Can a little PrEParation help prevent the spread of HIV periconception?

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Background

- HIV Transmission w/o medical intervention in heterosexual couples:
  1 per 1000 contacts (95% CI, 1/400 to 1/2000)
- Male to female transmission significantly greater than risk of female to male
- n=415 serodiscordant couples followed for 30 months
  - HIV+ partner NOT on ARV report protected intercourse 1.2% of time
  - 55% M+F- had 50/415 transmissions: incidence of 12 per 100 person years
  - Seroconversion highest in 15-19yo age group; uncircumcised male partners; VL >1500

Royce R et al. NEJM 1997; 336:1072-8
Quinn T et al. Rakai Project Study Group. NEJM 2000; 342:921-9.

Role of ARVs

- 2009 SR: HIV transmission during unprotected intercourse in serodiscordant couples (while infected partner is on ARV): 0.5 per 100 person years (95% CI 0.19-1.09)
  - 2 studies - Zero transmission when VL <400 on ARVs
- n=393 HIV serodiscordant couples
  - HIV incidence in non-infected partner during preHAART, early HAART, late HAART 10.3%, 6.8%, 1.9% respectively
  - No seroconversion in 60 couples on HAART, VL ≤ 310 and CD4 > 350

S. Attia et al. AIDS 2009; 23 (11): 1397-1404
Castilla J et al. J Acquir Immune Defic Syndr 2005; 40:96-101

However...

- Case reports: suppressed viremia does not guarantee individual is sexually non-infectious

- Up to 4% of men and 20% of women w/ undetectable plasma viremia may have detectable concentrations in sexual fluids

Coombs R et al. AIDS 2003; 17:455-80.
Sturmer M et al. Antiviral Therapy 2008; 13: 720-732.

Methods to reduce transmission periconception

Infected Partner	Strategy
M+F-	- Medical Male circumcision
Either	- Sperm Washing + Interuterine insemination - Limited unprotected coitus timed to peak fertility - Suppressive ARV for infected partner - ARV pre-exposure (PrEP) prophylaxis for uninfected - Topical pre-exposure (PrEP) prophylaxis for uninfected

Matthews LT et al. AIDS 2010; 24:1975-82.

ARV PrEP

- 16 July 2012 – FDA approved Truvada as pre-exposure prophylaxis (PrEP)

- Approved to reduce risk of HIV infection in uninfected individuals at high risk to be used in combination with safer sex practices

- No comment on use as periconception measure

FDA. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm. Accessed 17May2013

Consensus statements

WHO	CDC	UK
“Daily PrEP (TDF or TDF/FTC) considered as possible additional intervention for uninfected”	“PrEP use may be one of several options … in discordant couples during attempts to conceive Prescribe TDF + FTC (or one Truvada) daily”	“ … activities according to current guidelines should be implemented in preference to PrEP” “ We recommend that ad hoc prescribing is avoided and that PrEP only prescribed in context of research only”

McCormack S et al. International J of STD & AIDS. 2012; 23:1-4.
WHO Guidelines. July 2012: http://www-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/books/NBK132003
MMWR. 2012; 61(31): 586-89.

Current Practice

- 10 Question survey to members of IDSA Emerging Infections Network (EIN)
  - 48.8% response from 5June 2013 - 7July 2013 from US and Canada
  - 74% support PrEP; 14% unsure; 12% do not support PrEP
  - 9% provided PrEP; 43% had not provided but would;
    34% said irrelevant to their practice; 14% would not provide PrEP
  - Reasons not to provide:
    - 77% worried about adherence; 57% concern for cost issues
      53% worried for ADE; 53% worried insufficient evidence

Karris et al. CID 2013

Question

P	HIV serodiscordant couple (M+F-)
I	Oral Truvada or Tenofovir or Emtricitabine
C	Sperm washing + IUI; timed unprotected coitus; suppressive ARV for infected; no medication
O	1) Prevent HIV seroconversion in uninfected 2) Safety and ADE differences

Search Strategy

Databases	Cochrane, Google, Google Scholar, Embase, Medline, PubMed, IPA
Search Strategy	Serodiscordant, HIV, PrEP, prophylaxis, prevention, antiretroviral, Truvada, Tenofovir, Emtricitabine
Limits	English, humans, heterosexual
Results	1 SR 2 RCT 1 Case series

The NEW ENGLAND JOURNAL of MEDICINE

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Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

J.M. Baeten, D. Donnell, P. Ndase, N.R. Mugo, J.D. Campbell, J. Wangisi, J.W. Tappero, E.A. Bukusi, C.R. Cohen, E. Katabira, A. Ronald, E. Tumwesigye, E. Were, K.H. Fife, J. Kiarie, C. Farquhar, G. John-Stewart, A. Kakia, J. Odoyo, A. Mucunguzi, E. Nakku-Joloba, R. Twesigye, K. Ngure, C. Apaka, H. Tamooh, F. Gabona, A. Mujugira, D. Panteleeff, K.K. Thomas, L. Kidoguchi, M. Krows, J. Revall, S. Morrison, H. Haugen, M. Emmanuel-Ogier, L. Ondrejcek, R.W. Coombs, L. Frenkel, C. Hendrix, N.N. Bumpus, D. Bangsberg, J.E. Haberer, W.S. Stevens, J.R. Lingappa, and C. Celum, for the Partners PrEP Study Team*

Partners PrEP

M	R, DB, PC; July ’08 – Nov ’10; Kenya and Uganda			
P	N=4,747 Serodiscordant heterosexual couples (38%M+F-); HIV+ partner NOT on ARV, median CD4 495, median plasma VL 390 Excl: Pregnant/ planning pregnancy; breastfeeding; active infections			
I	1) TDF 300mg daily 2) TDF 300mg + FTC 200mg daily (Truvada)			
C	3) Placebo			
	Monthly F/U for 1.9yrs			
		TDF	Truvada	Placebo
O	HIV seroconversion	17	13	52

Partners PrEP

	TDF	Truvada	Placebo
# of seroconversions per 100person-yr	0.65**	0.50**	1.99

** p value <0.001

- No pregnancies occurred in seronegative woman
- 405 pregnancies occurred in seropositive women
- @ enrolment 27% of partners did not use a condom
  @ 12 weeks 13% did not
  @ 24 weeks 9% did not

Partners PrEP

- Clinically significant SE
  - ↓ neutrophil count 18% FTC/TDF vs 13% placebo
  - Fatigue, excessive intestinal gas and abdominal pain within first month that improved after

Partners PrEP

- Adherence
  - 99.5% completed ≥ 1 randomized HIV-1 test
  - 98% of study bottles returned monthly with 97% adherence
  - 902 random TDF plasma samples found 82% detectable
  - 29 of infected had TDF plasma samples with 9 (31%) detectable

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preexposure Prophylaxis for HIV Infection among African Women

Lut Van Damme, M.D., Amy Corneli, Ph.D., Khatija Ahmed, M.Med., Kawango Agot, Ph.D., Johan Lombaard, M.B., Ch.B., Saidi Kapiga, M.D., Mookho Malahleha, M.B., Ch.B., Fredrick Owino, M.B., Ch.B., Rachel Manongi, M.D., Jacob Onyango, M.A., Lucky Temu, M.D., Modie Constance Monedi, Adv.Dip.Mid., Paul Mak'Oketch, B.Pharm., Mankalimeng Makanda, M.B., Ch.B., Ilse Reblin, B.Soc.Sc., Shumani Elsie Makatu, M.A., Lisa Saylor, B.A., Haddie Kiernan, B.S.N., Stella Kirkendale, M.P.H., Christina Wong, Ph.D., Robert Grant, M.D., Angela Kashuba, Pharm.D., Kavita Nanda, M.D., Justin Mandala, M.D., Katrien Fransen, M.S., Jennifer Deese, M.P.H., Tania Crucitti, Ph.D., Timothy D. Mastro, M.D., and Douglas Taylor, Ph.D., for the FEM-PrEP Study Group*

FEM-PrEP

M	R, DB, PC, Jun ’09 - Apr ’11; Kenya, S Africa, Tanzania
P	N=2,120, Seronegative ♀, μ age 24yo, avg 3.7 intercourses daily (50% unprotected) Excl: HepB, abnormal hepatic/renal function; pregnant/breastfeeding
I	TDF-FTC (Truvada)
C	Placebo
O	Monthly F/U 1) Effectiveness and safety of Truvada in preventing HIV acquisition 2) Effect of Truvada on CD4 and HIV RNA level, rate of resistance, Δ in behaviour

FEM-PrEP

	TDF-FTC	Placebo	P value
HIV acquisition (# of events/100 person/yr)	4.7	5	p = 0.81
Pregnancies (# of events/100 person/yr)	11.2	7.5	p = 0.04
CD4 16wk after conversion (mean)	579.3	586.5	p = 0.94
Viral load 16wk after conversion (log value, mean)	4.4	4.3	p = 0.70

FEM-PrEP

- 266 (12.5%) lost to F/U; 113 (5.3%) stopped early
- N/V and ↑ ALT were significantly higher in TDF/FTC
- Study discontinued early on April 2011, for futility

	Infected	Uninfected
≥ 10ng/mL TDF at beginning of window	7/ 27 (26%)	27/78 (35%)
≥ 10ng/mL TDF at end of window	7/33 (21%)	35/95 (37%)

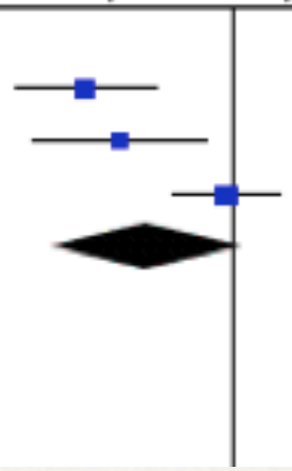
Summary of RCT: Efficacy

Figure 4. Forest plot of comparison: 1 TDF+ FTC vs placebo, outcome: 1.1 HIV infection (by risk group).

Study or Subgroup	TDF-FTC Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Heterosexual group						
Baeten 2011	13	1579	47	1584	23.6%	0.28 [0.15, 0.51]
Thigpen 2011	9	601	24	599	20.1%	0.37 [0.18, 0.80]
Van Damme 2011	33	1024	35	1032	27.3%	0.95 [0.60, 1.52]
Subtotal (95% CI)		**3204**		**3215**	**71.0%**	**0.47 [0.21, 1.08]**
Total events	55		106			

Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 11.18$, $df = 2$ ($P = 0.004$); $I^2 = 82\%$

Test for overall effect: $Z = 1.78$ ($P = 0.08$)



Okwundu CI et al. Cochrane databse. Syst Rev. 2009; CD007189.

Summary of RCTs: Safety

Adverse event or laboratory abnormality (study)	FTC/TDF (%)	Placebo (%)
Nausea		
TDF2	18.5	7.1
FEM-PrEP	4.9	3.1
Vomiting		
TDF2	11.3	7.1
FEM-PrEP	3.6	1.2
Diarrhoea		
Partners PrEP	1.7	1.4
Excessive intestinal gas		
Partners PrEP	7.9 (during first month)	4.6 (during first month)
Dizziness		
TDF2	15.1	11.0
Weight loss (≥5 %)		
iPrEx	2	1
Fatigue		
Partners PrEP	10.6 (during first month)	7.4 (during first month)
Elevated ALT		
FEM-PrEP	11.4	8.6
Neutropenia		
Partners PrEP	18[a]	13[b]

Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child

Pietro L. Vernazza[a], Irma Graf[b], Ulrike Sonnenberg-Schwan[c], Maria Geit[d] and Anja Meurer[c]

Many HIV-discordant couples express a strong wish to conceive a child. Insemination with processed semen is offered to these couples in many countries. Given the very low level of transmission risk during fully suppressive antiretroviral therapy, we offered timed intercourse combined with preexposure prophylaxis to further reduce the transmission risk. In 53 cases, natural conception was attempted using the proposed method. Pregnancy rates were high and reached a plateau of 75% after six cycles. Advanced age in the female partner was a predictor for infertility in these couples.

AIDS 2011, **25**:2005–2008

Vernazza et al. 2011

M	Series report, Feb 2007, Switzerland
P	n= 46 serodiscordant couples (37 M+F-) choosing PrEP + qualified 1) Infected on ARV w/ undetectable HIV-RNA <50copies/mL ≥ 6mo 2) No STI or unprotected coitus with other partners 3) LH urine test determine optimal conception (36h after LH-peak)
I	Tenofovir 300mg: first dose at LH-peak and second 24h after

Vernazza et al. 2011

- 46 couples had 53 different attempts and 244 documented unprotected vaginal intercourse
- median conception age 33 F and 38 M (6 F ≥ 40yo)
- pregnancy rate
  - 26% on first attempt
  - 66% after five attempts
  - 75% after twelve attempts
- No HIV seroconversion in any woman

Author's conclusions

- "Couples who wish to use timed intercourse ± PrEP should be counselled to limit conception to 5-6 cycles"

- "Method proposed … can be considered a psychological means to support couples"

- "We and others believe it is time for medical professionals to openly discuss the transmission risks"

Cost of PrEP

- Truvada $650/month in Canada
- Gilead Medication Assistance Program for PrEP
  - Eligible for HIV negative adults in US
- Mathematical modelling
  - unlikely for large HIV incidence ↓ at current drug costs
  - At population levels - providing ARV to infected earlier has better infections averted and QALY outcomes than PrEP

Cremin et al. AIDS 2013; 27(3):447-58

Summary

	Estimated risk ↓ of HIV transmission	Pro	Con
Sperm washing + IUI	100%	- pregnancy rates of 14-31% per insemination	- Expensive - Not readily accessible - Stigmatizing
ARV for infected	96%	- Protective for infected and partner - most protective if undetectable ≥ 6mo	- Efficacy dependent on adherence
Oral PrEP	47%	- Useful if cannot consistently guarantee condom use - No resistance to TDF/FTC seen in those who did seroconvert	- Requires ≥ 80% adherence - no RCT for on ARV and using PrEP - Out of pocket

Semprini A. Hum Reprod 2000; 15:59
Marina S et al. Fertil Steril 1998; 70:35
Cohen MS et al. NEJM 2011; 365:493-505.
Okwundu CI et al. Cochrane databse. Syst Rev. 2009; CD007189.

Summary

P	HIV serodiscordant couple (M+F-)	
I	Oral Truvada or Tenofovir	
C	Sperm washing + IUI; timed unprotected coitus; suppressive ARV for infected; no medication	
O	1) Prevent HIV seroconversion in uninfected	estimated RRR 47%
	2) Safety and ADE differences	Fatigue Nausea/Vomiting Neutropenia

Questions?

Why Truvada?

- Potent ARV activity – active against all subtypes
- Rapid onset of activity
- Early action in HIV lifecycle
- Long intracellular half life (>60hrs)
- Convenient daily dosing
- Few drug interactions
- From trial and ARV use no evidence of ADE among fetuses exposed to TDF/FTC at any stage

Foster C et al. HIV Med 2009;10:397–406.
Baseten JM et al. Curr HIV/AIDS Rep 2013; 10:142-51.
Dando et al. Drugs 2004; 64:2075-82.21

Up and coming

Trial	Method	Population	I	C	O	Status
VOICE	R, DB, PC, MS	n= 5029 sexually active uninfected women	TDF po TDF/FTC Placebo TDF 1%gel Placebo gel		Efficacy to prevent HIV transmission and Safety	Closed to F/U (Uganda, S Africa, Zimbabwe)
HPTN 067 (ADAPT study)	R, Open label	Uninfected MSM and WSM at high risk	Truvada daily or time driven or event driven (1:1:1)		Evaluate dosing regimens to ensure adherence	Enrolling (S. Africa, Thailand, US)
HPTN 069	R, DB, PC, MS	Uninfected MSM, WSM at high risk	MVC + 2 plb MVC + FTC + plb MVC + TDF + plb FTC + TDF + plb		Safety and tolerability of 4 ARV regimens	Enrolling (US)
FACTS	R, DB, PC, MS	Uninfected women	TDF 1% gel before and after sex	placebo	Efficacy to prevent HIV and HSV transmission	Enrolling (S. Africa)

Abdool et al Lancet 2011