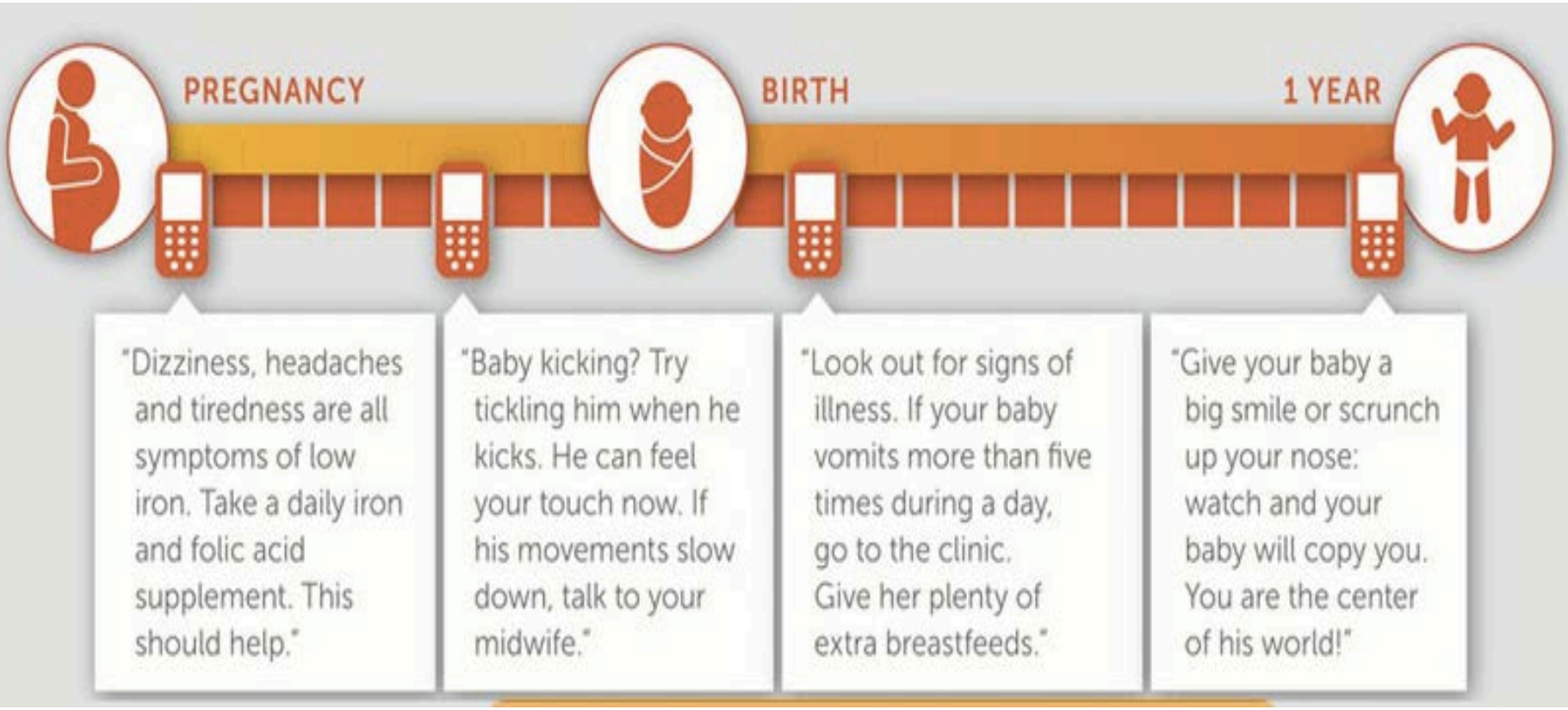
- **Adherence**
  - Tenofovir diphosphate (TFV-DP) levels measured through dried blood spots.
- **Safety (maternal and pregnancy)**
  - Adverse pregnancy outcomes will include:
    - Stillbirth
    - Low birthweight <2500g
    - Preterm delivery <37 weeks gestation
  - Maternal AE outcome will be a composite:
    - Grade 3 or higher signs and symptoms
    - Grade 2 or higher chemistry abnormalities
    - Grade 3 or higher pregnancy-related diagnosis

Study endpoints (2)

- **Safety (infant)**
  - Infant safety outcome measures:
    - Infant death
    - Creatinine clearance measured by Schwartz equation
    - Anthropometric growth
    - Lumbar spine and Whole Body bone mineral content
- **HIV-related outcomes**
  - HIV drug resistance in women who become infected while on PrEP
  - HIV drug resistance in infants who become infected while their mothers are on PrEP

Adherence support

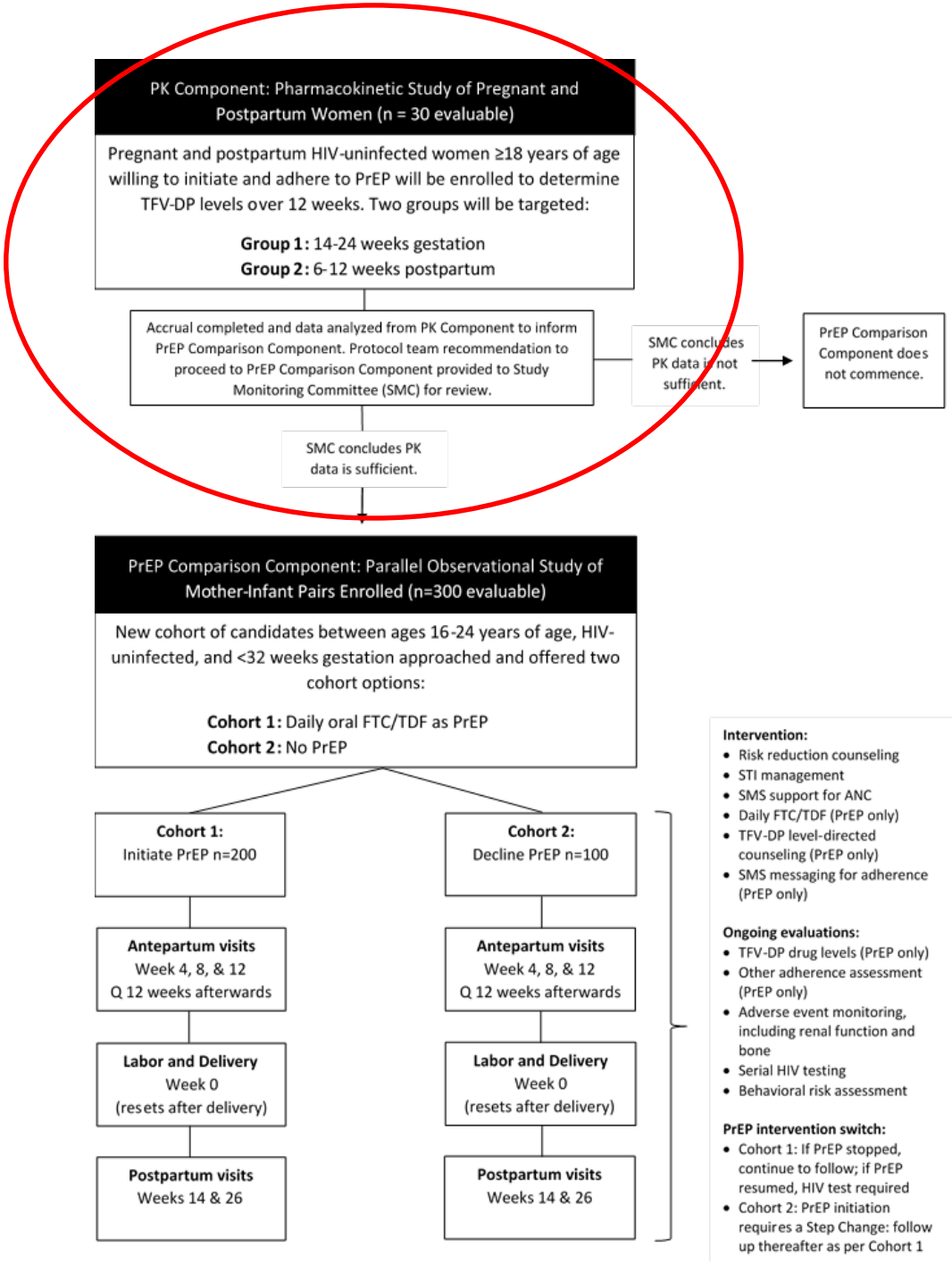
- **Drug-level guided counseling**
  - TVF-DP levels from DBS specimens
  - Tested centrally with return in 6-8 wks
  - Used to guide adherence counseling
- **mHealth support**
  - One-way messaging for ANC and infant care
  - Two-way (weekly) for adherence reminder


PREGNANCY
BIRTH
1 YEAR
"Dizziness, headaches and tiredness are all symptoms of low iron. Take a daily iron and folic acid supplement. This should help."
"Baby kicking? Try tickling him when he kicks. He can feel your touch now. If his movements slow down, talk to your midwife."
"Look out for signs of illness. If your baby vomits more than five times during a day, go to the clinic. Give her plenty of extra breastfeeds."
"Give your baby a big smile or scrunch up your nose: watch and your baby will copy you. You are the center of his world!"

Study endpoints (1)

Pregnancy?

- **Adherence**
  - Tenofovir diphosphate (TFV-DP) levels measured through dried blood spots.
- **Safety (maternal and pregnancy)**
  - Adverse pregnancy outcomes will include:
    - Stillbirth
    - Low birthweight <2500g
    - Preterm delivery <37 weeks gestation
  - Maternal AE outcome will be a composite:
    - Grade 3 or higher signs and symptoms
    - Grade 2 or higher chemistry abnormalities
    - Grade 3 or higher pregnancy-related diagnosis


PK Component: Pharmacokinetic Study of Pregnant and Postpartum Women (n = 30 evaluable)
Pregnant and postpartum HIV-uninfected women ≥18 years of age willing to initiate and adhere to PrEP will be enrolled to determine TFV-DP levels over 12 weeks. Two groups will be targeted:
Group 1: 14-24 weeks gestation
Group 2: 6-12 weeks postpartum
Accrual completed and data analyzed from PK Component to inform PrEP Comparison Component. Protocol team recommendation to proceed to PrEP Comparison Component provided to Study Monitoring Committee (SMC) for review.
SMC concludes PK data is not sufficient.
PrEP Comparison Component does not commence.
SMC concludes PK data is sufficient.
PrEP Comparison Component: Parallel Observational Study of Mother-Infant Pairs Enrolled (n=300 evaluable)
New cohort of candidates between ages 16-24 years of age, HIV-uninfected, and <32 weeks gestation approached and offered two cohort options:
Cohort 1: Daily oral FTC/TDF as PrEP
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PK Component (1)

- Approved by SLG in Feb 2016
- Designed to establish drug thresholds for optimal adherence to PrEP during pregnancy
  - Refines adherence outcome measure
  - Informs drug level-based counseling
- 15-20 participants in each of two groups:
  - Antepartum: 14-24 weeks gestation
  - Postpartum: 6-10 weeks postpartum
- Pregnant women ≥ 16 yrs eligible
- All participants agree to take daily TDF-FTC

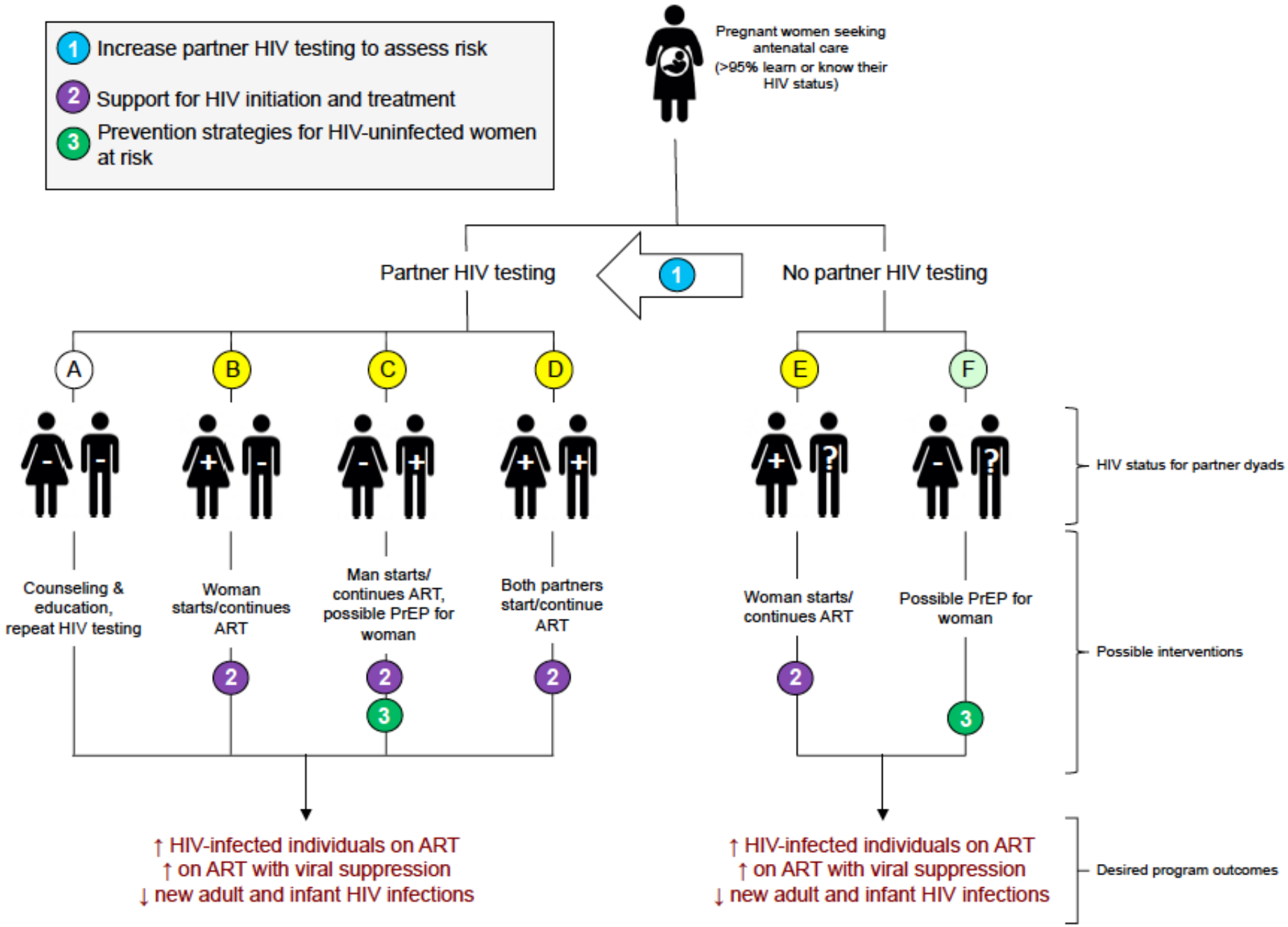
PK Component (2)

- 12 weeks of PK monitoring, with weekly DBS specimens for drug levels
  - Followed by an observational period to 6 weeks postpartum
- Specimens to be shipped to U.S. for testing
- Intensive monitoring of drug adherence

Daily observed PrEP

- Sites will develop plans to monitor daily adherence.
- Possible strategies may include:
  - Directly observed therapy at the clinic
  - Directly observed therapy at the home, via community health workers
  - “Real-time” video-based monitoring via smartphone, tablet, or computer
  - Recorded video of drug ingestion, with time/date stamp

End


1 Increase partner HIV testing to assess risk
2 Support for HIV initiation and treatment
3 Prevention strategies for HIV-uninfected women at risk
Pregnant women seeking antenatal care (>95% learn or know their HIV status)
Partner HIV testing
1
No partner HIV testing
A
B
C
D
E
F
Counseling & education, repeat HIV testing
Woman starts/continues ART
Man starts/ continues ART, possible PrEP for woman
Both partners start/continue ART
Woman starts/ continues ART
Possible PrEP for woman
HIV status for partner dyads
Possible interventions
↑ HIV-infected individuals on ART
↑ on ART with viral suppression
↓ new adult and infant HIV infections
↑ HIV-infected individuals on ART
↑ on ART with viral suppression
↓ new adult and infant HIV infections
Desired program outcomes