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

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for **Global**
Reproductive
Health

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**

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	<i>Strong</i>	<i>High</i>

NEW

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**

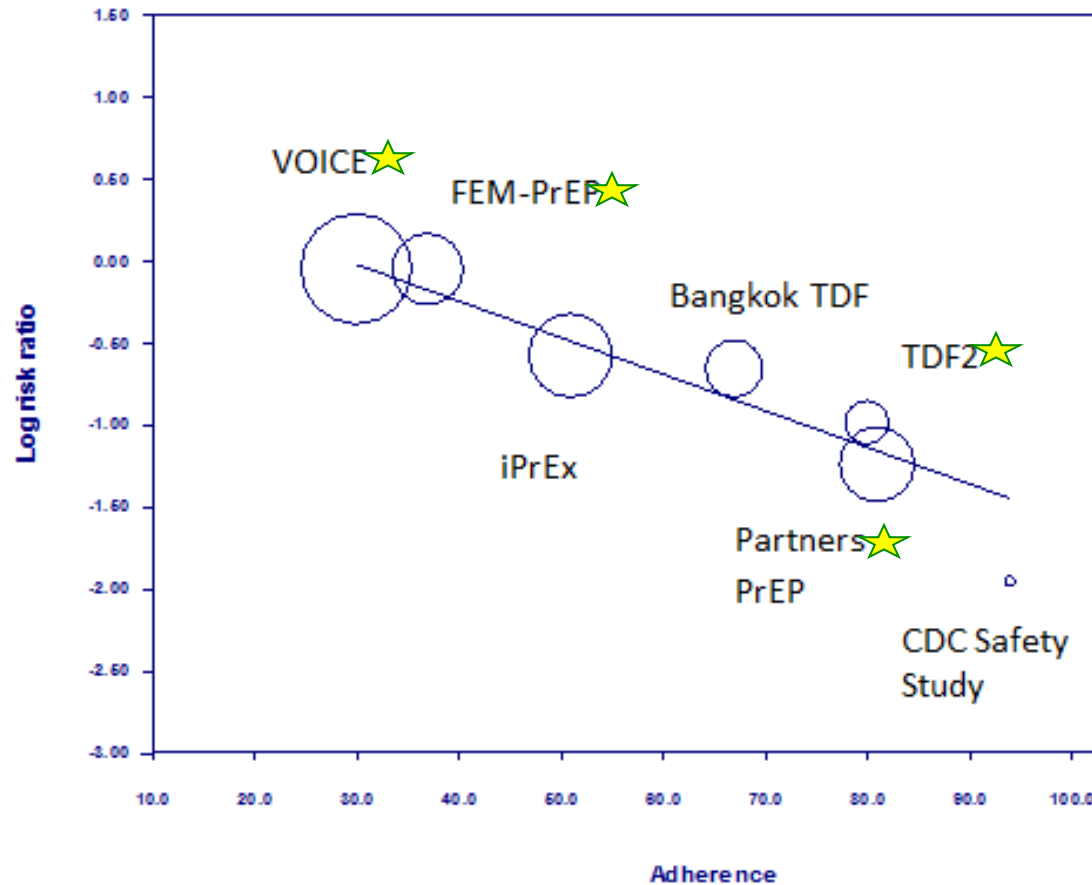
WHO meta-analysis

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	<i>ref</i>
Mode of Acquisition					
Rectal	4	3167	0.34 (0.15-0.80)	0.01	
Vaginal/penile	6	14252	0.54 (0.32-0.90)	0.02	0.36
Biological sex¹					
Male	7	8706	0.38 (0.25-0.60)	<0.0001	0.19
Female	6	8716	0.57 (0.34-0.94)	0.03	
Age²					
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	
FTC/TDF	7	5693 active	0.51 (0.31-0.83)	0.007	0.88
Drug Dosing					
Daily	8	17024	0.54 (0.36-0.81)	0.003	
Intermittent	1	400	0.14 (0.03-0.63)	0.01	0.14

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.

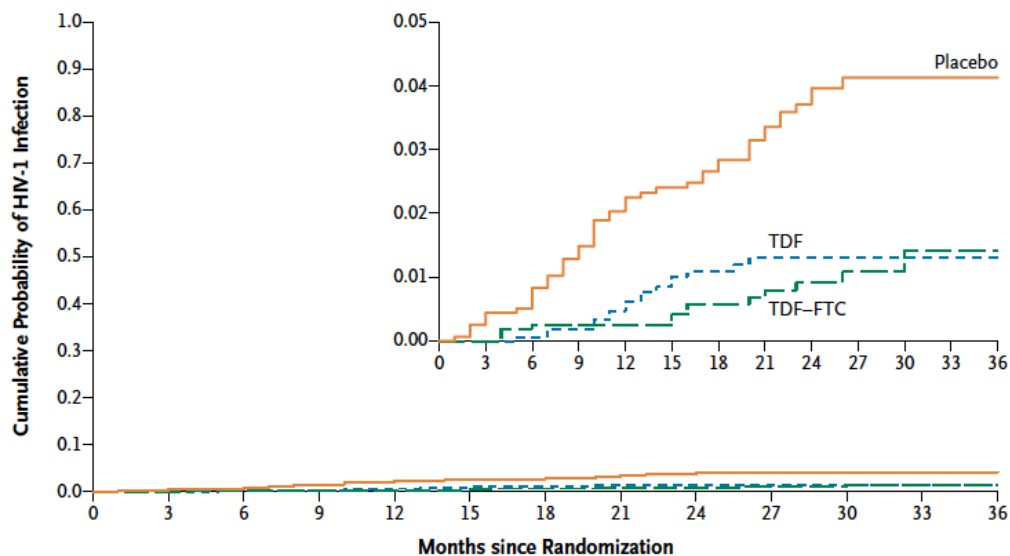
WHO meta-analysis: adherence & effectiveness

Regression of Log risk ratio on Adherence



★ 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

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

Drug resistance in setting of PrEP

Study	Infected at Entry		Incident Infection	
	Study Drug	Placebo	Study Drug	Placebo
	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	6/16	1/18	5/164	1/254
%	37.5%	5%	3%	0.3%
(95% CI)	(18 to 61%)	(1 to 26%)	(1 to 7%)	(.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

FEM-PrEP resistance data

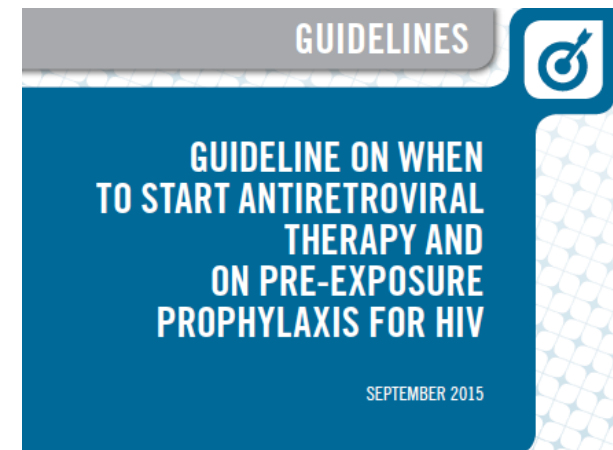
- **Analysis of seroconversions: 35 in placebo and 33 in drug arm**
 - Seroconversions in setting of low or undetectable drug levels → little resistant virus
 - Seroconversions in setting of detectable drug → resistant virus, but suggestive of seroconversion prior to initiation of PrEP

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**

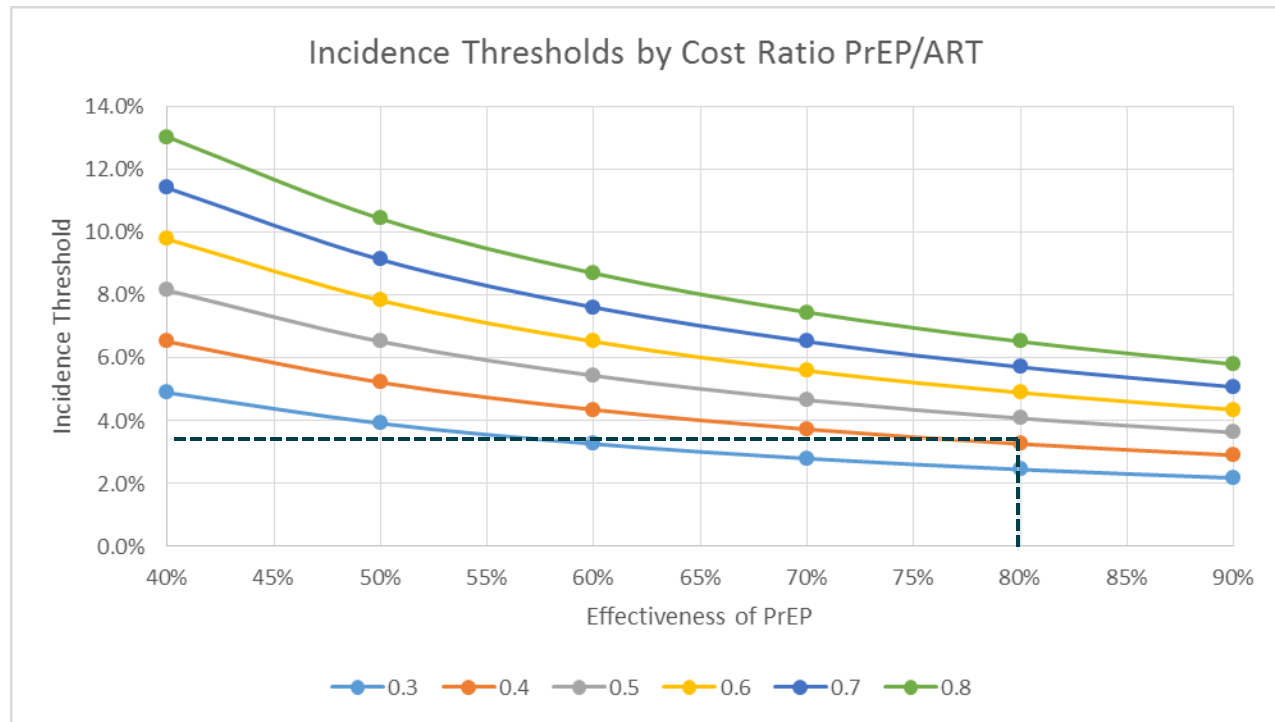
WHO: PrEP eligibility

- 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



Defining “substantial risk”

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

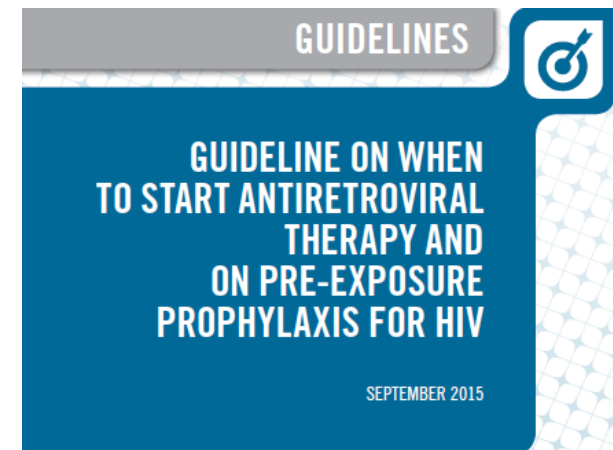


“Substantial risk” incidence in control arms of PrEP trials

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

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**



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**

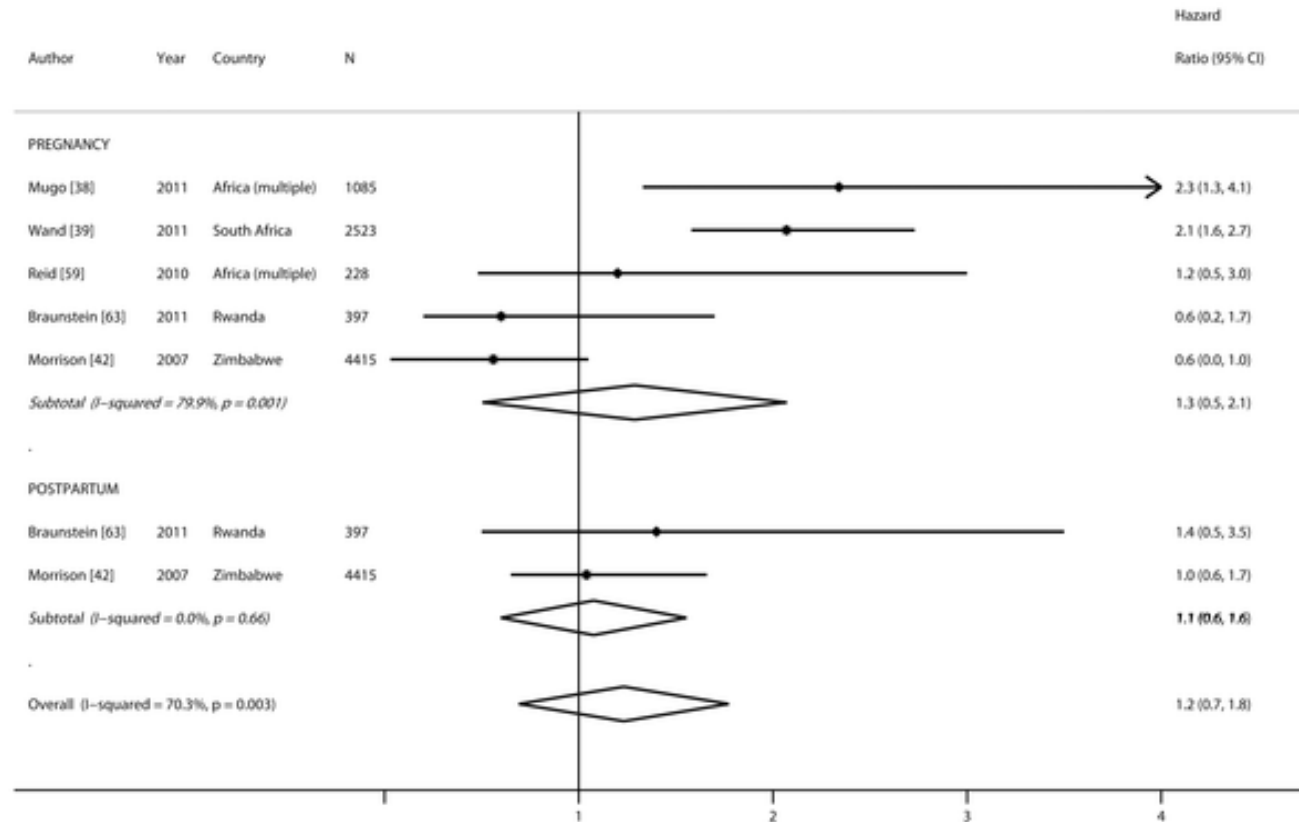
Mugo et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. AIDS 2011.

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

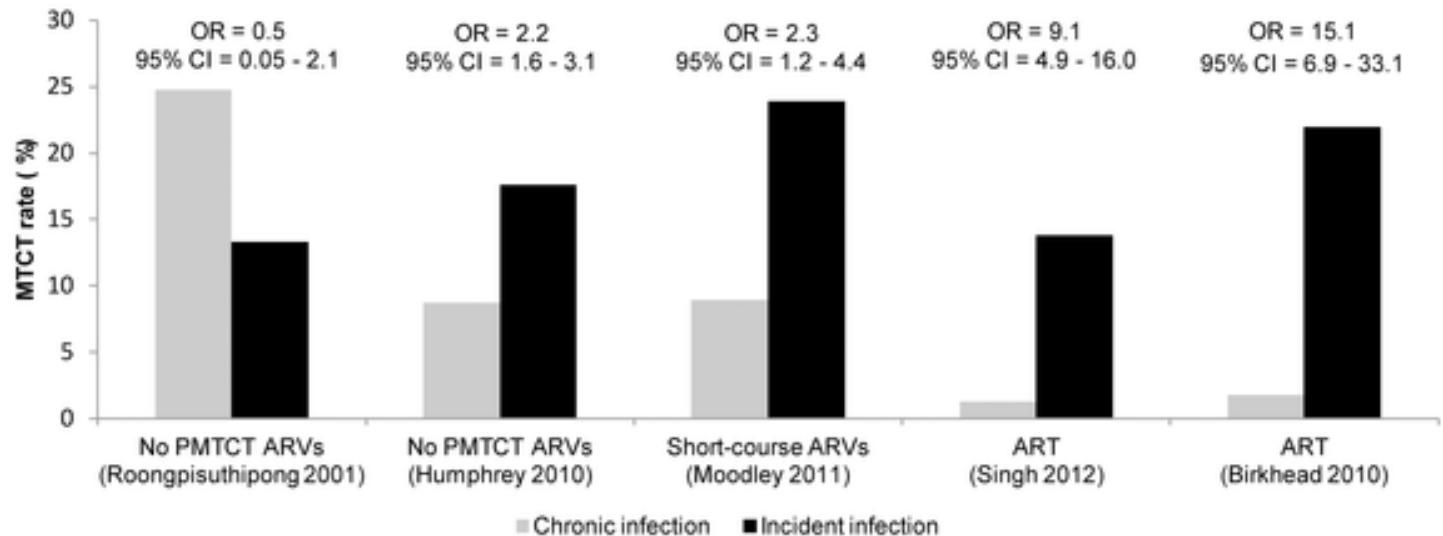
Risk of HIV acquisition by pregnancy & postpartum status



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



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%; $p = 0.16$)
- **CI for pregnancy outcomes were wide → definitive statements about safety of PrEP periconception cannot be made**

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.

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**

TDF during lactation

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

PrEP & Contraception

- **No difference in PrEP's efficacy among women using DMPA vs. no hormonal contraception (adjusted $p_{\text{interaction}}=0.65$, comparing aHR 0.35 versus aHR 0.25)**
- **No change in contraceptive efficacy in women using PrEP and combination oral contraceptives, injectables, and implants**

PrEP in adolescent women

- ~140,000 15-19 yo women living in areas with HIV prevalence $\geq 3\%$
- 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.

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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