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WHO's early release guidelines on PrEP: implications for eMTCT

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October 13, 2015

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Outline

- Evidence behind WHO early release guidelines on PrEP
- PrEP eligibility according to the WHO
- Rationale for PrEP during pregnancy & lactation
- What we know about PrEP during safer conception, pregnancy, lactation & contraception
- Unanswered questions & future directions

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WHO: Oral PrEP should be offered to people at "substantial risk"

Recommendation 2: Oral pre-exposure prophylaxis to prevent HIV acquisition			
Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High* NEW

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WHO meta-analysis of PrEP: inclusion criteria

1. RCT or demonstration project evaluating use of oral PrEP (containing TDF) to prevent HIV infection among people at "substantial risk"
2. Measured one or more key outcomes, comparing those randomized to oral PrEP vs. placebo or oral PrEP vs. no PrEP
3. Published before April 2015

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Fonner G, Grant R, Baggaley R. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, and sexual and reproductive health outcomes. Presented at WHO Guidelines Development Meeting. Geneva: June 2015.

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WHO meta-analysis

Analysis	No. of studies	N	Risk Ratio (95% CI)	p-value	p-value (meta-regress.)
Overall	10	17424	0.49 (0.33-0.73)	0.001	--
Adherence					
High (>70%)	3	6150	0.30 (0.21-0.45)	<0.0001	<0.0001
Moderate (41-70%)	2	4912	0.55 (0.39-0.76)	<0.0001	0.009
Low (≤40%)	2	5033	0.95 (0.74-1.23)	0.70	*ref*
Mode of Acquisition					
Rectal	4	3167	0.34 (0.15-0.80)	0.01	0.36
Vaginal/penile	6	14252	0.54 (0.32-0.90)	0.02	
Biological sex[1]					
Male	7	8706	0.38 (0.25-0.60)	<0.0001	0.19
Female	6	8716	0.57 (0.34-0.94)	0.03	
Age[2]					
18 to 24 years	3	2997	0.71 (0.47-1.06)	0.09	0.29
≥25 years	3	5129	0.45 (0.22-0.91)	0.03	
Drug Regimen					
TDF	5	4303 active	0.49 (0.28-0.86)	0.001	0.88
FTC/TDF	7	5693 active	0.51 (0.31-0.83)	0.007	
Drug Dosing					
Daily	8	17024	0.54 (0.36-0.81)	0.003	0.14
Intermittent	1	400	0.14 (0.03-0.63)	0.01	

[1] iPrEx included 313 (13%) transgender women. [2] Includes only studies stratified age by <25 and ≥25.
Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.

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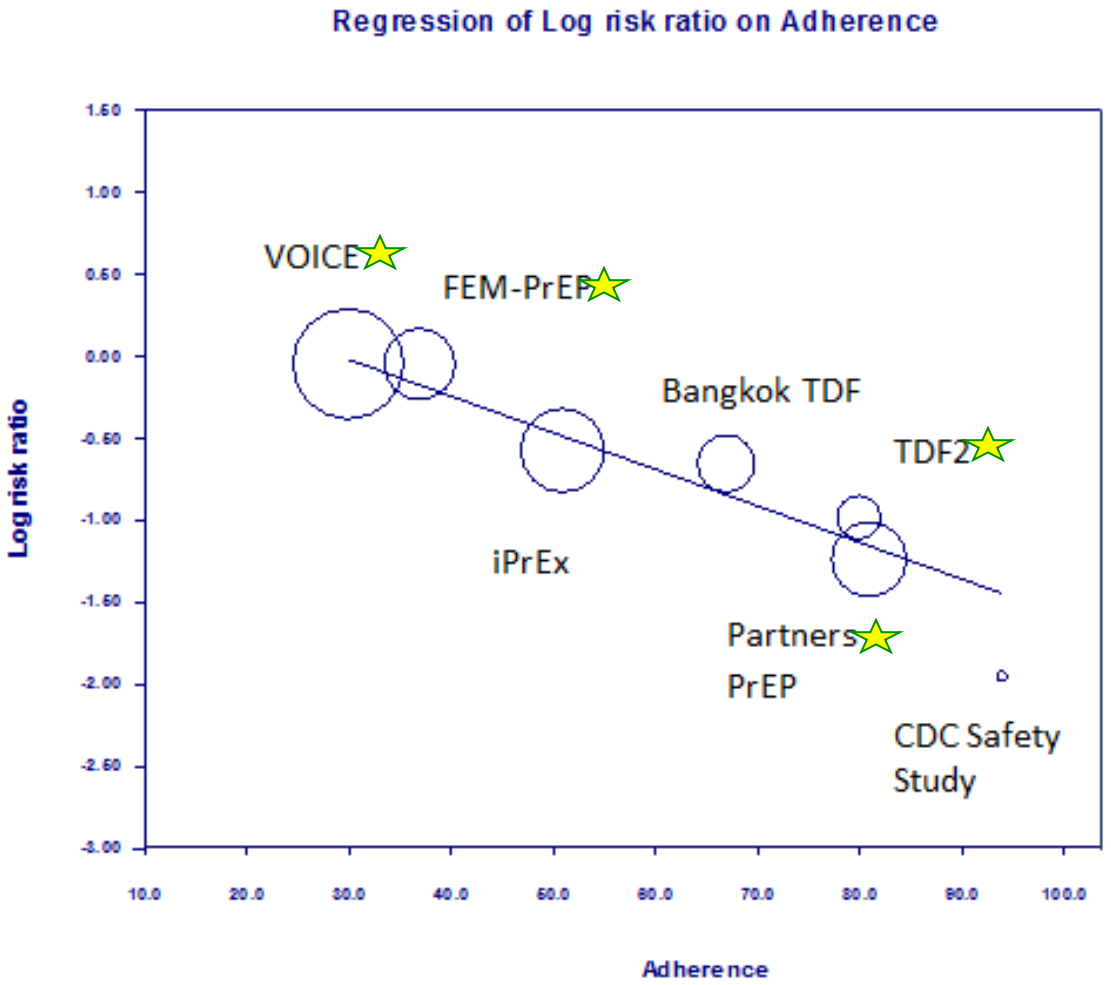
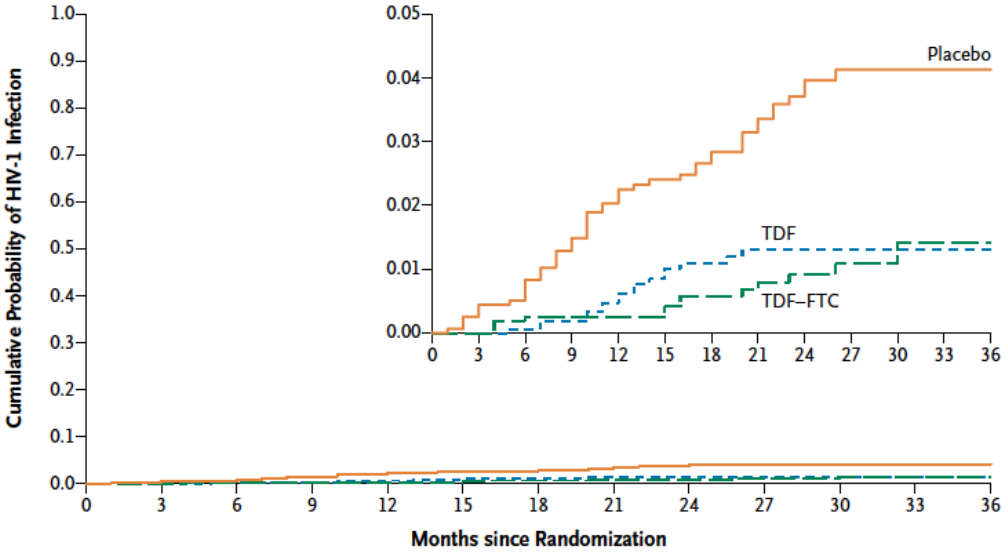
WHO meta-analysis: adherence & effectiveness



★ Studies of sexual transmission of HIV that included biologic females
Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.

Partners PrEP Trial



	TDF HR 95% CI	TDF+FTC HR 95% CI
All women	0.29 0.13 - 0.63	0.34 0.16-0.72
Women with detectable drug	0.14 0.05 – 0.43	0.10 0.02 – 0.44

Baeten et al. et al, Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. NEJM 2012

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Open-label studies

Partners Demo Project

- 1,000 sero-different couples in Kenya & Uganda; ~50% HIV-negative women
- PrEP as bridge to ART
- 1 HIV infection (expected: ~21)

ADAPT

- 179 young women in Cape Town
- Randomized to daily, twice weekly + boost, and event-driven dosing
- Highest adherence & coverage of sex acts with daily dosing; no difference in HIV infections

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Baeten et al. Near Elimination of HIV Transmission in a Demonstration Project of PrEP and ART. CROI; Seattle, WA 2015.
Bekker et al. HPTN 067/ADAPT Cape Town: A Comparison of Daily and Nondaily PrEP Dosing in African Women. CROI; Seattle, WA 2015.

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Drug resistance in setting of PrEP

	Infected at Entry		Incident Infection	
	Study Drug	Placebo	Study Drug	Placebo
Study	Resist/Tot	Resist/Tot	Resist/Tot	Resist/Tot
iPrEx	2/2	1/8	0/48	0/83
Partners PrEP	1/3	0/6	0/13	0/52
TDF2	1/1	0/2	0/9	0/24
FEM-PrEP	0/1	0/1	4/33	1/35
VOICE	2/9	0/1	1/61	0/60
Total % (95% CI)	6/16 37.5% (18 to 61%)	1/18 5% (1 to 26%)	5/164 3% (1 to 7%)	1/254 0.3% (.06 to 2%)

11 infections with resistance occurred in active arms

Overall risk of resistance = ***11/9222 or 0.1%***

Adapted from Liegler and Grant in *Drug Resistance*, Springer, in press

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FEM-PrEP resistance data

- **Analysis of seroconversions: 35 in placebo and 33 in drug arm**
  - Seroconversions in setting of low or undetectable drug levels → little resistant virus
  - Seroconversions in setting of detectable drug → resistant virus, but suggestive of seroconversion prior to initiation of PrEP

Grant et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS 2015.

WHO: safety data

- **10 RCTs presented data on adverse events**
- **Risk of any adverse events did not differ between PrEP vs. placebo (RR 1.01, 95% CI 0.99-1.03, p=0.27).**
  - No differences in sub-groups based on sex, age, mode of acquisition, drug regimen or dosing
- **Subclinical decline in renal function and bone mineral density; no clinical events & no decline with time**

Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.

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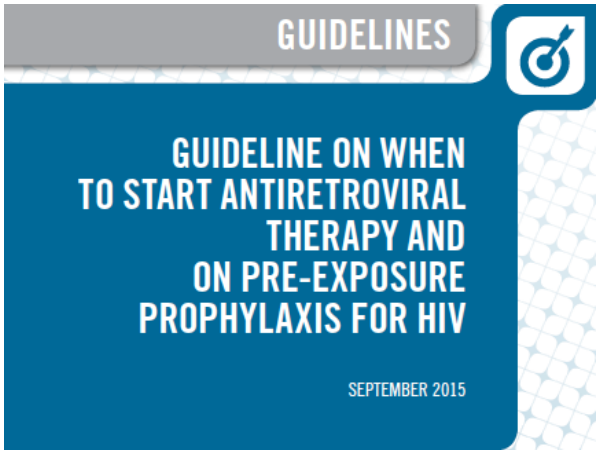
WHO: PrEP eligibility

- **Offer PrEP to anyone at "substantial risk" of HIV**
- **Individual-based vs. group-based risk assessment**
- **Discuss risks/benefits/alternatives of PrEP with pregnant & breastfeeding women**



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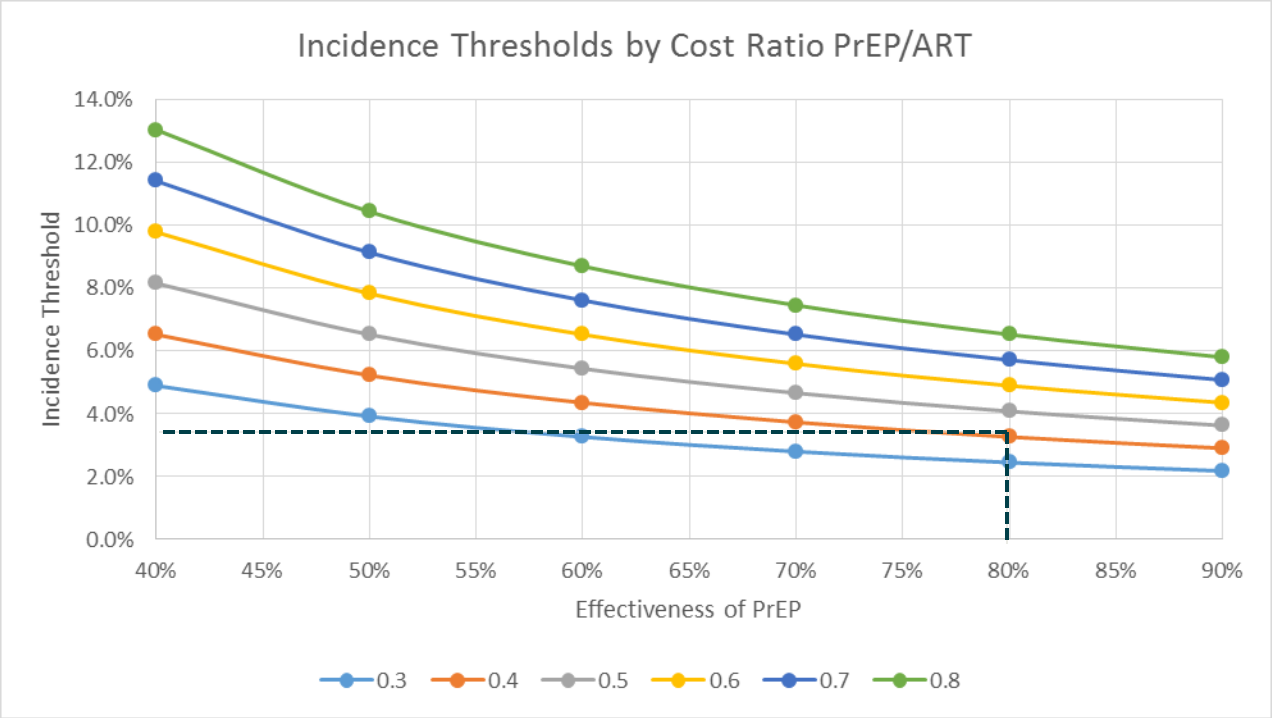
Defining "substantial risk"

- **Incidence threshold: incidence at which cost of PrEP is less than cost of ART to treat averted infection**



Ghys PD, Stover J, Mahy M, Daher J, Godfrey-Faussett P. Presented at the UNAIDS/WHO PrEP PICO Scoping Meeting, March 2015 and IAS2015, Vancouver July 2015.

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"Substantial risk" incidence in control arms of PrEP trials

Study	Population	Incident HIV Infections	Person Years	HIV Incidence Rate	95% CI
BKK TDF	IDU	33	4823	0.7	0.47 to 0.96
FEM PREP	Women	35	n/a	5.0	n/a
VOICE	Women	60	1308	4.6	3.5 to 5.9
iPrEx RCT	MSM and TGW	83	2113	3.9	3.1 to 4.8
Partners PrEP RCT	Men and women in SDC	52	1578	2.0	n/a
TDF2	Men and Women	24	n/a	3.1	n/a
PROUD	MSM	19	214	8.9	6.0 to 12.7
Ipergay	MSM	14	n/a	6.6	n/a

Van Damme NEJM 2012; Baeten NEJM 2012; Marrazzo NEJM 2015; Thigpen NEJM 2012; Choopanya Lancet 2013; Grant CROI 2013; Grant Lancet Infectious Diseases 2014.

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WHO: PrEP eligibility

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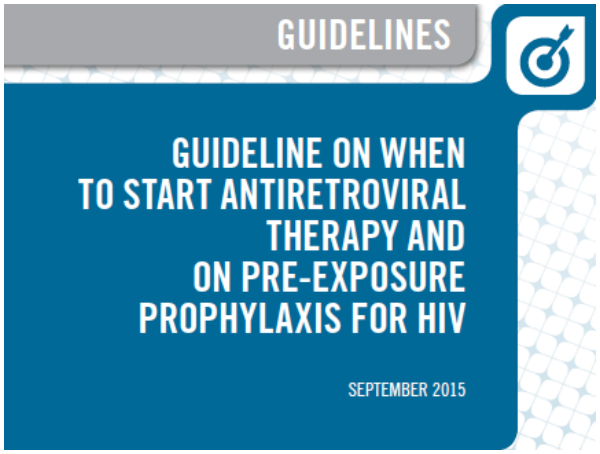

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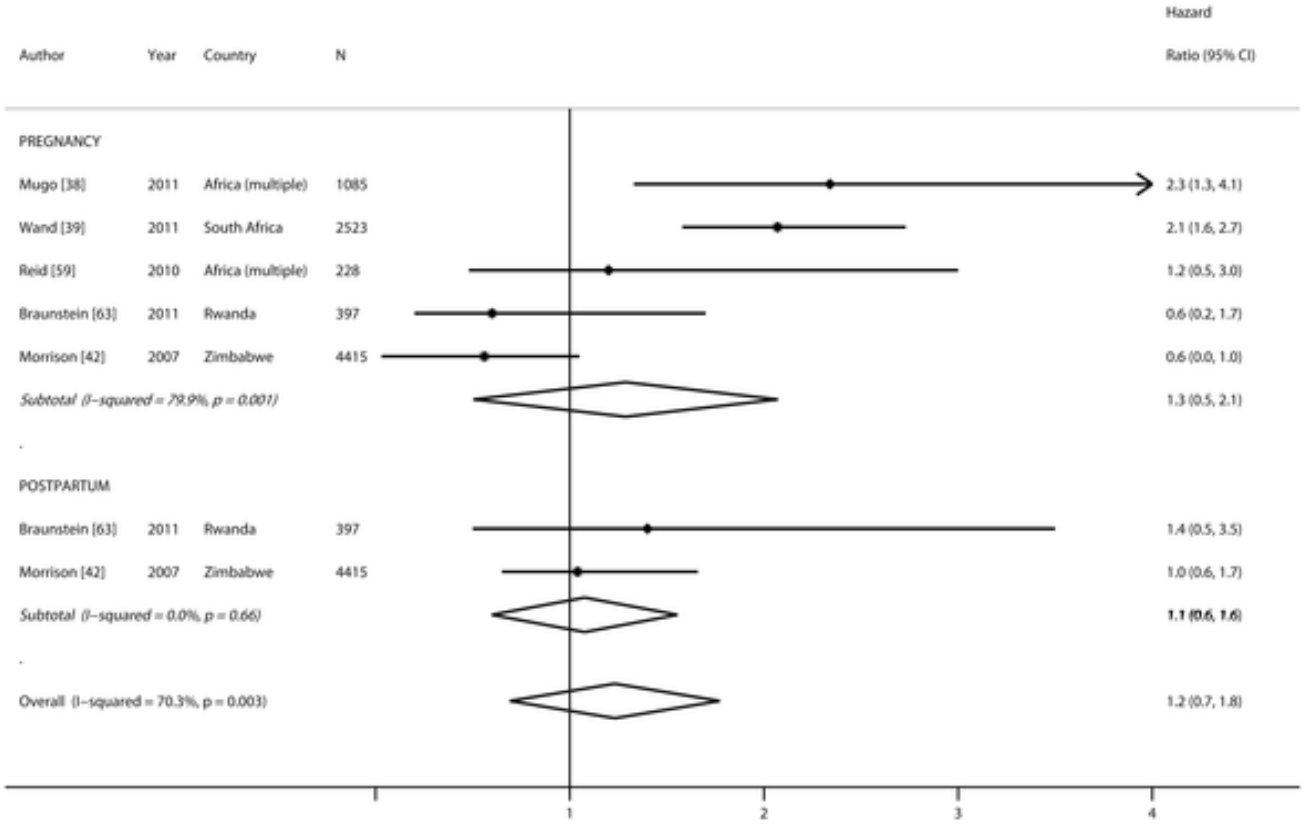
Rationale for PrEP during pregnancy & lactation

- **Pregnancy is associated with ~2X increased risk of HIV acquisition**
- **Acute HIV during pregnancy associated with ~8X increased risk of perinatal transmission**
- **Acute HIV during breastfeeding associated with ~4X increased risk of neonatal transmission**

Mugo et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. AIDS 2011.
Humphrey et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. BMJ 2010.
Singh et al. HIV seroconversion during pregnancy and mother-to-child HIV transmission: data from the enhanced perinatal surveillance projects, United States, 2005–2010. CROI 2013, Atlanta, GA.

Rationale for PrEP during pregnancy & lactation

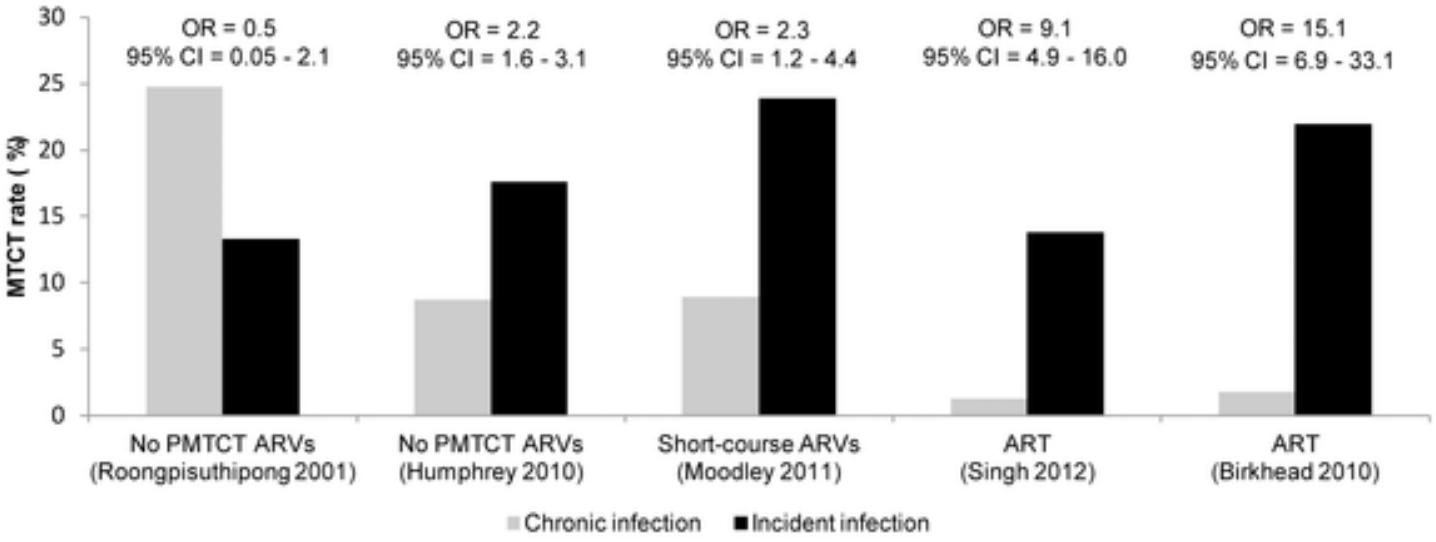
Risk of HIV acquisition by pregnancy & postpartum status



Drake AL, Wagner A, Richardson B, John-Stewart G (2014) Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis. PLoS Med 11(2): e1001608.

Rationale for PrEP during pregnancy & lactation

Effect of ART on perinatal HIV transmission in setting of incident infection during pregnancy



Drake et al. Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis.

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Safer conception with PrEP: safety

- **Partners PrEP: PrEP discontinued when pregnancy detected, mean 5 wks gestation**
- **No difference in pregnancy incidence, birth outcomes, and infant growth**
- **"Signal" for PrEP associated with pregnancy loss?**
  - 42.5% for FTC+TDF vs. 32.3% for placebo (difference 10.2%; 95% CI, −5.3% to 25.7%; *p* = 0.16)
- **CIs for pregnancy outcomes were wide → definitive statements about safety of PrEP periconception cannot be made**

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Mugo et al. Pregnancy Incidence and Outcomes Among Women Receiving PrEP. JAMA July 2014.

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TDF in pregnancy

- APR: adequate 1st trimesters exposures to detect 1.5X risk of overall birth defects
- No impact on intrauterine growth
- Conflicting data on birth outcomes
- DART: no dif. in growth, fractures at 2 yrs
- IMPAACT: no dif. in growth at 6 months
- PHACS (US): decreased length (0.4 cm) and head circumference (0.3 cm) at 1 year

The Antiretroviral Pregnancy Registry Interim Report. Jan 1 1989 – Jan 31 2015.
Siberry et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS 2012.
Ransom et al. Infant growth outcomes after maternal tenofovir use during pregnancy. JAIDS 2013.
Gibb et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. PLoS Med 2012.

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TDF exposure and infant BMC

- **SMARRT: 12% decreased bone mineral content (p=0.002) in TDF-exposed infants; no long-term data available**
- **PHACS: no association between meconium TDF concentration and birth weight, length or bone mineral content**

Siberry et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. CID 2015.
Himes et al. Meconium Tenofovir Concentrations and Growth and Bone Outcomes in Prenatally Tenofovir Exposed HIV-Uninfected Children. J Pediatric Infect Dis 2015.

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TDF during lactation

- **Little data**
- **TDF/FTC is secreted in breast milk, but infant levels are extremely low (<2% proposed infant doses)**

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Benaboud et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire. Antimicrobial agents and Chemotherapy 2011.
CDC/US Public Health Service. *Preexposure Prophylaxis for the Prevention of HIV Infection in the US: A Clinical Practice Guideline.* 2014

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PrEP & Contraception

- **No difference in PrEP's efficacy among women using DMPA vs. no hormonal contraception (adjusted $p_{interaction}$=0.65, comparing aHR 0.35 versus aHR 0.25)**

- **No change in contraceptive efficacy in women using PrEP and combination oral contraceptives, injectables, and implants**

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Heffron et al. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. AIDS 2014.
Murnane et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception. AIDS 2014.

PrEP in adolescent women

- ~140,000 15-19 yo women living in areas with HIV prevalence ≥3%

- Research agenda for young women:
  - Drug safety, acceptability & use patterns
  - Long-term impact of multiple cycles of starting/stopping PrEP
  - Implementation strategies in sub-populations
  - Address ethical/legal/regulatory barriers to PrEP use in young people

UNICEF. PrEP use among sexually active older adolescents. Vancouver, Canada: July 2015.

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Next steps

- **Implementation science & expanded access**
  - Anticipate WHO implementation guidelines in 2016
- **Improve understanding of female reproductive tract biology**
- **Pharmacokinetic data in women**
- **Studies in pregnancy & breastfeeding**
- **Changing risk/benefit ratios in setting of universal ART recommendations**
- **Alternate dosing regimens**
- **Alternate modes of delivery**
- **Drug-drug interactions**
- **Multipurpose prevention technologies**

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Acknowledgements

- Shaffiq Essajee
- Bob Grant
- Jessica Rodrigues

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