Innovation in the Inclusion of Pregnant and Lactating People in (ARV) Clinical Research

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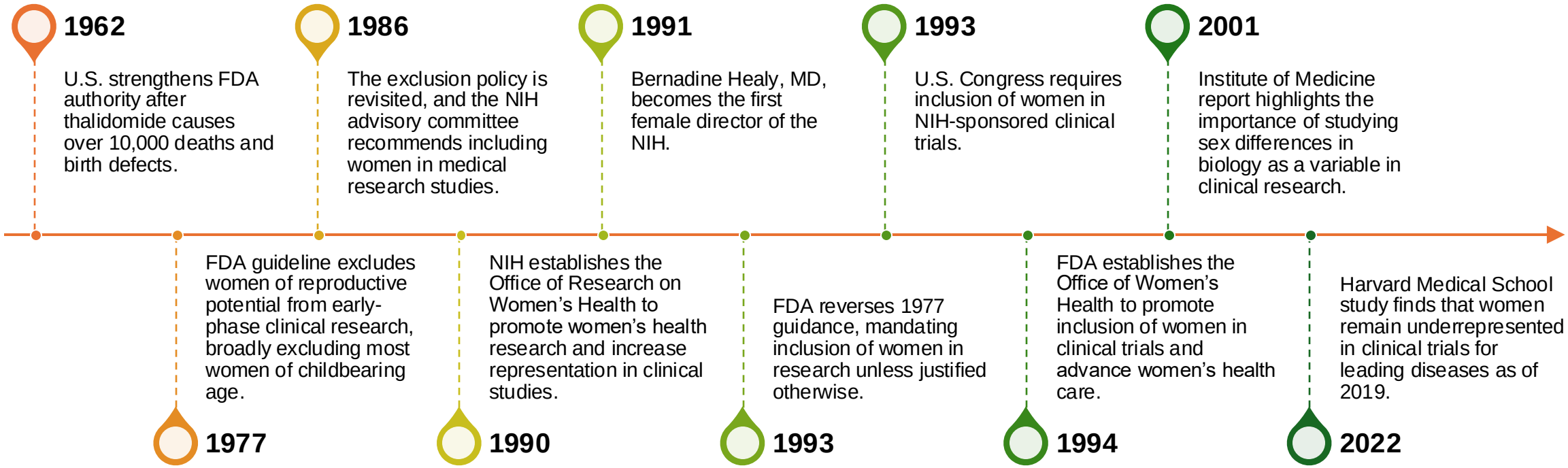
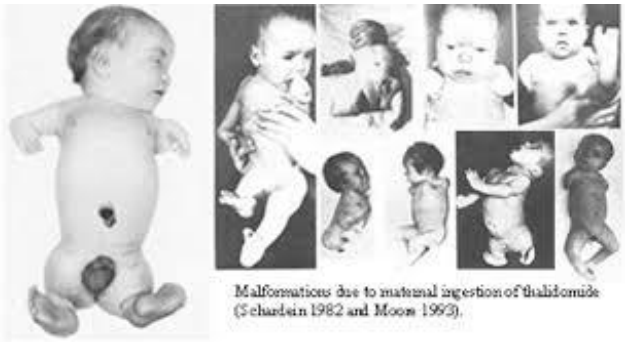
R4PLima, Oct 2024

A timeline for women's involvement in clinical research



Source: Liu KA & Mager NA, Pharm Pract, 2016

Thalidomide saga : exclusion of WCBP

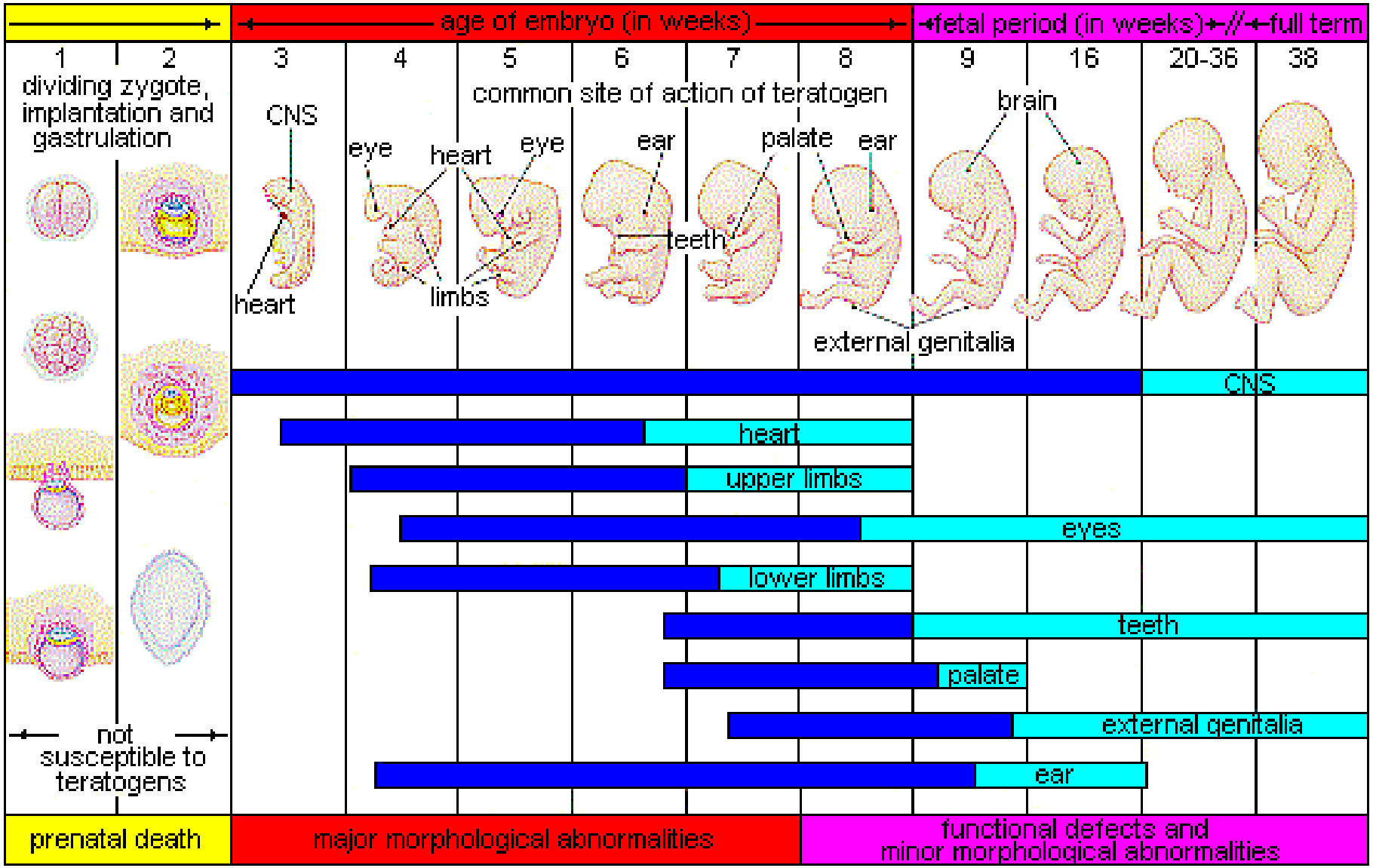

Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

- German drug developed in 50s as a sedative
  - Found to also have anti-emetic properties
  - used widely by pregnant people in 1950s
  - Increasing awareness of congenital abnormalities specifically phycomelia (10 000 affected children)
- FDA given more strength in 1962
- Led to FDA guidance: exclusion of pregnant and essentially women of child bearing age…..1973
- Prior: female hormones thought to complicate clinical research so male participants preferred, even preclinically!

In 2001 , 20% of drug use was off label and most without any scientific support

Radley D, et al

Risk to foetus changes over gestation.....

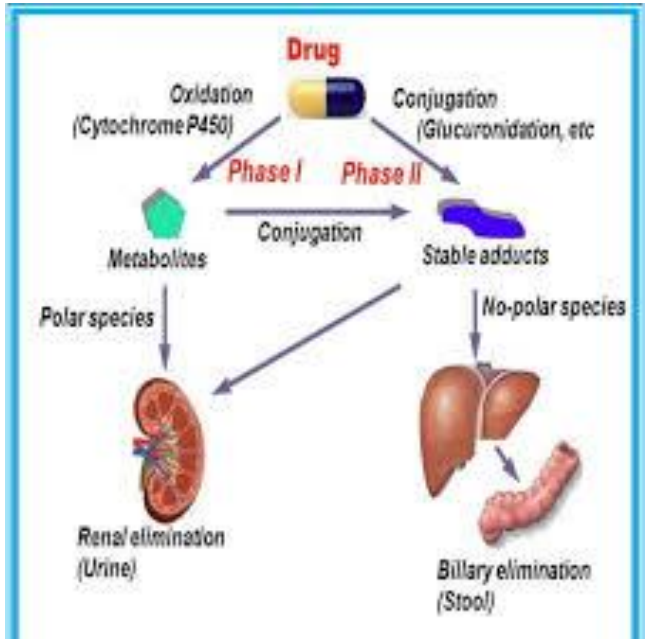


Women excluded from clinical research

"Potential risks to individuals of childbearing potential and wrongly thought that studies in men apply to women without modification"

- Despite reversal of 1977 guidance – still great deal of inertia…
- 2018 review of 107 NIH funded RCTs enrolling both men and women
  - reporting even on item by sex or has both sexes as covariate: 26%
  - no reporting by sex in the analysis: 72%
- 2020 review of 86 FDA approved drugs
  - higher PK in women – 76/86
  - clinically identified ADRs – 59/86
  - sex based PK predicted direction of sex-biased ADRs – 88% of cases

Differences between men and women

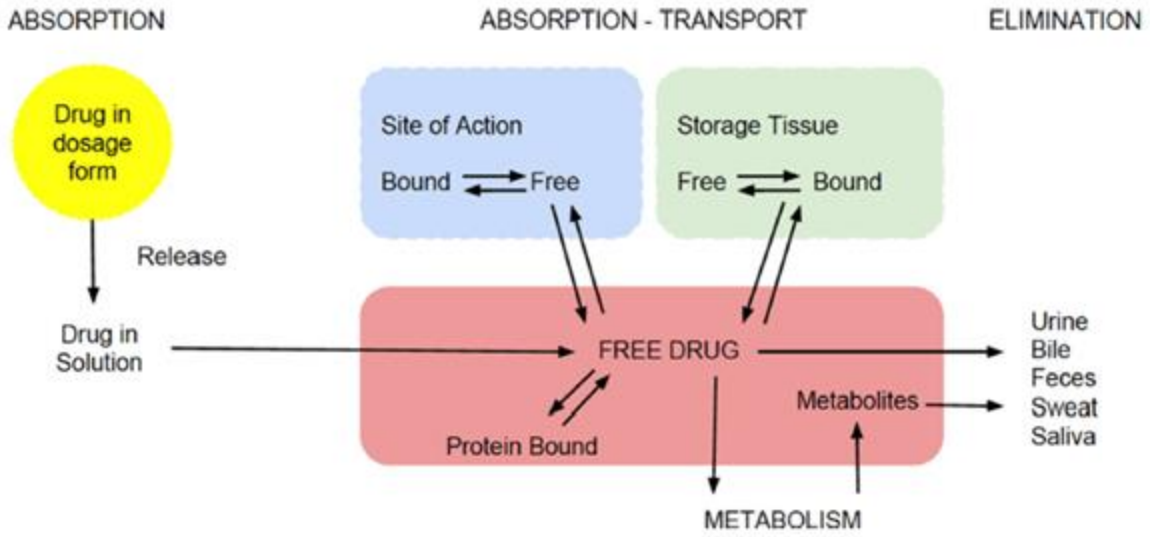


- women have a nearly 2 fold greater risk of ADRs across all drug classes
- more likely to be hospitalized due to ADR
- women are more likely to be using >2 drugs concomitantly
- women use more unique medications per year than men
- women generally have a lower body weight and organ size
- they have a higher percentage body fat which affects absorption and distribution of drugs
- as well as other biological (hormones), psychological (reporting of reactions) and cultural aspects.

Zucker I, Prendergast B. Biology of sex differences 2020

Layer on pregnancy……

- Nausea and Vomiting
- Increase in gastric pH
- slower intestinal mobility
- Increased cardiac output
- Increased blood flow
- Increase in plasma volume
- Increase in body fat
- Changes in cytochrome P450family of enzymes' activity
- Increase in glomerular filtration rate



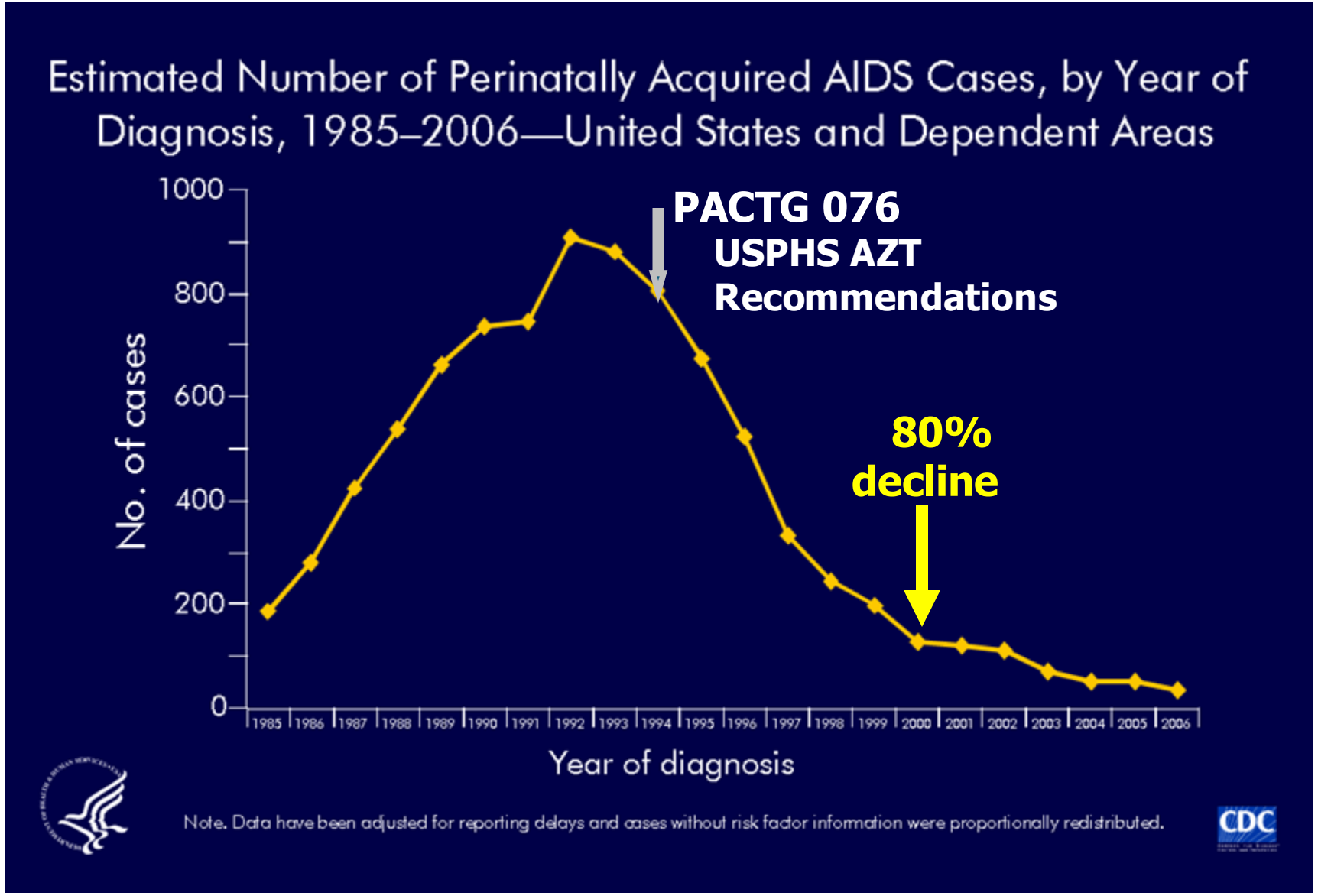
- A drug must reach the tissues (site of action)
- Pharmacokinetics describes the time course of drug concentrations in body
- If administered IV then 100% bioavailable
- SC and IM may be subject to variations in absorption
- Oral drugs have greatest variation due to absorption and first pass effects (metabolism)

Fegall M, et al 2015

Innovations using ARVs as reference….

- Extrapolate from women …..but could be extrapolating from men !
  - Monitor individual closely
- Pregnancy registries/ phase 4 surveillance at population level
- Test safety and model PK for effectiveness
- Design efficacy for specific pregnancy indication, eg PVT
- Solid animal preclinical work that includes reproductive toxicity/adverse events followed by testing in phase 2 or 3:
  - Allow women to be exposed late in pregnancy
  - Allow women to conceive on an efficacy/safety trial and continue after informed consent and with careful monitoring
  - Allow women to come into a trial pregnant with informed consent and monitor carefully throughout including for birth and neonatal outcomes

Zidovudine ACTG 076 landmark – to interrupt vertical transmission



Ban Ki Moon
NY, September 2009

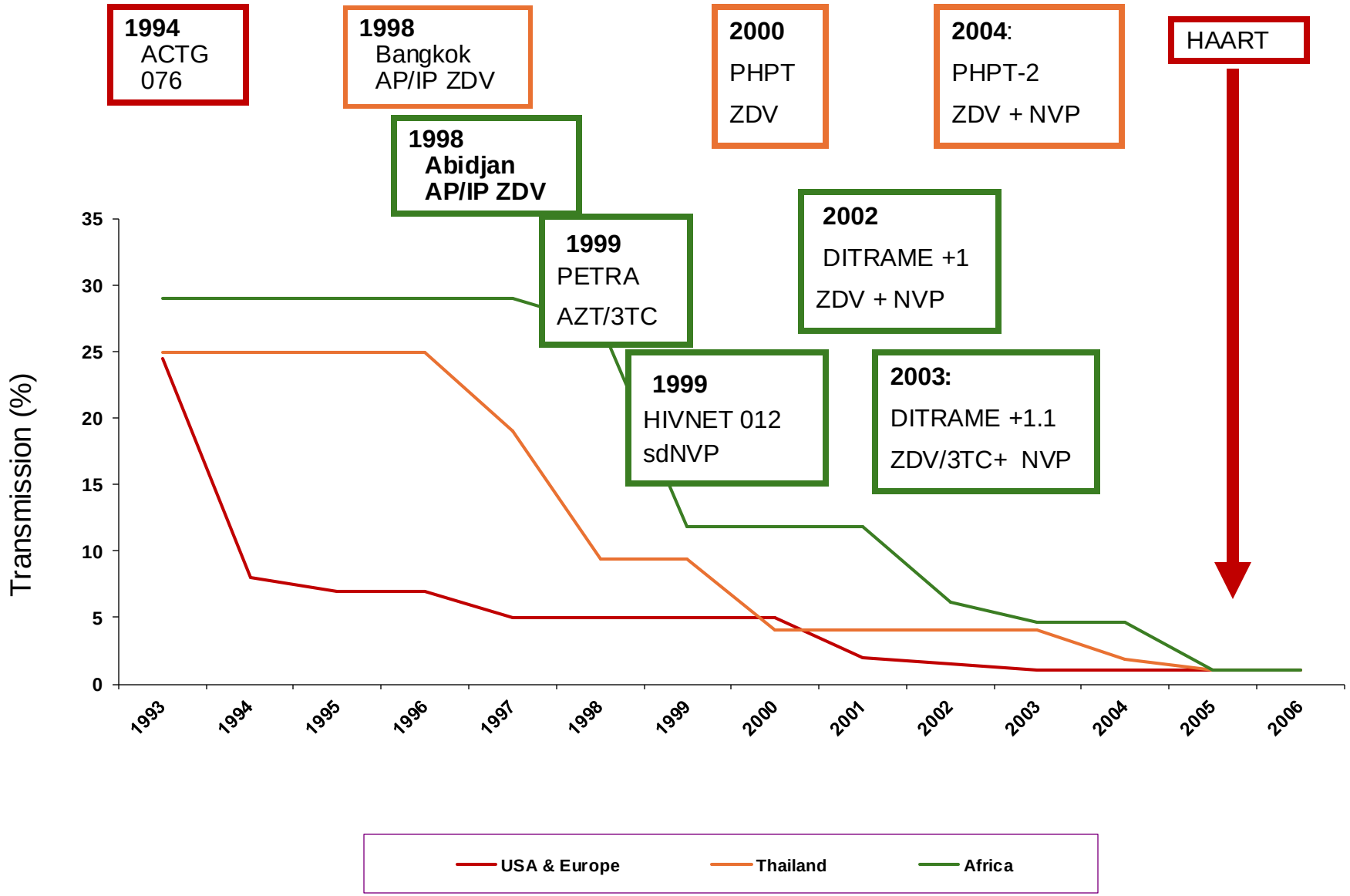
"We have effective drugs.

There is no reason why any mother should die of AIDS.

There is no cause for any child to be born with HIV

If we work hard enough we can virtually eliminate mother-to-child transmission."

Trends in Vertical Tx reduction over time by study result



Sometimes can lead astray

Efavirenz “black box” for pregnancy

Dolutegravir pregnancy ban…..

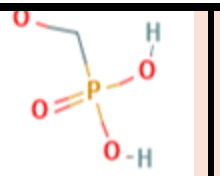
PrEP 1: TDF/FTC: Daily oral HIV prevention pill

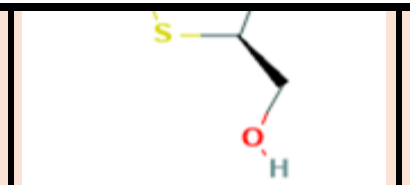
Agent class:
TDF: Tenofovir and FTC: Emtricitabine

When adherence is high, HIV protection

SAMJ EDITORIAL

Urgent appeal to implement pre-exposure prophylaxis for pregnant and breastfeeding women in South Africa





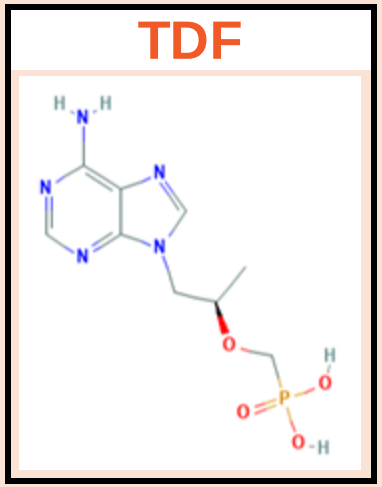
			count)
iPrEx	51%	44%	92% (tenofovir in blood)
FEM-PrEP & VOICE	<30%	No HIV protection	N/A

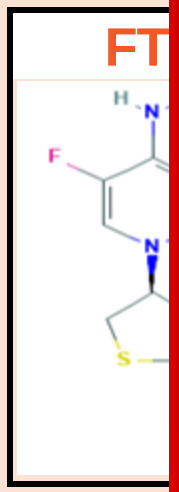
Dosing Strategy: Daily oral PrEP

Baeten et al N Engl J Med 2012; Thigpen et al N Engl J Med 2012; Choopanya et al Lancet 2013; Grant et al N Engl J Med 2010; Van Damme et al N Engl J Med 2012; Marrazzo et al CROI 2013 Lui A, et al Science Translation 2018; Marrazzo J etal Lancet HIV 2024

PrEP 1.5: TDF/FTC: Oral HIV prevention – On Demand!

Agent class:
TDF: Tenofovir and FTC: Emtricitabine are nucleotide reverse transcriptase inhibito





Dosing Strategy:
Oral PrEP, On demand 2-1-1: two tablets 2-24 hours before engaging in sex, a single tablet 24 hours after the first two, and another tablet 24 hours after that.

Randomized Double-Blinded vs. Placebo then Open-Label Extension among MSM (TDF/FTC on demand

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

months from D0

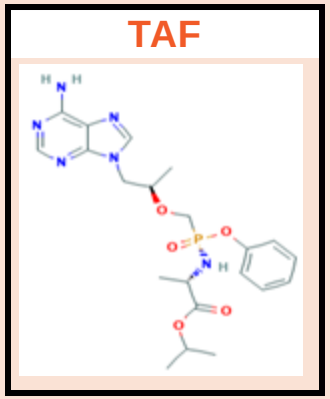
N at risk :	*Placebo*	*201*	*142*	*74*	*55*	*42*
	TDF/FTC	*199*	*141*	*82*	*58*	*43*

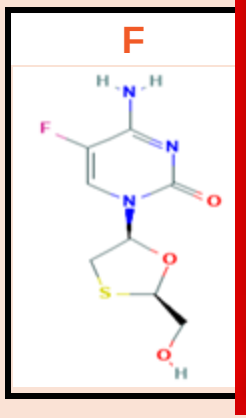
Median follow-up of 9.3 months: 16 subjects infected
14 in placebo arm (incidence: 6.60 /100 PY) and **2 in TDF/FTC arm** (0.91 /100PY)

86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)
NNT to avert one HIV-infection: 18 (95% CI: 11-50)

PrEP 1.5: DESCOVY F/TAF: Daily/on demand Oral prevention

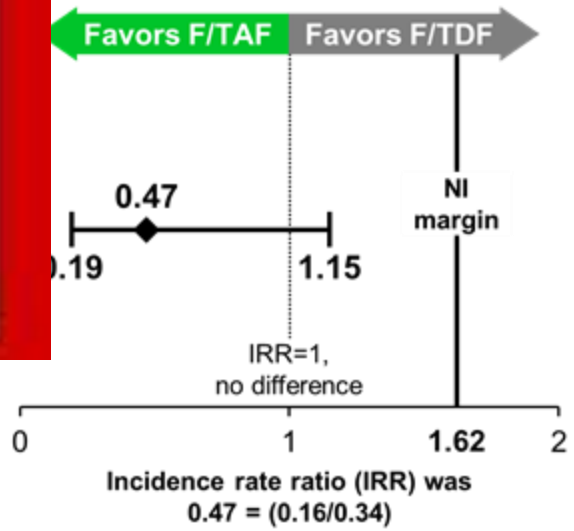
Agent class:
F/TAF = Emtricitabine/ Tenofovir Alafenamide are nucleotide reverse transcriptase inhibitors





Dosing Strategy: Daily oral PrEP
Better PK and fewer side effects

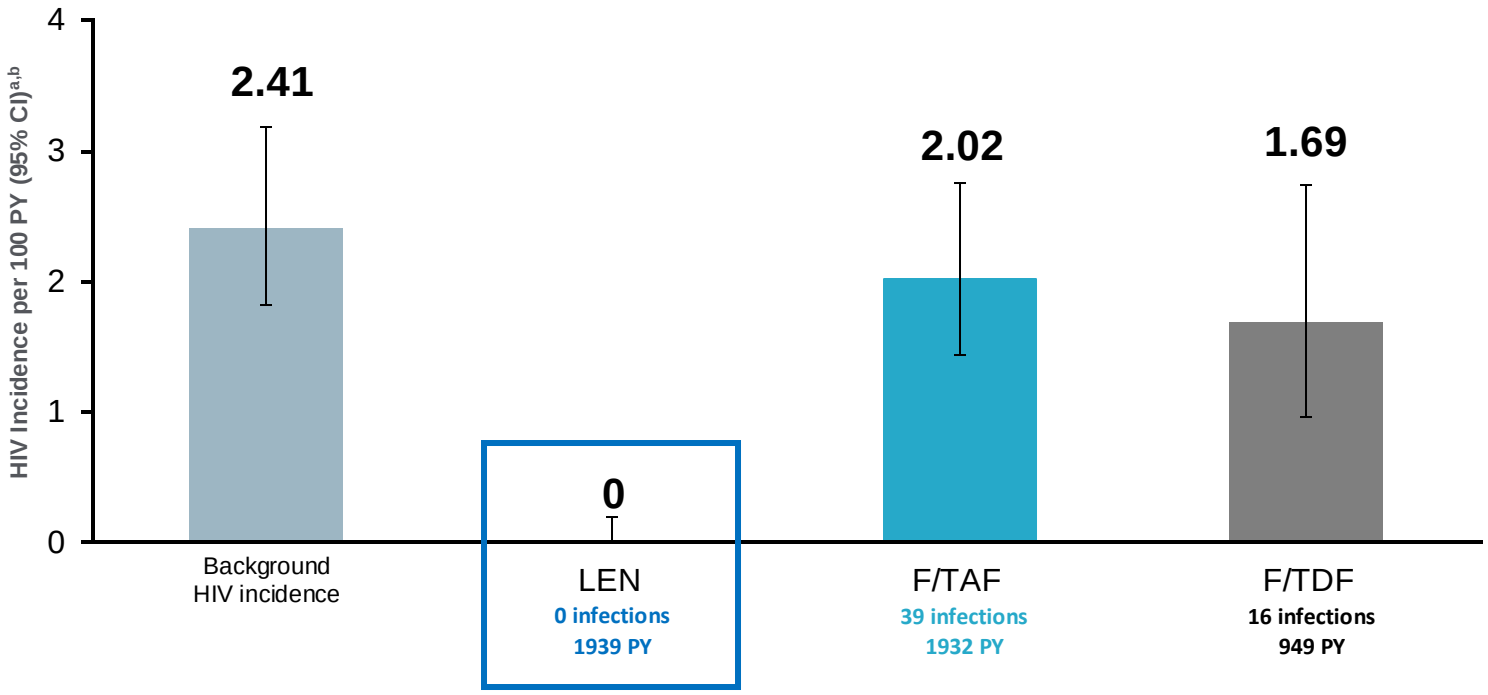
in a sensitivity analysis



*Under evaluation for on-demand and Meyer et al Lancet 2020

Spinner et al., IAS 2019 Mexico, Oral

Zero HIV Infections in Cisgender Women receiving LEN



[a]Overall n: background HIV incidence group 8094; LEN, 2134; F/TAF, 2136; F/TDF, 1068. [b]95% CIs: background HIV incidence group 1.82, 3.19, LEN 0, 0.19, F/TAF 1.44, 2.76. F/TDF 0.96, 2.74.
CI, confidence interval; PY, person-years.

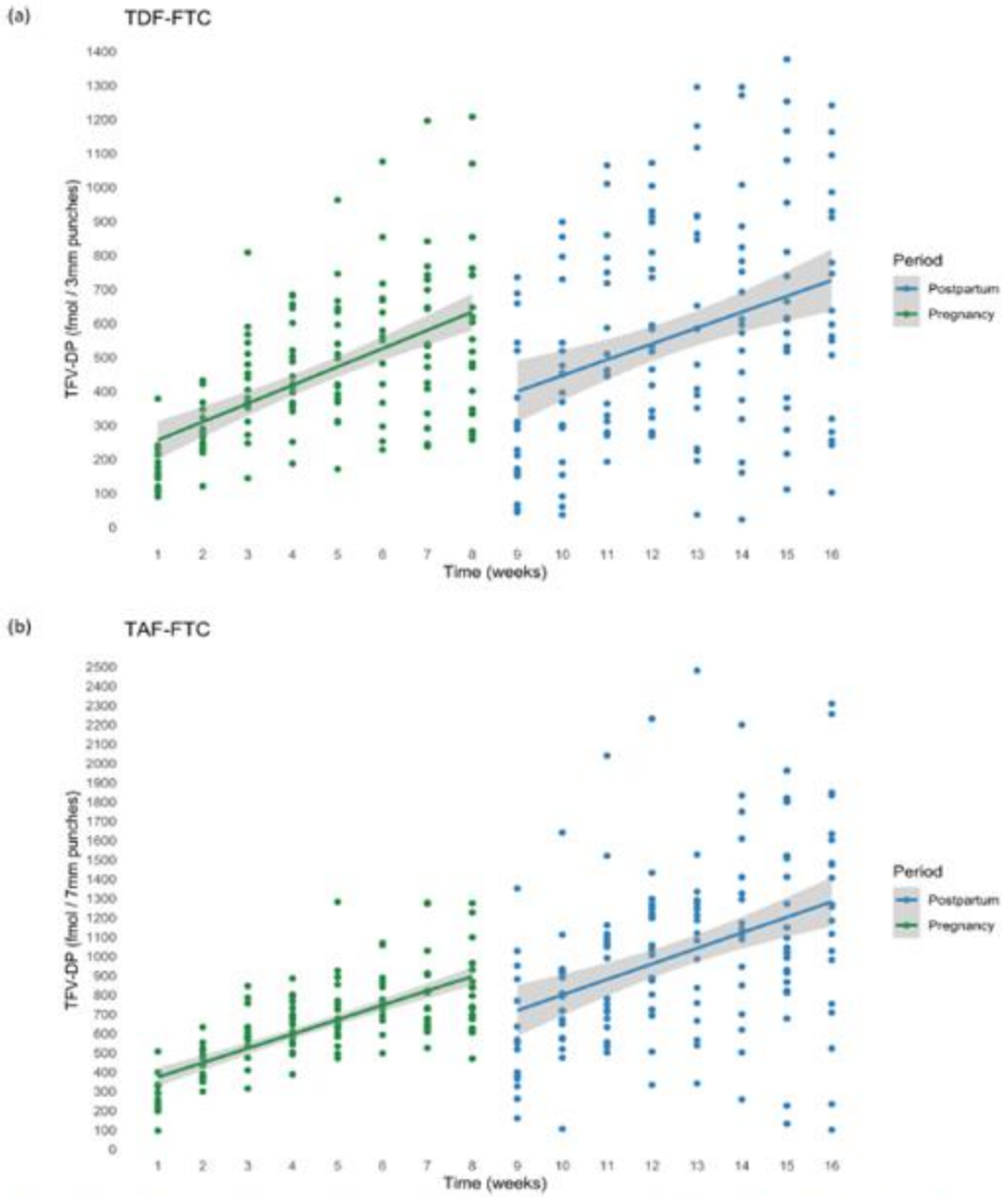


Fig. 3. Linear relationship, adjusted for age and haematocrit at baseline, of: a) TFV-DP (fmol/3 mm punch) in the TDF-FTC arm and b) TFV-DP (fmol/7 mm punch) in the TAF-FTC arm.

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

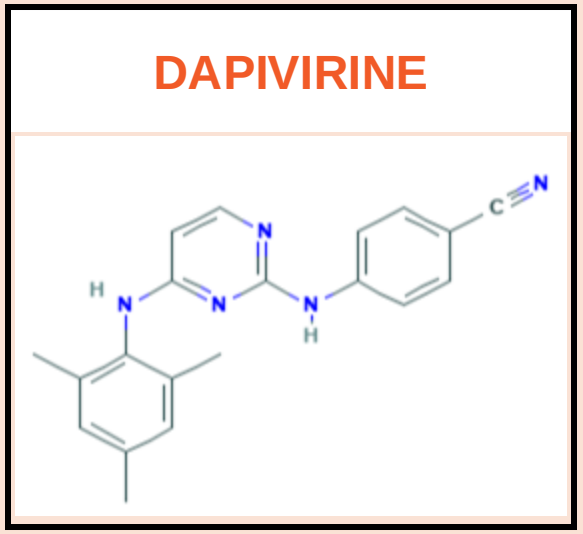
Evaluation of pharmacokinetics of Tenofovir Alafenamide (TAF) and Tenofovir Disoproxil (TDF) in pregnant and postpartum women in South Africa: PrEP-PP PK study

Dvora Joseph Davey [a,b,*,1], Sumaya Dadan [a,1], Kalisha Bheemraj [a], Catriona Waitt [d,e], Saye Khoo [d], Landon Myer [a], Lubbe Wiesner [f], Laura Else [d], Beth Thompson [d], Sandra Castel [f], Nafisa Wara [b], Peter L. Anderson [c], Catherine Orrell [g]

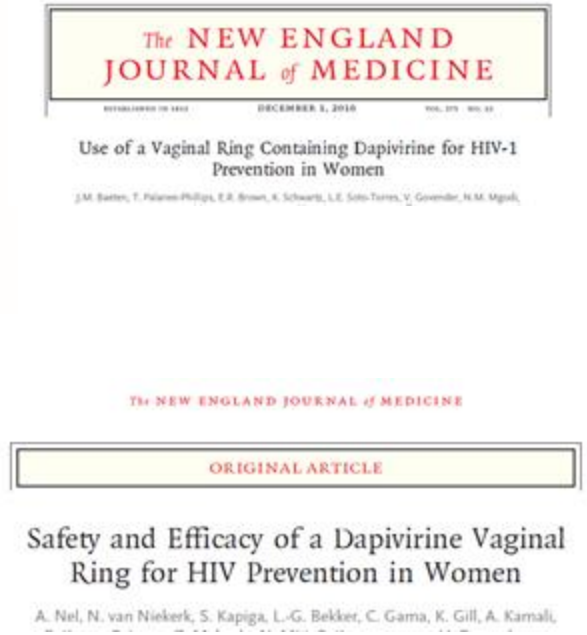
In conclusion, we found that TFV-DP concentrations were not significantly different during pregnancy than postpartum, in both DBS as well as PBMC, and for TDF-FTC, while TAF-FTC formulations of oral PrEP were slightly higher in postpartum in DBS measures. We found high concentrations of TFV-DP in PBMC in pregnancy and postpartum on TAF, suggesting PrEP efficacy is retained. Further research is needed to explore the implications of lower PrEP levels in pregnant women on the efficacy of PrEP and levels of protection afforded during this time. Efficacy and safety studies are warranted to evaluate TAF-FTC for PrEP in pregnant and postpartum women.

Dapivirine Ring: Use of a vaginal ring for HIV prevention

Agent class:
Non-nucleoside reverse transcriptase inhibitors (NNRTI)



Dosing Strategy:
Monthly dapivirine ring



In both studies: Open label extension improved effectiveness - RR 0.50
EMA approved for section 58: (1) WHO recommendations, (2) Women in LMIC ; Second line to PrEP.

DVR: New studies

THE DELIVER STUDY, REPORTED IN INTERIM FINDINGS:

- No safety concerns were found in:
  - Cohort 1 (36+ weeks/8-9 months pregnant);
  - Cohort 2 (30-35+ weeks/7-8 months pregnant);
  - Cohort 3 (12-29 weeks/3-7 months pregnant).
- Follow up for cohort 3 concluded in mid 2023, babies followed up for an additional year after birth
- Final results anticipated late 2024 or early 2025

THE B-PROTECTED STUDY, REPORTED FINDINGS:

- Favourable safety profile and previous data showing low drug transfer to breastmilk supports updates of WHO to include breastfeeding women when recommending PrEP Ring as an HIV prevention option

REACH study: Adolescent girls and young women

Safety and use of dapivirine ring and oral PrEP among 300 young women ages 16-21 in South Africa, Uganda, Zimbabwe; began February 2019

- **Choice** Twice as many adolescents chose the ring over oral PrEP (67% vs 31%)
- **Safety** No safety concerns noted for either
- **Acceptability** Ring: High adherence – drug release ≥ 4.0mg

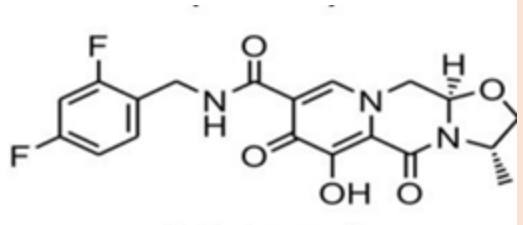
Source: Nair, Celum et al., Lancet 2023

Cabotegravir LA: Long-acting suspension for delivery via IM injection

Agent class:
Strand-transfer integrase inhibitor

Trials:
HPTN 084 & 083

CABOTEGRAVIR

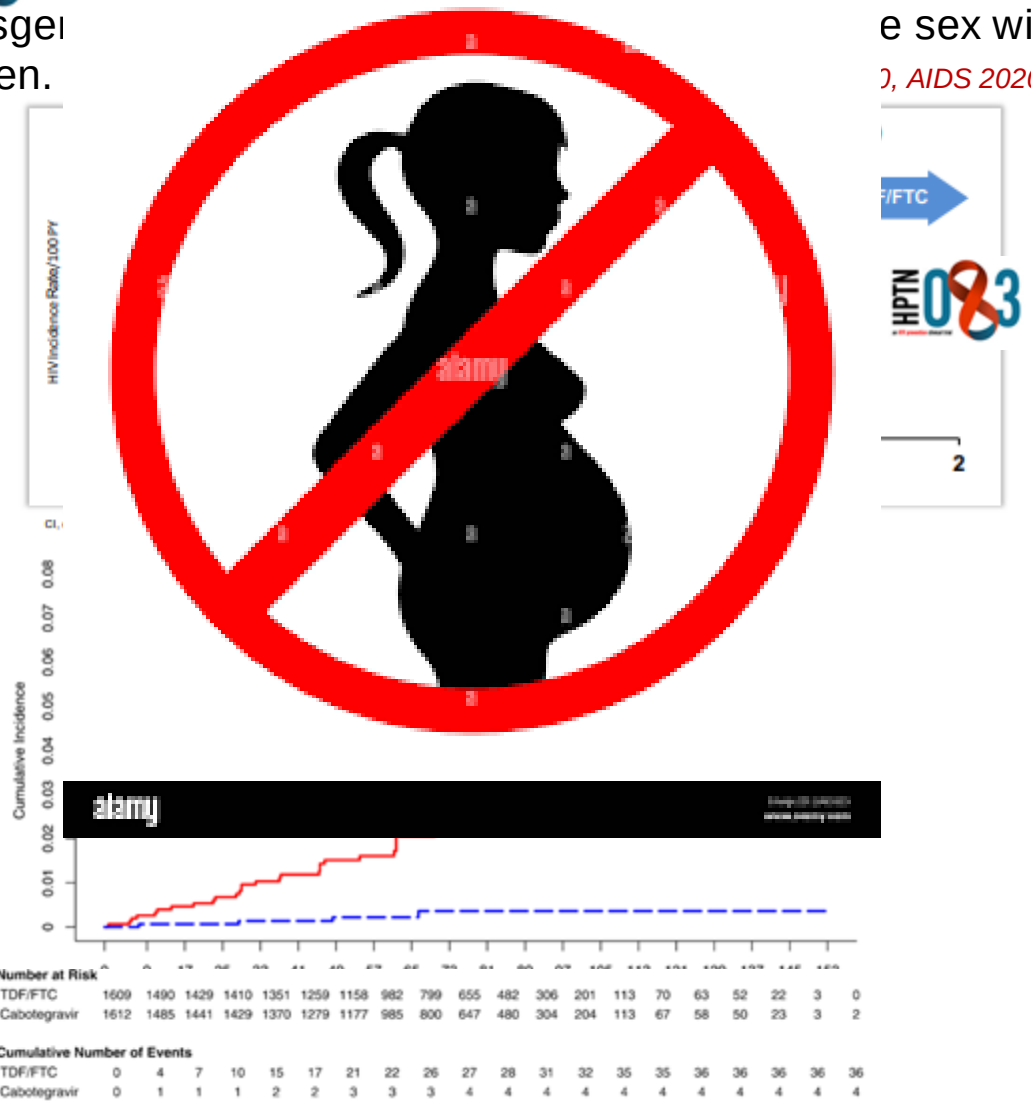


Half-life:
Oral: 40 hours
Injectable: 40-65 days

Dosing Strategy:
Single injection every 8 weeks

HPTN 083 : Long-acting CAB vs daily oral TDF/FTC among cisgender men who have sex with men.

..., AIDS 2020 Virtual



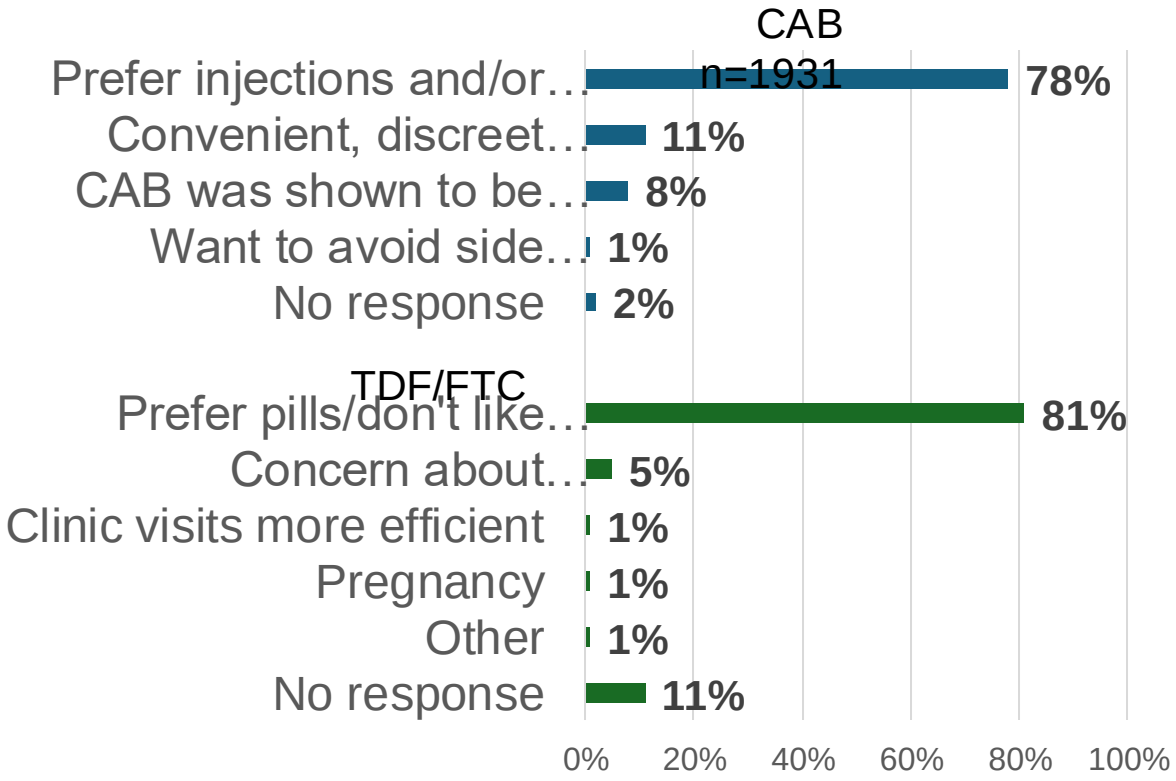
HPTN 084 : Final results (reported at IAS R4P 2021) show LA CAB is safe and superior to TDF/FTC amongst cisgender African women

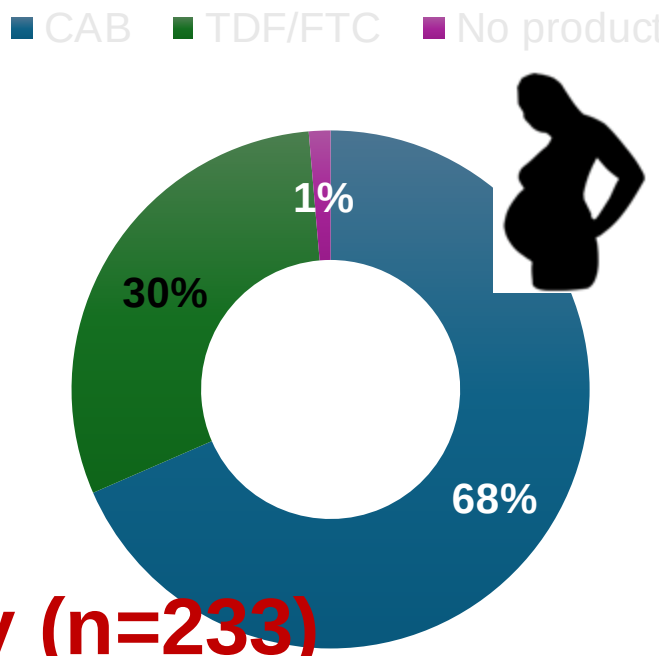
*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

- As safe and well-tolerated as TDF/FTC
- Pregnancy incidence in the study was 1.5 per 100 person-years in the CAB group, with **no congenital abnormalities** reported
- STI incidence (CT and NG) was similar in both arms

Delany-Moretlwe et al., IAS 2021

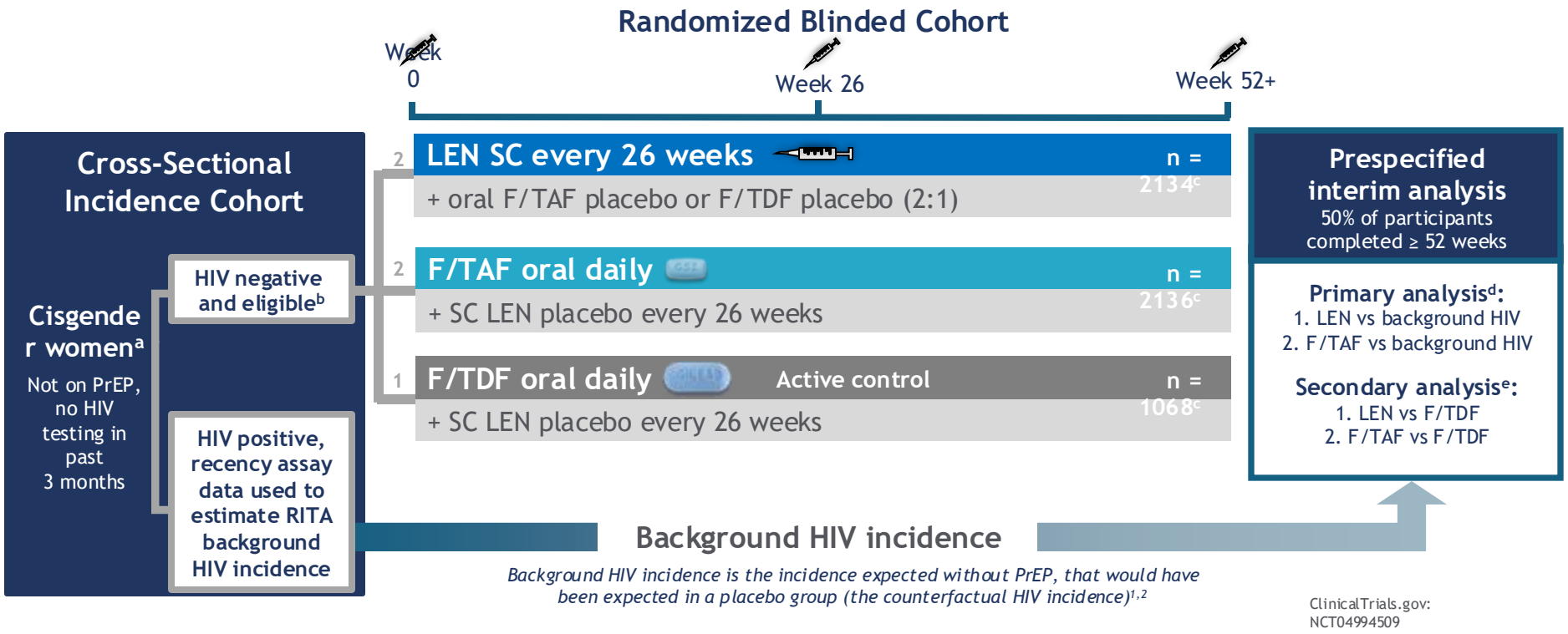
Reasons for product choice





Product choice, pregnancy (n=233)

PURPOSE 1 Study Design



[a]The first participant was screened in August 2021, the 50th percentile participant was randomized in May 2023, and the last participant was randomized in September 2023. [b]Eligibility criteria included: weight ≥35 kg, eGFR ≥60 ml/min, not pregnant. [c]n numbers represent the full analysis set for efficacy analyses. [d]IRR was assessed using a Wald test or likelihood ratio test if there were zero infections.[1,2] [e]IRR was assessed using Poisson regression or an exact conditional Poisson regression model in case of zero infections. eGFR, estimated glomerular filtration rate; IRR, Incidence rate ratio; RITA, recent-infection testing algorithm.

1. Gao F, et al. *Stat Commun Infect Dis*. 2021;13(1):20200009. **2.** Shao Y, Gao F. *Stat Commun Infect Dis*. 2024;16(1):20230004.

Pregnancies Were Common and Outcomes Similar to Expected Rates in the Population

Participants and Pregnancies, n (%)	LEN n = 2138	F/TAF n = 2137	F/TDF n = 1070
Participants with confirmed pregnancies	184	208	95
Confirmed pregnancies	193	219	98
Completed pregnancies	105 (54.4)	119 (54.3)	53 (54.1)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)
Births[a]	55 (28.5)	45 (20.5)	21 (21.4)
Interrupted pregnancies	50 (25.9)	74 (33.8)	32 (32.7)
Induced abortion	30 (15.5)	40 (18.3)	20 (20.4)
Spontaneous miscarriage[b]	20 (10.4)	34 (15.5)	12 (12.2)

Expected spontaneous miscarriage rate[1,2]:

- **~10-20% of clinically recognized pregnancies**
- **~30% of biochemically detected pregnancies**

Available pregnancy outcomes were similar to those expected for the population[3]

[a]Completed uninterrupted pregnancies which includes live births and 8 still births: 3 in the LEN group, 4 in the F/TAF group, and 1 in the F/TDF group. [b]Spontaneous miscarriage defined as occurring at < 20 weeks' gestation.

1. ACOG Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2018;132(5):e197-e207. **2.** Wilcox AJ, et al. *N Engl J Med.* 1988;319:189-94. **3.** Mugo NR, et al. *JAMA.* 2014;312(4):362-71.

Acknowledge

- Champions
- Phases
- Prepare
- WHO working group- tool box
  - IS on CABLA WG
- Academics