MASSACHUSETTS GENERAL HOSPITAL
MEDICAL PRACTICE EVALUATION CENTER

HIV and Pregnancy

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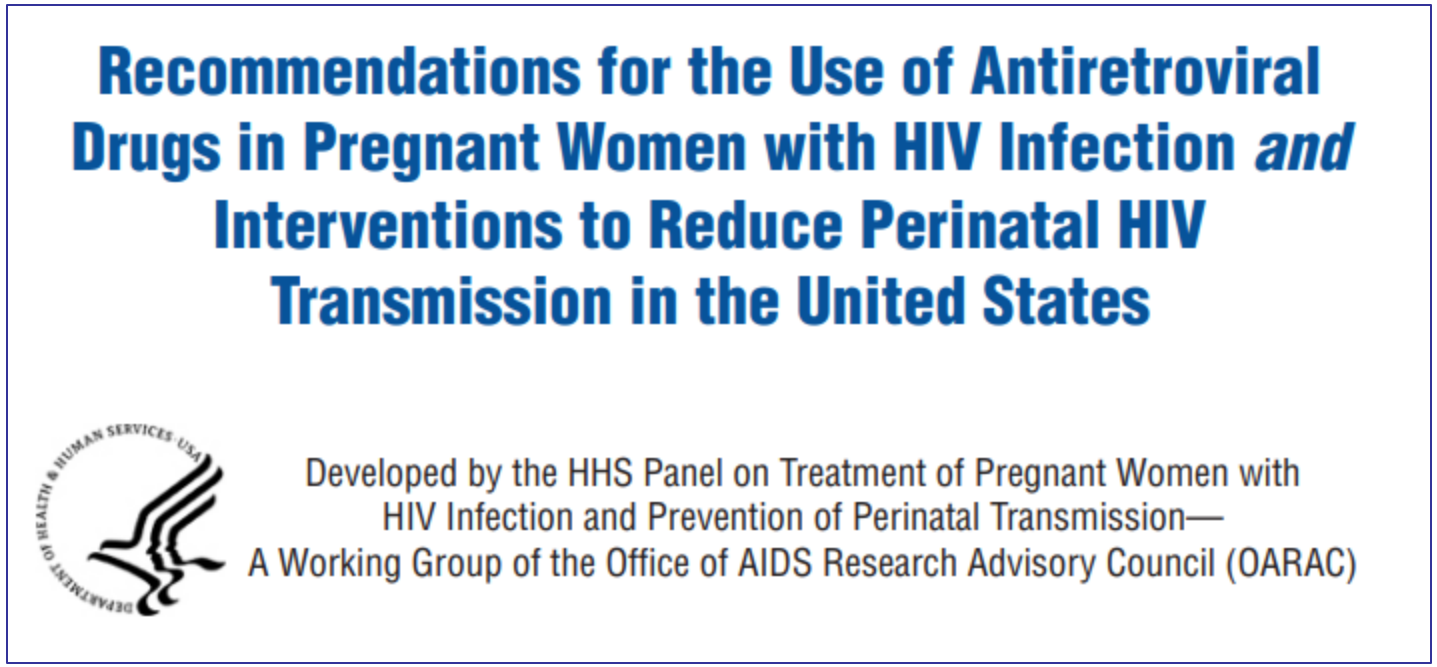
Disclosures

- No conflicts of interest
- HHS Guidelines



Overview

- Review of epidemiology and transmission risks
- Choice of ARVs in pregnancy (WHO and HHS)
  - Updates in 2020 (& 2021?) HHS HIV & Pregnancy guidelines
- Monitoring during pregnancy and breastfeeding

Spectrum of Pregnancy-Related Care

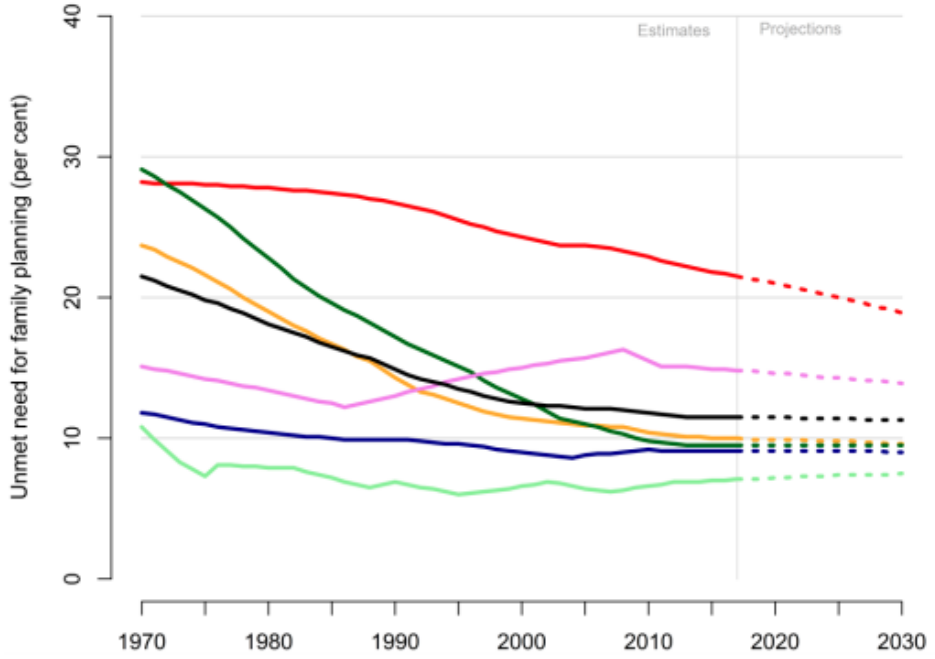
- Two goals: Healthy parents & healthy babies

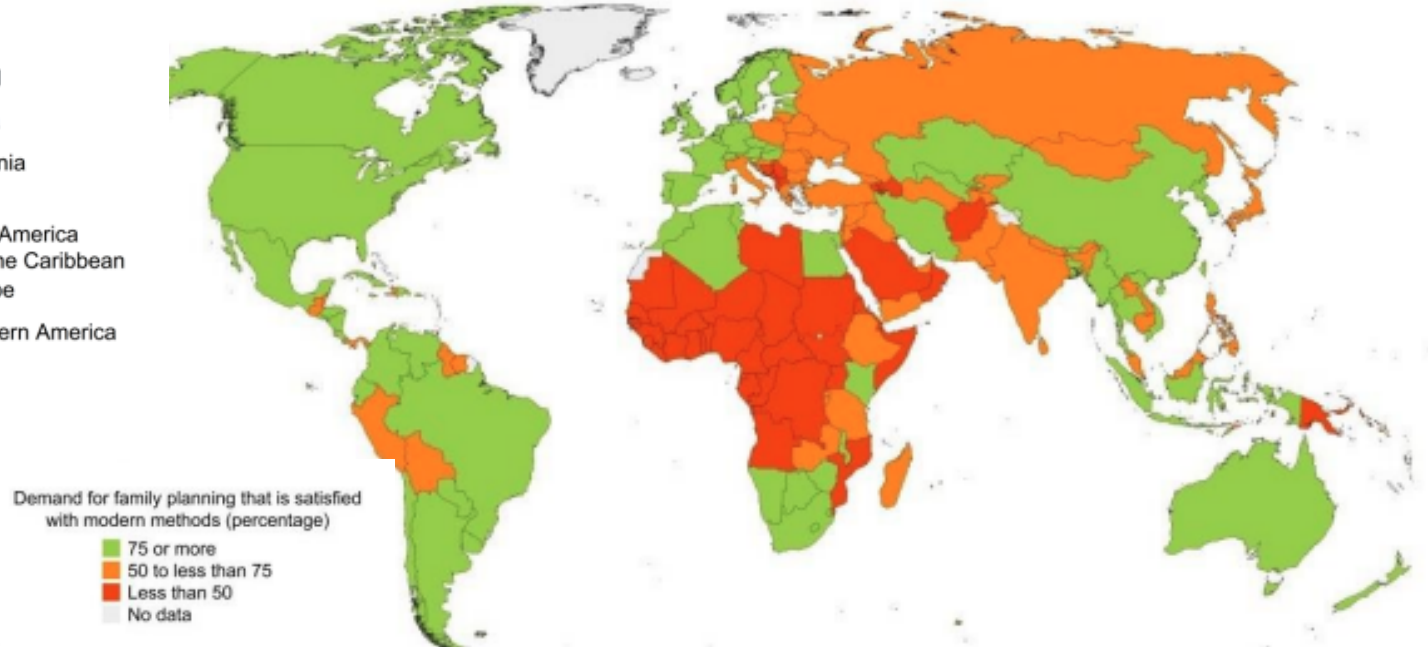
- Four steps:
  - Planned pregnancies
  - Prevention of new infections in people of childbearing potential
  - Safer conception strategies for people with and without HIV
  - HIV-specific care for pregnant people

UNICEF/WHO

Planned Pregnancies

- 2017: 12% of women (married/in-union) had unmet family planning need; 19% in Africa
- 85 million unplanned pregnancies/year (40%)





Data source: United Nations, Department of Economic and Social Affairs, Population Division (2017b). *Model-based Estimates and Projections of Family Planning Indicators 2017*. New York: United Nations.

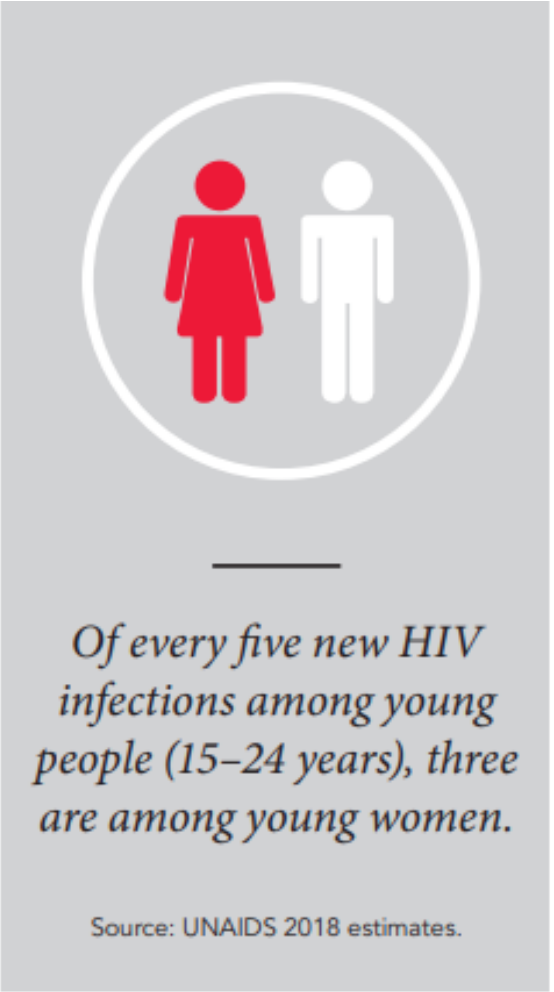
Sedgh Studies in Family Planning 2014; United Nations 2017

Planned Pregnancies

- All women:
  - Plan families, space children safely
  - Screen and treat STIs, cervical dysplasia, etc
- Women with HIV:
  - Safe, well tolerated regimen, good adherence
  - Full viral suppression from before conception: near zero transmission to baby, zero transmission to partners (U=U)

Prevention of New Infections in Women

- Women and girls:
  - 48% of all new infections in 2019
  - 59% in sub-Saharan Africa in 2019
- Women aged 15-24:
  - 5,500 new infections/week in 2019 (290,000/year)
- Adolescent girls/women risk > boys/men
  - SSA: 5 in 6 new adolescent infections are in girls; women 15-24 2x more likely to have HIV than men
- Incidence in pregnancy: 4.7/100PY
- Incidence in breastfeeding: 2.9/100PY



https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf; Drake PLoS Med 2014

Prevention of New Infections in Women

- In addition to women's health:
  - Vertical transmission 2-3-fold higher with incident > chronic maternal infection
  - Preventing maternal infection critical to "elimination" of pediatric HIV
- Cornerstones:
  - Testing - women *and partner*s
  - PrEP
  - ART

WHO 2016; Mofenson IAS 2017; Drake PLoS Med 2014

Safer Conception Strategies for Women Living with HIV

- Regardless of partner HIV status
  - ART for her
    - Sustained viral suppression before trying to conceive
    - Optimize maternal health, reduce infant transmission, prevent partner transmission if uninfected
- Male partner without HIV
  - ? PrEP for him
  - Self-insemination: turkey baster, syringe

Matthews AIDS and Behavior 2017

ART in Pregnancy

Treatment goals:

Early and sustained virologic control

Viral load undetectable throughout pregnancy and at delivery

ART in Pregnancy

- If already on ART at conception:

  * DO NOT ROUTINELY STOP ART *

  – ART interruptions:
    - 1st-trimester: 10-fold increase in MTCT risk
    - 3rd-trimester: 47-fold increase in MTCT risk

  – May rarely need to change regimen (teratogenicity, tolerance)

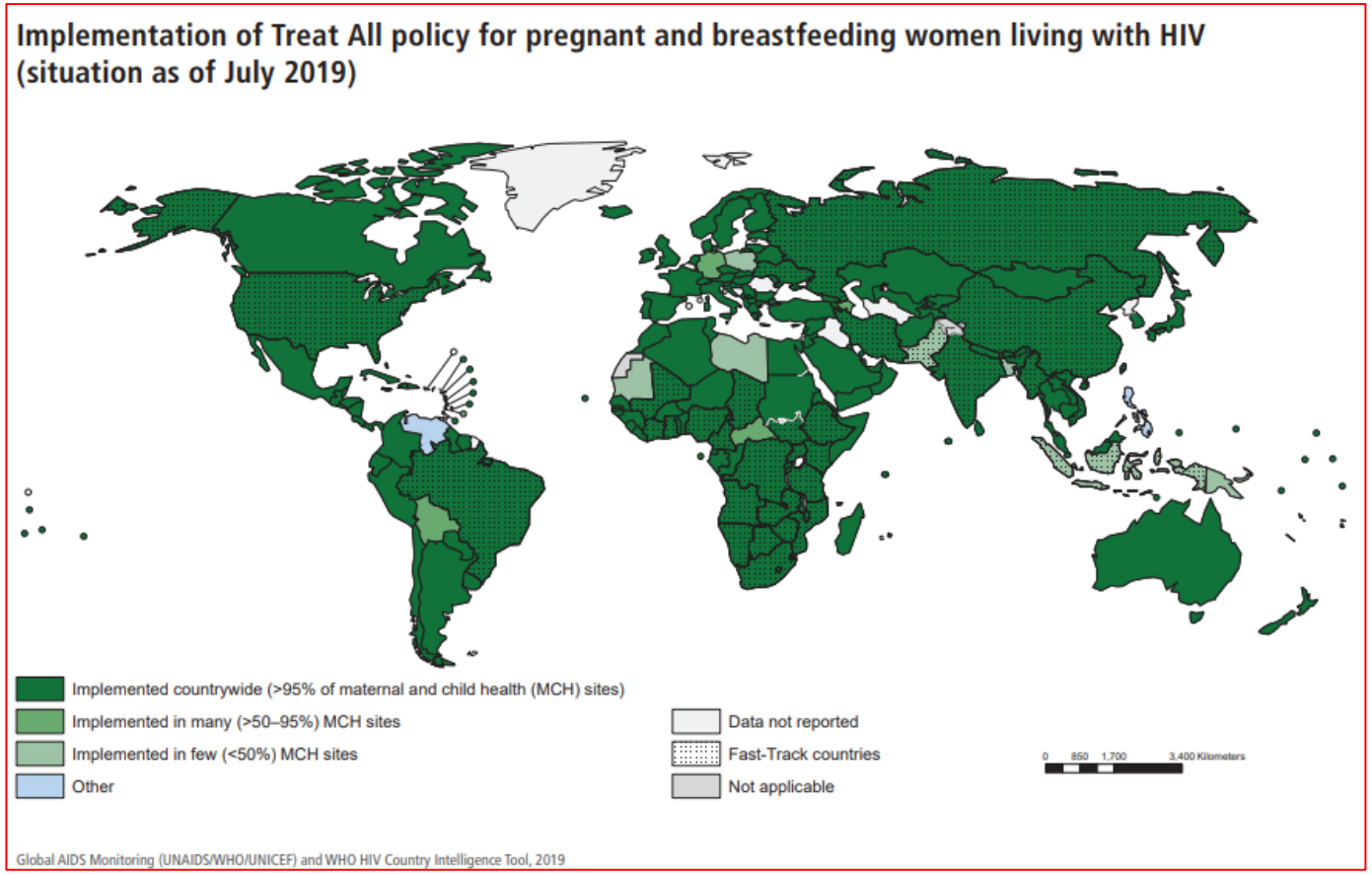
Galli, CID 2009

ART in Pregnancy: Goals

- Emphasize ART initiation as early as possible
  - Do not routinely wait for 2nd trimester
  - Start before resistance testing results available; modify regimen if needed

Choice of ARVs

- Complete 3-drug ART regimen recommended in pregnancy – now worldwide
- First-line ART
  - Preferred: DTG + TDF + (3TC or FTC)
  - Alternatives: EFV 400 or 600; TAF, ABC, AZT; boosted PI; RAL



http://www.who.int/hiv/pub/arv/treat-all-uptake/en/; https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/

Choice of ARVs: WHO Guidelines (2019)

Table 1. Preferred and alternative first-line ART regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a]
Children	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r ABC + 3TC + RAL[e] TAF + 3TC (or FTC) + DTG[f]	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV[g] (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

[a]Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (Box 2).

[b]EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. DTG-based ART is preferred, and if DTG is unavailable, a boosted PI-based regimen should be used. The choice of PI/r depends on programmatic characteristics.

[c]TAF may be considered for people with established osteoporosis and/or impaired kidney function.

[d]For age and weight groups with approved DTG dosing.

[e]RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.

[f]For age and weight groups with approved TAF dosing.

[g]EFV should not be used for children younger than three years of age.

[h]Neonates starting ART with an RAL-based regimen should transition to an LPV/r solid formulation as soon as possible.

[i]LPV/r syrup or granules can be used if starting after two weeks of age.

https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/

US: HHS Categories of ARVs

- Preferred
  - Efficacy and safety in non-pregnant adults, pregnancy-specific PK data, favorable risk-benefit compared to other options in pregnancy
- Alternative
  - Efficacy in non-pregnant adults, limited but favorable pregnancy data (e.g., abstracts)
- Insufficient data
  - Approved for non-pregnant adults, but limited PK and safety data in pregnancy
- Not recommended except in special circumstances
  - ART-experienced may need to initiate or continue
- Not recommended
  - Inferior efficacy or potentially serious maternal or fetal safety concerns

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/0

US 2020: HHS Preferred Regimens

ART-naïve	Conceive on suppressive, well-tolerated ART	Restarting ART	Conceive on not well tolerated/not suppressive ART	Trying to conceive
INSTIs				
DTG, RAL (BIC = insufficient data)	DTG, RAL Consider switch: EVG/c	DTG, RAL	DTG, RAL	DTG, RAL
PIs				
ATV/r, DRV/r (cobi=not rec)	ATV/r, DRV/r	ATV/r, DRV/r	ATV/r, DRV/r	ATV/r, DRV/r
NNRTIs (No preferred agents; EFV and RPV = alternative)				
NRT(s)Is ABC, TDF, FTC, 3TC preferred in all categories ZDV, TAF = alternative; both = continue if conceived-on				Red = changes in 2020

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/522/table-5--situation-specific-recommendations-for-use-of-arvs

US 2020: HHS Preferred Regimens

ART-naïve	Conceive on suppressive, well-tolerated ART	Restarting ART	Conceive on not well tolerated/not suppressive ART	Trying to conceive
INSTIs				
DTG, RAL (BIC = insufficient data)	DTG, RAL Consider swit			DTG, RAL
PIs				
ATV/r, DRV/r (cobi=not rec)	ATV/r, DRV/r			ATV/r, DRV/r
NNRTIs (No preferred agents; EFV and R. alternative)				
NRT(s)Is ABC, TDF, FTC, 3TC preferred in all categories ZDV, TAF = alternative; both = continue if conceived-on				Red = changes in 2020

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/522/table-5--situation-specific-recommendations-for-use-of-arvs

US 2020: ART in Pregnancy: Two of These and One of Those

- Two of: NRTIs
  - Preferred: tenofovir difumarate (TDF) or abacavir (ABC)
  - With either lamivudine (3TC) or emtricitabine (FTC)
  - Tenofovir alafenamide (TAF): now alternative (may move up to preferred?)
- Preferred coformulations in US: ABC/3TC, TDF/FTC, TAF/FTC
- Considerations:
  - TDF: equivocal data on bone growth, concern for premature delivery with LPV/r
  - TAF: fewer data, possibly weight gain (may be beneficial)
  - ABC: requires HLA-B5701 testing
  - Avoid: 2-drug regimens (DTG/3TC)

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/488/overview

US 2020: ART in Pregnancy: Two of These and One of Those

- One of: PI, INSTI, or NNRTI
  - PI: Darunavir or atazanavir + ritonavir
  - INSTI: Raltegravir, dolutegravir
  - NNRTIs: No preferred agent
- Only preferred single-pill regimen in US: ABC/3TC/DTG (Triumeq)
- Considerations:
  - Dolutegravir: QD, rapid viral load reduction, neural tube defect counseling
  - Raltegravir: BID in pregnancy, rapid viral load reduction
  - Darunavir/r: BID in pregnancy, 2 pills
  - Atazanavir/r: QD, 2 pills; avoid PPIs, 2h before or 10h after H2 blockers; hyperbilirubinemia
  - Avoid: cobicistat-boosted regimens

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/488/overview

US 2020: People Who Conceive on ART (1)

- Doing well → continue
- Need new regimen → choose as for new ART initiation
- Some “not recommended” regimens may be used in special circumstances
    - E.g., extensive drug resistance or intolerance

US 2020: People Who Conceive on ART (2)

- Uncertainty about best management of cobi-boosted regimens
  - Darunavir/cobi, atazanavir/cobi, elvitegravir/cobi
  - Reduced drug levels (cobi and primary agent) in 2nd and 3rd trimesters
    - Viral breakthrough in up to 25%
  - Monitor VL frequently: may need to switch in 3rd trimester, when transmission risk is high, little time to suppress before delivery
  - Switch early: may be unnecessary, may → rebound (but early when transmission risk lower, time to address)

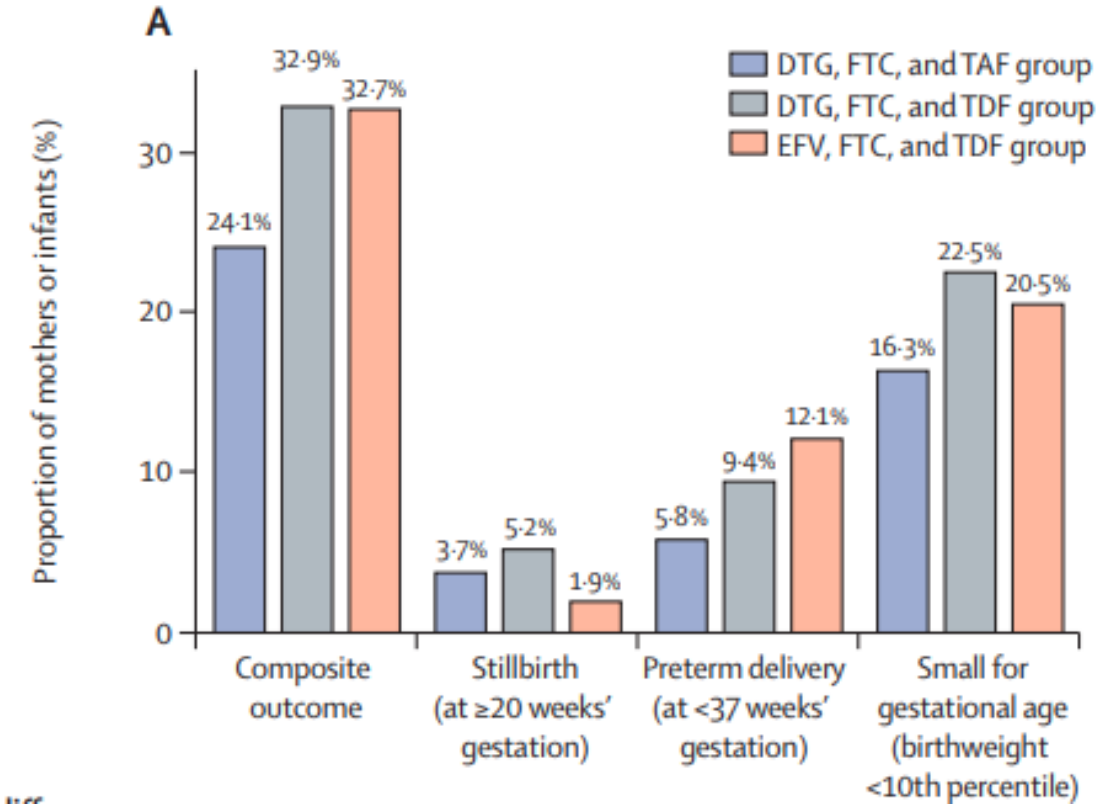
US 2020: People Who Are Trying to Conceive

- If well-tolerated, suppressive ART: continue in most cases
  - May change away from cobi-boosted regimens
  - 2021: how to manage ART in people who conceive on long-active CAB/RPV
- If need to switch ART:
  - Use principles of initiating ART, adjust for prior resistance/intolerance
- Counsel around all ARVs and known/unknown fetal risks

Momper, AIDS 2018, Crauwels HIV Med 2019

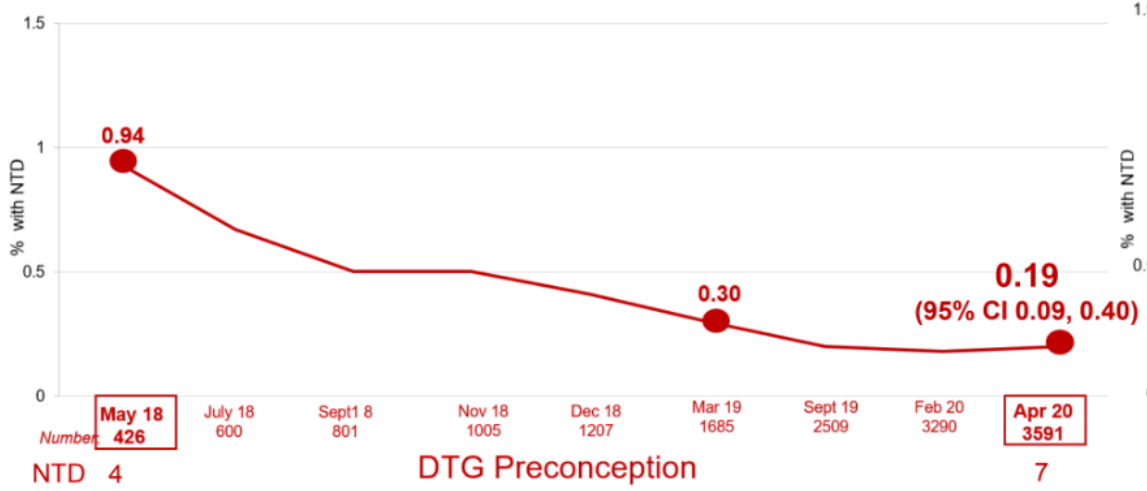
VESTED (IMPAACT 2010)

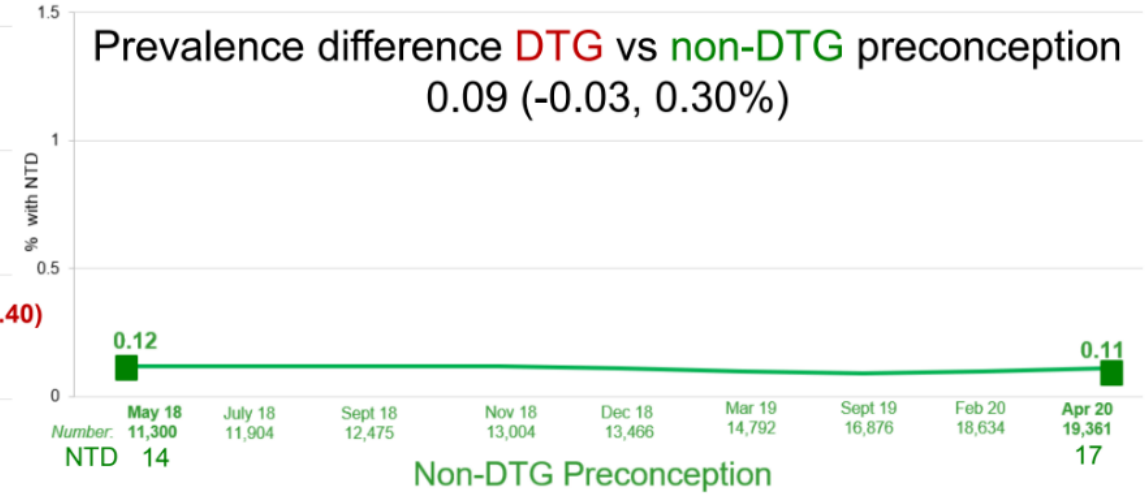
- RCT of 3 ART regimens initiated at 14-28 weeks
  - Efavirenz/TDF/FTC
  - Dolutegravir/TDF/FTC
  - Dolutegravir/TAF/FTC
- Viral suppression at delivery:
  - Both DTG arms: 97.5%
  - EFV: 91%
- Weight gain: TAF+DTG > other 2 arms
  - EFV → insufficient weight gain (~ Tsepamo study)
  - DTG + TAF greatest, but still < goal
- Adverse pregnancy outcomes (TAF < both TDF)
- Fewer infant deaths in DTG groups (similar risk for combined infant death + stillbirth)

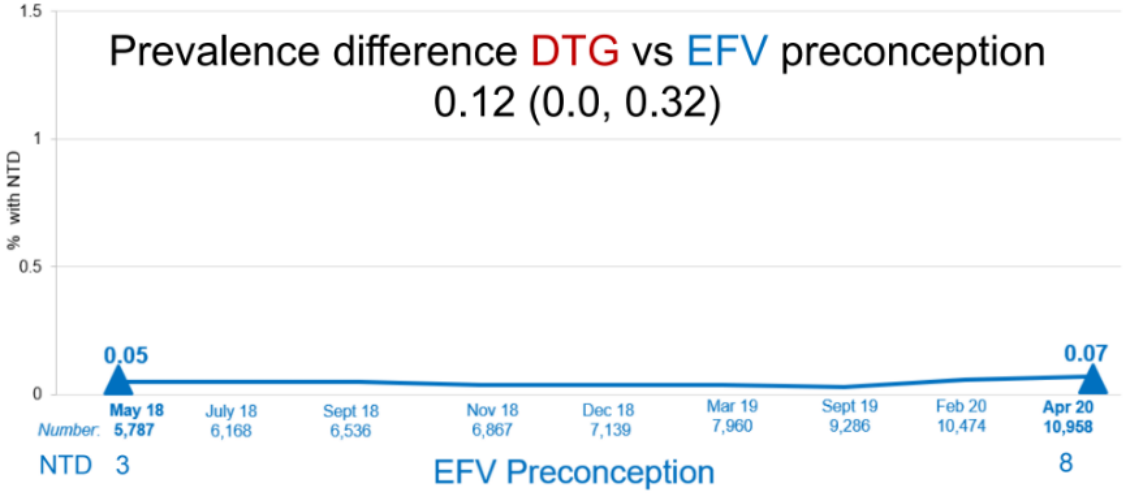


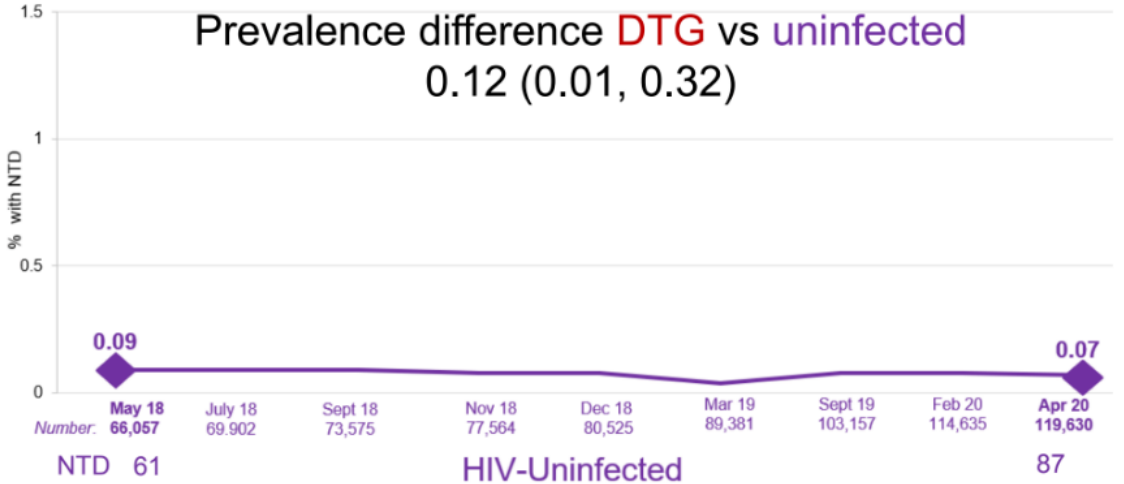
Lockman *et al., Lancet,* 2021

Ongoing Data Collection: Tsepamo









Zash, IAS 2020; Slide, Lynne Mofenson

Balancing Risks and Benefits of Preconception Use: Known vs. Unknown

- What are the alternatives to DTG, and what is known (or not known) about risks with their use preconception?

Drug	**Sample size**	**Data quality**	**NTD risk**	**Other adverse outcomes**	**Maternal considerations**
Dolutegravir	*Large*	*Excellent*	*Low*		*Weight gain w/ TAF*
Efavirenz	Large	Excellent	Lower	? Preterm birth	Toxicity (CNS), resistance
Lopinavir/RTV	Moderate	Excellent	Lower	Preterm birth	BID
Darunavir/RTV	Small	Variable	?	Preterm birth	BID
Atazanavir	Moderate	Variable	?	Preterm birth	QD, no PPI/H2 antagonist
Raltegravir	Small	Variable	?	?	BID
Bictegravir	Very small	Variable	?	?	Structure ~ DTG

Lack of data does not equal lack of risk

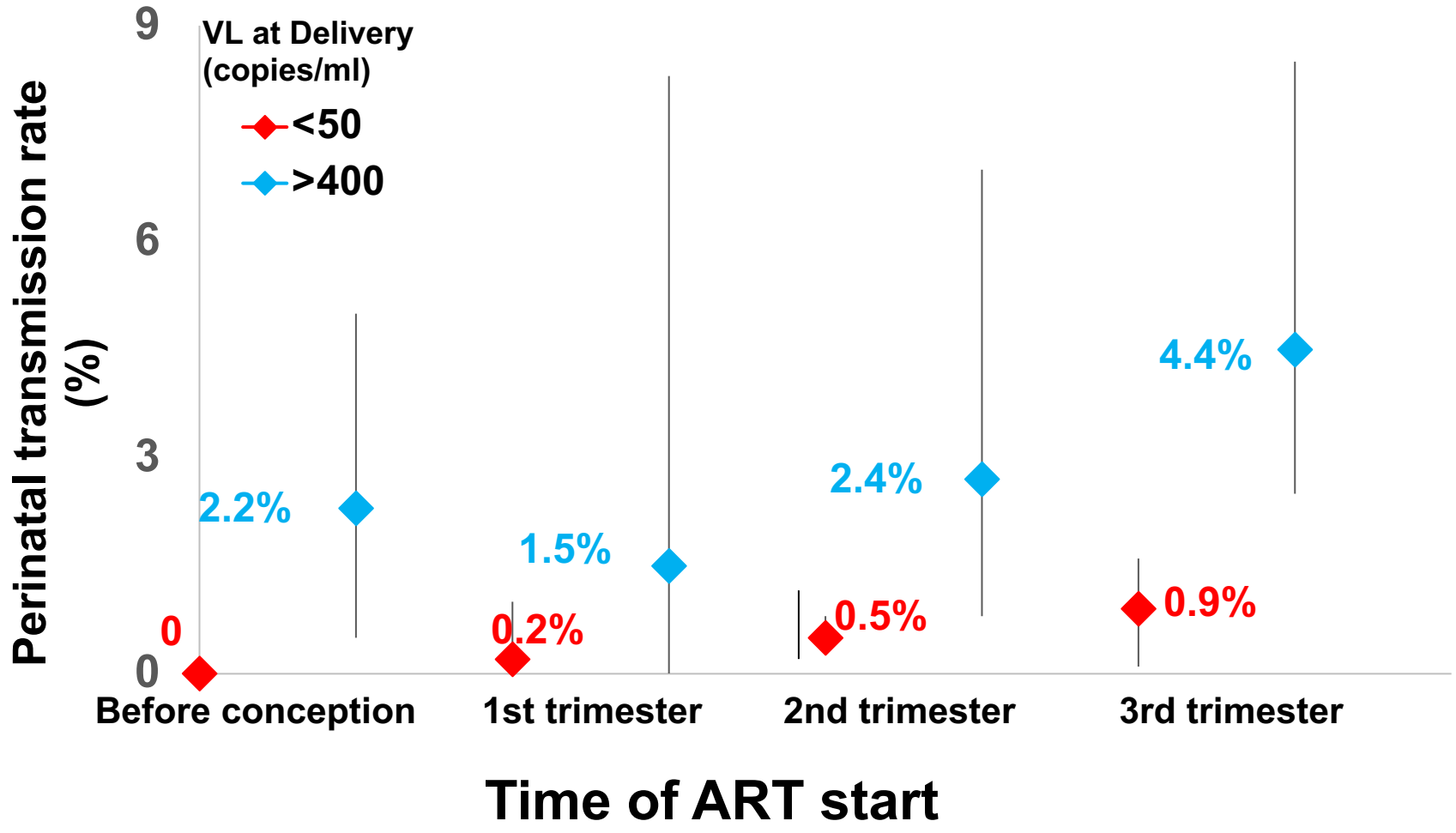
Better Data: Trials and Pharmacosurveillance

- Pregnant and breastfeeding women are excluded from most clinical trials
  - Women: 19% of research participants in ART studies
- Collection of data only when drugs are used in clinical practice
  - Less robust: ascertainment, definitions, measurements
- “A public health approach that maintains gender equity requires pregnancy safety data.” (Zash)
- WHO, DHHS, others call for development of pharmacosurveillance systems
- Lessons not learned for COVID, PrEP…

apregistry.com

Lyerly CROI 2019; Curno JAIDS 2016; Fairlie JIAIS 2019; Havlir and Doherty NEJM 2019; Zash HIV Pediatrics, 2019; Mofenson JIAS 2019

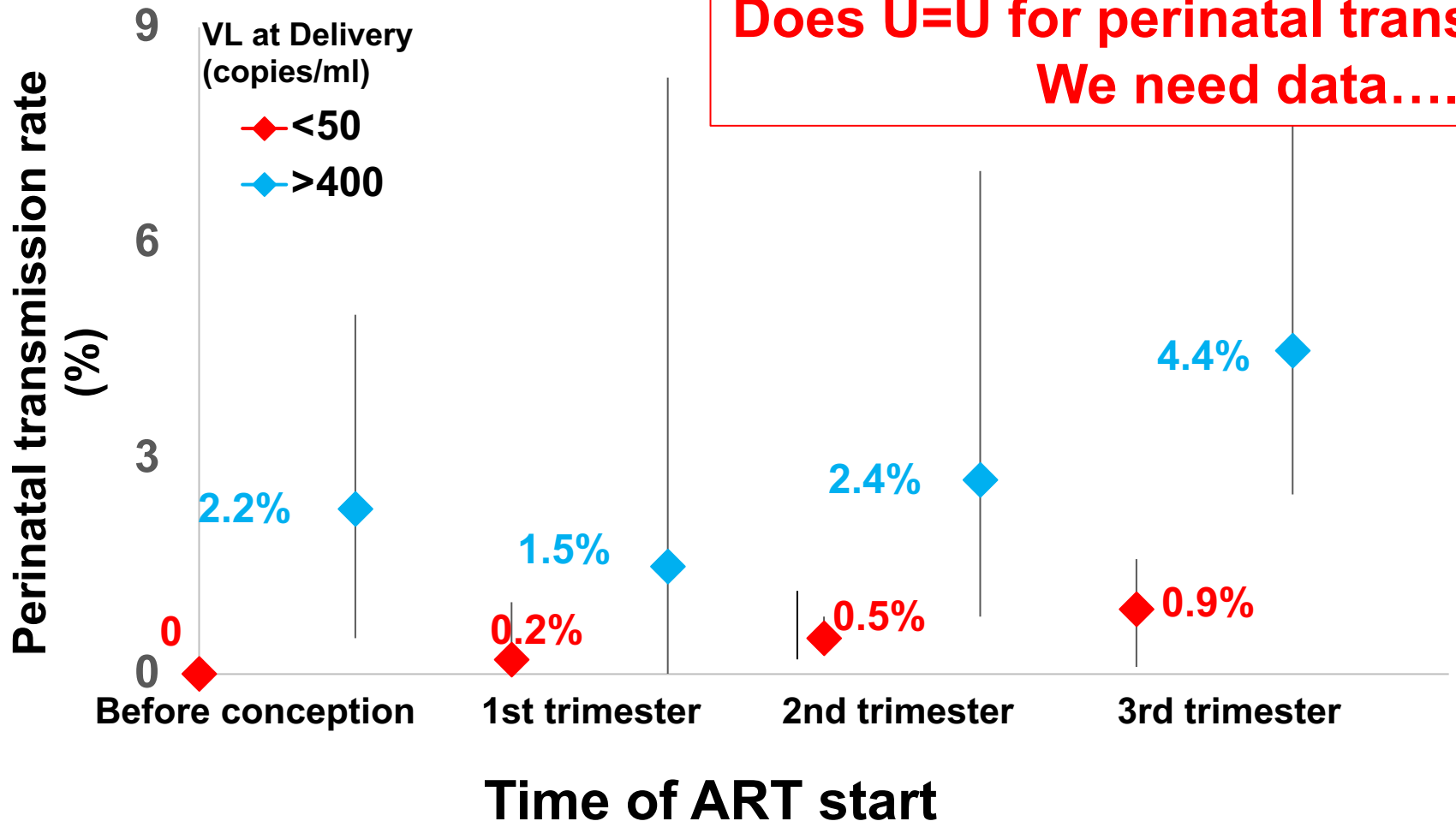
Monitoring in Pregnancy:
Early and Sustained Suppression is Critical



Mandelbrot CID 2015; graph Lynne Mofenson

Monitoring in Pregnancy:
Early and Sustained Suppression is Critical

Does U=U for perinatal transmission??
We need data….



Mandelbrot CID 2015; graph Lynne Mofenson

US: Monitoring During Pregnancy

- Viral load 2-4 weeks after ART initiation/switch, then every 4 weeks until suppressed
  - Then every 3 months including at 34-36 wks
    - Informs mode of delivery and infant prophylaxis regimen
  - Detectable virus: adherence, tolerability, dosing, resistance testing
- CD4 at first visit
  - Every 3 months if <300, on ART <2 years, uncertain adherence, or viremia
- "Safety labs" based on specific ARVs
  - 2 weeks after ART initiation/change: liver function (+ 3-monthly)
  - CBC (ZDV), creatinine (tenofovir)
- Glucose tolerance at 24-28 wks (? earlier with PIs)

US: Intrapartum Management

- If VL>1,000 or unknown near delivery:
  - IV ZDV in labor
  - Cesarean section (38 weeks)
- Continue PO ART regimen
  - With sips of water if NPO

US: Infant Prophylaxis

- Previous: 6 weeks ZDV
- New terms (introduced in 2018-19):
  - ARV prophylaxis: infant without confirmed HIV
    - Not higher risk: 4 weeks ZDV if sustained viral suppression near delivery, no adherence concerns
  - Presumptive HIV therapy: for infants at high risk
    - Serves as preliminary treatment, but also prophylaxis
    - High risk: no antepartum ARVs, no viral suppression, acute infection during pregnancy or breastfeeding
    - 3-drug regimen x 6 weeks: ZDV, 3TC, and NVP (treatment dose) or RAL
    - Option (clinical judgement): ZDV x 6 weeks plus 3 doses of NVP (prophylaxis dose)
  - HIV therapy: infants with confirmed HIV (3 drugs, treatment doses)
- PCP prophylaxis: start at 4-6 weeks (after prophylaxis) unless HIV excluded

US: Infant Laboratory Evaluation

- HIV testing by PCR (ideally DNA > RNA, but hard to order; total NA also ok)
  - "By 14-21 days"
  - At 1-2 months
  - At 4-6 months
  - Consider: at birth (high risk), 2-4 weeks after prophylaxis
  - Confirmatory testing is critical
- CBC + differential at birth, 4 weeks

Postpartum Maternal Care

- Retention in care and adherence to ART
  - Postpartum depression, social support
  - Simplification of regimens after delivery
- Contraception and future pregnancies
  - Initial concern about hormonal contraception and transmission to partners
    - WHO systematic review → no restrictions
  - Drug interactions with ART

Polis, Lancet ID 2013; http://www.who.int/reproductivehealth/publications/rtis/rhr_10_21/en/

Breastfeeding Transmission

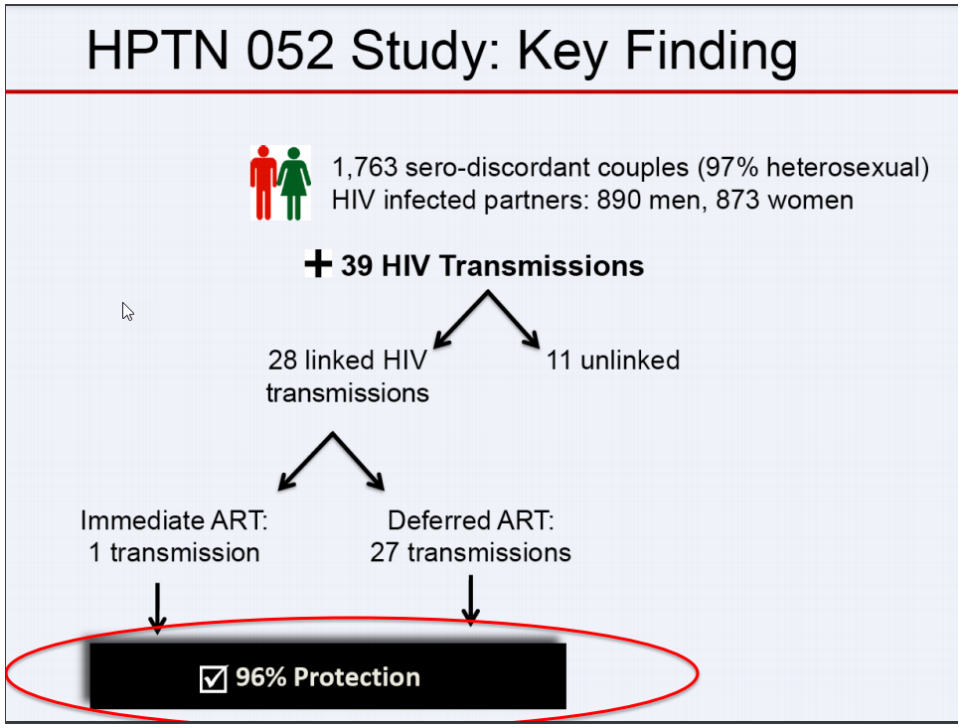
- Dugdale *et al.* (in progress)

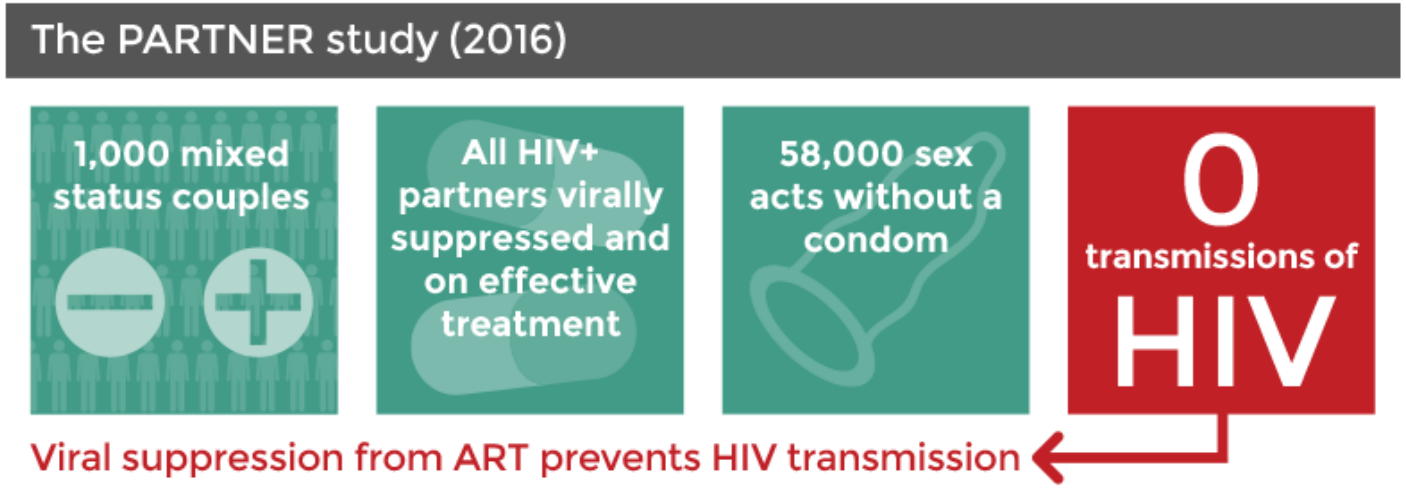
Maternal HVL, c/mL	Person-months at risk	# Events	Pooled estimate, % (95% CI)	Unadjusted Relative risk (95% CI)	p-value
Undetectable	8,423	8	**0.10** (0.02, 0.47)	*REF*	<0.05
Detectable	2,832	19	**0.47** (0.12, 1.84)	4.59 (1.02, 20.65)	

- Counseling, informed choice, harm reduction
  - Adherence support, frequent VL monitoring
  - Pump and discard if mastitis, treat infant thrush
  - Exclusive breastfeeding otherwise through 6m (pre-ART data)
  - Extended infant prophylaxis – at least 6 weeks, +/- through weaning
  - Infant virologic testing at least every 3m through 6m after weaning

PrEP

- Undetectable = untransmittable
- Data from HPTN 052 and PARTNER (male-female)
  - Also PARTNER2 and Opposites Attract (male-male)

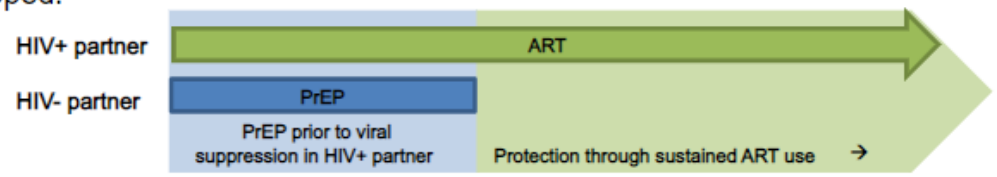




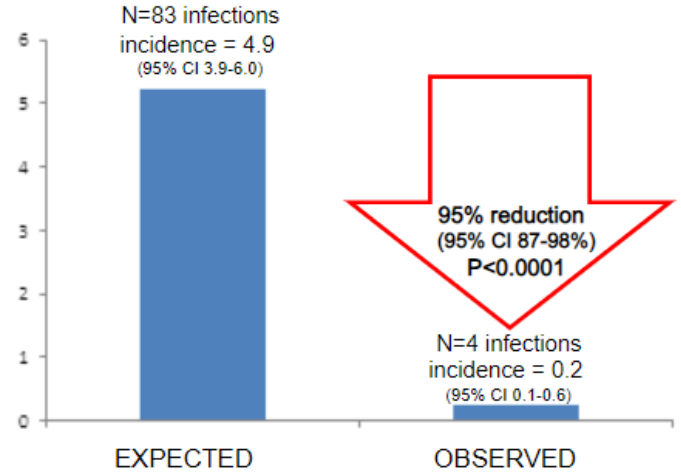
PrEP

- Partners PrEP Demonstration: PrEP as bridge to ART

  - For couples initiating ART at enrollment, PrEP was offered through 6 months, then stopped:



  - In subgroup analyses, similarly high HIV protection was seen for:
    - **Men** (97% p<0.0001)
    - **Women** (93% p<0.0001)
    - **Those in which the HIV-partner was <25 years of age** (95% p<0.0001)
    - **Couples in which the HIV+ partner had a plasma viral load ≥50,000 copies/mL** (95% p<0.0001)



- Indications:
  - Partner with HIV not yet suppressed (first 6 months)
  - Adherence and suppression not certain in partner with HIV
  - Additional assurance is desired

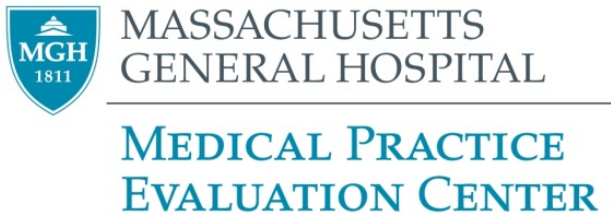
PrEP

- Meds:
  - TDF/FTC (US for PrEP in 2012 for adults, 2018 for adolescents; WHO 2017)
  - TAF/FTC (US for PrEP in 2019)
    - Excluded people who have receptive vaginal sex
    - DISCOVER trial included MSM and TGW, excluded cis women
    - Women's HIV Prevention Study (Gilead) ongoing: TDF/FTC, TAF/FTC, lenacapravir
- No adverse pregnancy outcomes with TDF/FTC
  - 1 study (PDP) lower body length at birth, normal by 1 year
- Other options – timed intercourse to maximal fertility, semen analysis
- Long-acting injectable cabotegravir: need pregnancy/lactation data

Take-aways

- Comprehensive sexual and reproductive health services benefit parents and children
- Many ARV options for use in pregnancy and breastfeeding
- Goals: sustained virologic suppression & informed patient choice
- Critical to involve pregnant and breastfeeding people in research

Thank You



Slides: Lynn Matthews, Lynne Mofenson, Caitlin Dugdale

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