Quale monitoraggio della tossicità nelle persone sieronegative che assumono PrEP

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8° WORKSHOP NAZIONALE CISAI
PERUGIA, 30 - 31 MARZO 2017
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

PrEP: Pre-exposure Prophylaxis

How does it work?

HIV-uninfected individuals take **antiretrovirals**

May prevent replication of virus & infection

- **Who? (PrEP Candidates)**

– Men who have sex with men (**MSM**)

- HIV-positive sexual partner
- Recent bacterial STI
- High number of sex partners
- History of inconsistent/no condom use
- Commercial sex work

– Transgender individuals

- Engaging in high-risk sexual behaviors

PrEP: Pre-exposure Prophylaxis

- **Who? (PrEP Candidates)**

– Heterosexual women and men
  - HIV-positive sexual partner
  - Recent bacterial STI
  - High number of sex partners
  - History of inconsistent/no condom use
  - Commercial sex work

– Injection Drug Users (IDU)
  - HIV-positive injecting partner
  - Sharing injection equipment

www.hivguidelines.org

Which antiretroviral therapy?

- **TENOFOVIR (TDF):**

- Achieve high concentrations in genital compartments, particularly high in rectal mucosa
- High genetic barrier to resistance
- Rapid antiretroviral activity
- Long intracellular and plasma half-lives

- **EMTRICITABINE (FTC)**

- Excellent safety profile and achieves high concentrations in the female genital tract
- Long intracellular and plasma half-lives

Krakowe SD et al. *Pre-Exposure Prophylaxis to Prevent HIV Infection: Current*
Status, Future Opportunities and Challenges, Drugs (2015)

Key PrEP studies

Studies	ART, dosing regimen, and study population
iPrEx[1]	OD FTC/TDF vs placebo in 2,499 **MSM**
Partners PrEP[2]	OD FTC/TDF vs TDF in 4,747 HIV-1 negative individuals within **heterosexual** HIV-1-serodiscordant couples
PROUD[3]	OD FTC/TDF in 544 HIV-negative **MSM**, with immediate vs deferred start of the study drug
IPERGAY[4]	'On-demand' dosing of FTC/TDF vs placebo in 400 HIV-seronegative **MSM***
KAISER[5]	Patterns of FTC/TDF use in 657 mostly **MSM in a real-world setting**
TDF 2[6]	OD FTC/TDF vs placebo in 1,219 **heterosexual** young adults without HIV-1 infection
Bangkok Tenofovir Study[7]	OD TDF† vs placebo to prevent parenteral HIV infection among 2,413 **IDU**‡
FEM PrEP[8]	OD FTC/TDF vs placebo in 2,120 HIV-negative **women**
VOICE[9]	OD FTC/TDF, oral TDF†, or TFV-containing vaginal microbicide gel vs placebo in 5,029 HIV-negative **women**

- TVD for PrEP SmPC based on Partners PrEP and iPrEx studies

*FTC/TDF is only licensed as a daily dosage for PrEP, the recommended dose of Truvada (FTC/TDF) is one tablet, taken orally, once daily; †TDF is not licensed for PrEP as a single agent, but as a component of Truvada

FTC, emtricitabine; IDU, intravenous drug user; MSM, men who have sex with men; OD, once daily; SmPC, summary of product characteristics; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TVD, Truvada

1. Grant RM et al. N Engl J Med 2010;363:2587–2599; 2. Baeten JM et al. N Engl J Med 2012;367:399–410; 3. McCormack S et al. Lancet 2016;387:53–60; 4. Molina J-M et al. New Engl J Med 2015;373:2237–2246; 5. Volk JE et al. Clinical Infectious Diseases 2015;61(10):1601–1603; 6. Thiepen MC et al. New Engl J Med 2012;367:423–434; 7. Center for Disease Control. MMWR 2013;62(23):463–465; 8. van Damme L et al. N Engl J Med 2012;367:411–422;
9. Marrazzo JM et al. N Engl J Med 2015;372:509–518

Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Sheena McCormack*, David T Dunn*, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Clarke, Iain Reeves, Gabriel Schembri, Nicola Mackie, Christine Bowman, Charles J Lacey, Vanessa Apea, Michael Brady, Julie Fox, Stephen Taylor, Simone Antonucci, Saye H Khoo, James Rooney, Anthony Nardone, Martin Fisher, Alan McOwan, Andrew N Phillips, Anne M Johnson, Brian Gazzard, Owen N Gill

- Randomized, open-label trial of **daily oral TDF/FTC** PrEP in HIV- MSM in 13 clinics in London
  - Immediate (n = 267) **vs**
  - Deferred for 12 mos (n = 256)
- **Primary endpoint**: HIV infection in first 12 mos
- **86%** reduction in risk seen over 60 wks with **immediate PrEP** (90% CI: 58% to 96%, *P* = .0002)
  - Rate difference: 7.6 (90% CI: 4.1-11.2)
  - Number needed to treat to prevent 1 infection: 13 (90% CI: 9-25)

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	enrolment			
A	44	Hospital-acquired pneumonia	Potentially life threatening	Unlikely
B	43	Chest pain musculoskeletal	Potentially life threatening	Unrelated
C	4	Headache	Severe	Probable
D	2	Fall	Severe	Unrelated
E	35	Anxiety or panic attack	Severe	Unrelated
F	43	Depression	Severe	Unrelated
G	52	Manic depression	Severe	Unrelated
H	0	Nausea, abdominal pain	Moderate	Probable
C	0	Headache	Moderate	Probable
I	5	Nausea	Moderate	Probable
J	24	Polyarthralgia	Moderate	Probable
K	49	Nausea	Moderate	Probable
L	0	Influenza-like illness	Moderate	Possible
M	4	High creatinine concentration	Moderate	Possible
H	1	Breathlessness, palpitations, chest pain	Moderate	Unlikely
N	1	Anxiety or depression	Moderate	Unlikely
O	1	Gastroenteritis	Moderate	Unlikely
H	2	Chest pain	Moderate	Unlikely
P	46	Loin pain	Moderate	Unlikely
B	47	Central chest pain	Moderate	Unlikely
Q	6	Headache	Moderate	Unrelated
O	6	Intermittent nausea	Mild	Definite
A	39	High creatinine concentration	Mild	Probable
R	12	Lipoatrophy	Mild	Possible
R	28	Fatigue, arthralgia	Mild	Possible
S	47	Arthralgia	Mild	Possible
T	5	High creatinine concentration	Mild	Unlikely
U	14	Abnormal liver function	Mild	Unlikely

Events in participants in the immediate group during the deferral phase of follow-up. All participants other than participant B restarted study drug. *As assessed by participant's clinician.

Table 2: Interruptions to treatment because of clinical or laboratory adverse events, by participant

VOICE STUDY:Vaginal and Oral Intervention to Control the Epidemic

Study Design

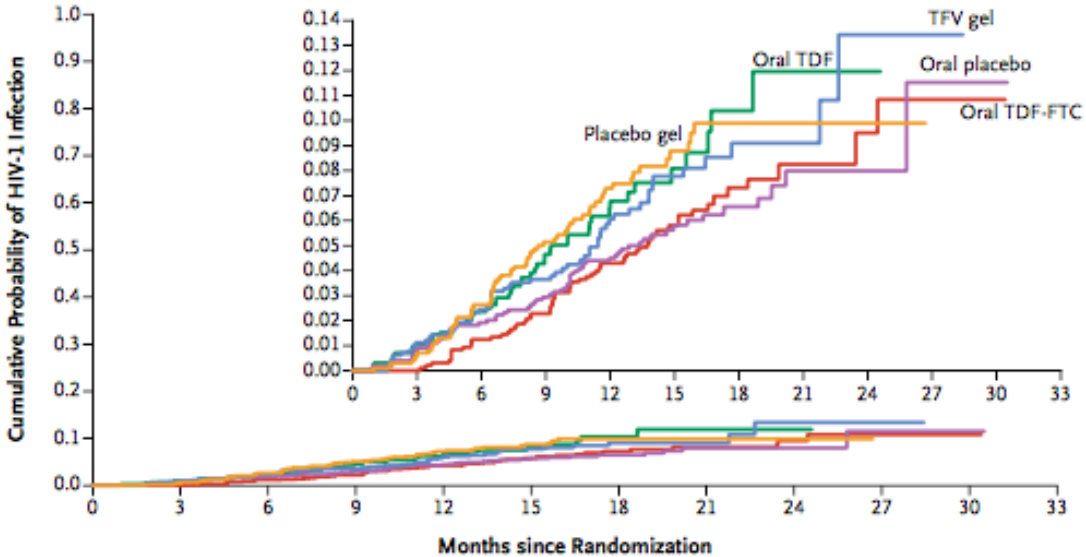
- 15 trial sites in Uganda, South Africa and Zimbabwe enrolled **5,029** sexually active HIV-negative women
- 5 study groups (each of~ 1000 pts):
  - tenofovir gel
  - inactive placebo gel
  - oral tenofovir
  - oral tenofovir/emtricitabine
  - inactive placebo tablet

Primary Objectives:

- To estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among women at risk for sexually transmitted infection (STI)
- To evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection

VOICE STUDY:Vaginal and Oral Intervention to Control the Epidemic

Results



No. at Risk											
Oral TDF	1002	966	752	504	309	155	72	23	2	0	0
Oral TDF-FTC	994	971	953	931	802	467	271	143	71	22	2
Oral placebo	1008	982	966	943	818	485	281	152	72	22	1
TFV gel	1003	973	944	702	486	288	154	64	14	1	0
Placebo gel	1000	985	952	699	493	278	145	64	16	0	0

Figure 2. Cumulative Probability of HIV-1 Infection, According to Study Group.

The numbers shown below the graph are the numbers of participants who were at risk at the start of each quarterly interval. The inset shows the same data on an enlarged y axis.

Marrazzo JM et VOICE study team. *Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women*, NEJM Feb 2015

Bone Mineral Density Changes Among Young, Healthy African Women Receiving Oral Tenofovir for HIV Preexposure Prophylaxis

Brenda G. Mirembe, MBChB, MSc, Clifton W. Kelly, MS,† Nyaradzo Mgodi, MBChB, MMed,‡ Susan Greenspan, MD,§ James Y. Dai, PhD,† Ashley Mayo, MSPH,‖ Jeanna Piper, MD,¶ Carolyne A. Akello, MBChB, MSc,* Flavia M. Kiweewa, MBChB, MSc,* Tsitsi Magure, MBChB, MMed,‡ Clemensia Nakabiito, MBChB, MMed,* Jeanne M. Marrazzo, MD, MPH,# Z. Mike Chirenje, MD, FRCOG,‡ and Sharon A. Riddler, MD, MPH,§ for the MTN-003B Protocol team*

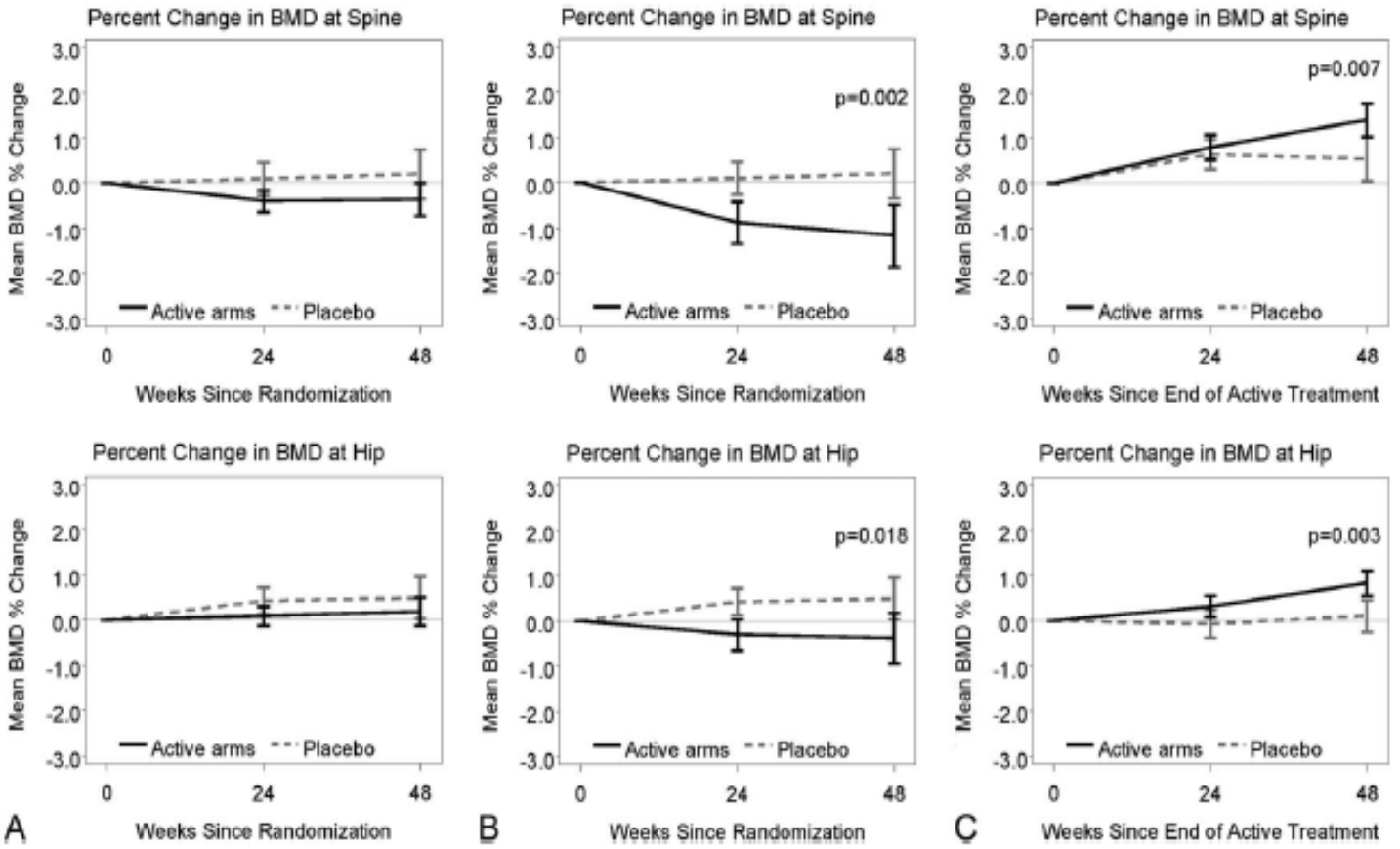


FIGURE 2. Percent change in spine and TH BMD for during and after study treatment TDF-containing PrEP or placebo. The solid line shows the combined results for the TDF and FTC/TDF groups and the dashed line for the placebo group. When presented *P*-values come from Student t-test of difference in mean percentage change between the 2 groups at 48 weeks. The first panel (A) shows the percentage change in BMD by study week from baseline to week 48 of active treatment for all study participants (active arms n = 235, placebo n = 119). In panel (B), the percentage change in BMD from baseline to week 48 for the subset of participants with good adherence defined as plasma tenofovir detected in 75%–100% of samples obtained during the first 48 weeks, combined TDF, and FTC/TDF groups (n = 81) compared with placebo (n = 119). In panel (C), percentage change in BMD during the 48 weeks from end of active treatment for the combined TDF and FTC/TDF groups (n = 238) and placebo (n = 116). BMD, bone mineral density.

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ESTABLISHED IN 1812 DECEMBER 30, 2010 VOL. 363 NO. 27

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

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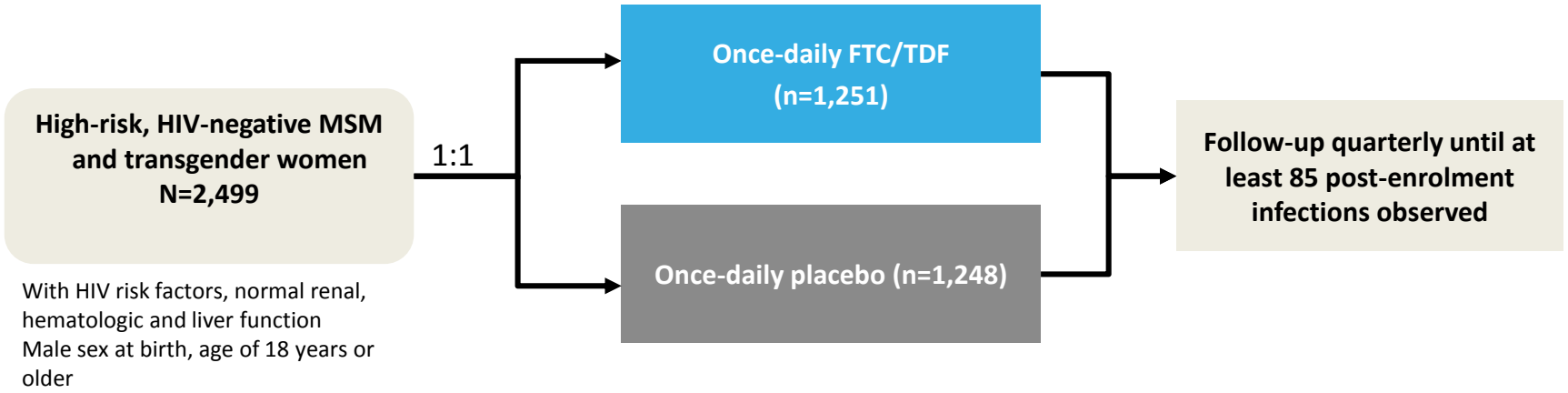
Study design

iPrEx (Preexposure Prophylaxis Initiative): placebo-controlled, double-blind, randomised, multicentre trial in the Americas, South Africa, and Thailand



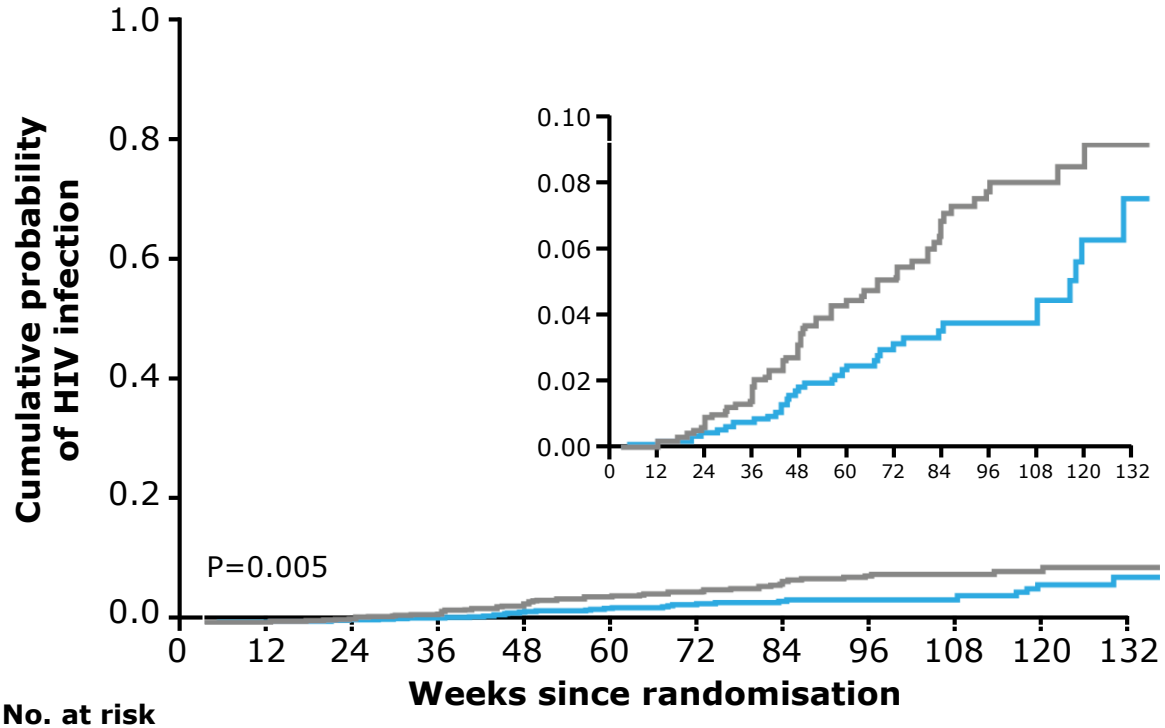
ClinicalTrials.gov Identifier: NCT00458393

- **Study objective** : to determine whether once-daily use of FTC/TDF versus placebo can prevent HIV-1 infection in 2,499 MSM who also receive HIV counselling, condoms, and treatment for STIs
- **Primary endpoint**: HIV seroconversion between randomisation and Month 12
- **Secondary endpoints**: safety, adherence, sexual behaviour, resis

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate
MSM, men who have sex with men
Grant RM et al. N Engl J Med 2010;363:2587–2599; Michael NL. N Engl J Med 2010;363:2663–2664

Efficacy results

Kaplan–Meier estimates of time to HIV infection (Modified ITT Population).



No. at risk

Placebo	1248	1194	1108	1005	852	647	546	444	370	258	137	60
FTC–TDF	1251	1188	1097	988	848	693	558	447	367	267	147	65

Of the 100 incident infections:

- **64** infections in the placebo group
- **36** infections in the FTC/TDF group
- No resistance to FTC or TDF was detected among these individuals

44% risk reduction

- **Once-daily oral FTC/TDF provided 44% additional protection from HIV among MSM who received a comprehensive package of prevention services**

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate

Grant RM & al. N Engl J Med 2010; 363:2587-99

Safety data

Adverse events reported for the iPrEx study

Adverse event	FTC/TDF (N=1,251)		Placebo (N=1,248)		P value
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	
Any adverse event	867 (69)	2630	877 (70)	2611	0.50
Any serious adverse event	60 (5)	76	67 (5)	87	0.57
Elevated creatinine level	25 (2)	28	14 (1)	15	0.08
Nausea	20 (2)	22	9 (<1)	10	0.04
Unintentional weight loss (≥5%)	27 (2)	34	14 (1)	19	0.04
Death	1 (<1)	1	4 (<1)	4	0.18

- **All elevations in serum creatinine level resolved after the discontinuation of the study drug**
- **Moderate nausea was reported more frequently in the FTC/TDF group than in the placebo group as was unintentional weight loss**

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate

Grant RM et al. N Engl J Med 2010;363:2587–2599

MAJOR ARTICLE

Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial

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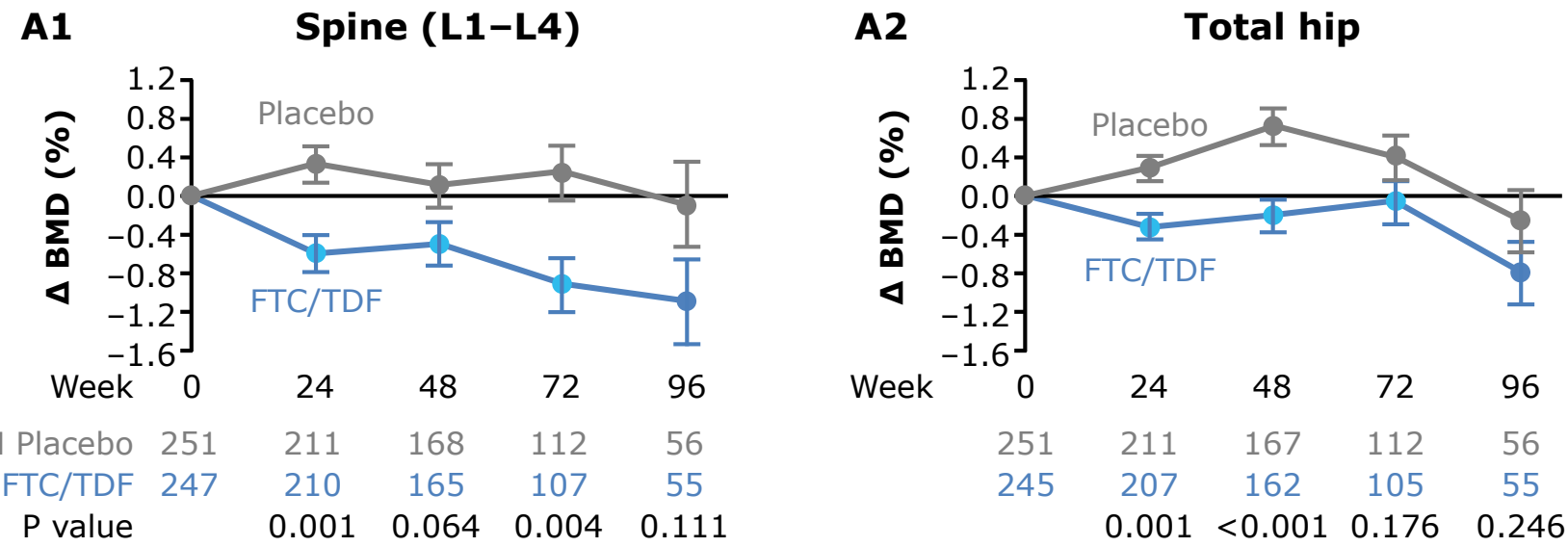
(See the Editorial Commentary by Falutz on pages 581–3.)

iPrEx
Bone mineral density (BMD) sub-study

iPrEx sub-study measured BMD using DEXA in 498 HIV-negative MSM or TGWMSM individuals, randomised to receive either FTC/TDF or placebo

Changes from baseline in BMD during treatment in the spine and hip

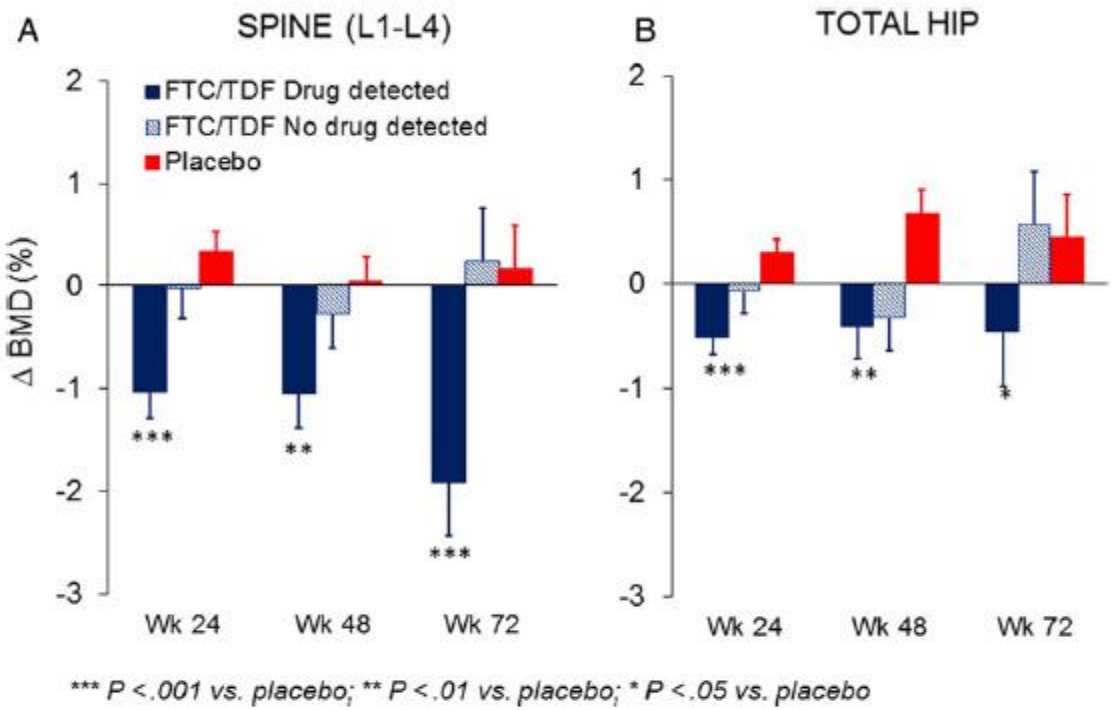


- **A decrease in BMD was observed for both spine (p=0.001) and hip (p=0.001) in the FTC/TDF group vs placebo within 24 weeks; however, further net changes were non-significant**
- **There was no difference in rate of bone fractures between the FTC/TDF and placebo groups (p=0.62)**

BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; FTC, emtricitabine; MSM, men who have sex with men; TDF, tenofovir disoproxil fumarate; TGWMSM, transgender women who have sex with men

Mulligan K et al. Clin Infect Dis 2015;61(4):572–580

iPrEx
Bone mineral density (BMD) sub-study



*** P <.001 vs. placebo; ** P <.01 vs. placebo; * P <.05 vs. placebo

Figure 3. Changes from baseline in bone mineral density (BMD) through week 72 during randomized treatment, based on detection of drug in plasma at each time-point. In plasma, tenofovir (TFV) or emtricitabine (FTC) was detected in 57%, 48%, and 53% of those randomized to FTC/tenofovir disoproxil fumarate (TDF) at weeks 24, 48, and 72, respectively. Decreases in BMD in the spine (*A*) and hip (*B*) were statistically significant vs placebo in the groups with detectable drug levels at each time-point (for drug detection vs placebo: ***P<.001; **P<.01; *P<.05).

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Lancet HIV. 2016 November ; 3(11): e521–e528. doi:10.1016/S2352-3018(16)30153-9.

Age, baseline kidney function, and medication exposure are associated with declines in creatinine clearance on PrEP: an observational cohort study

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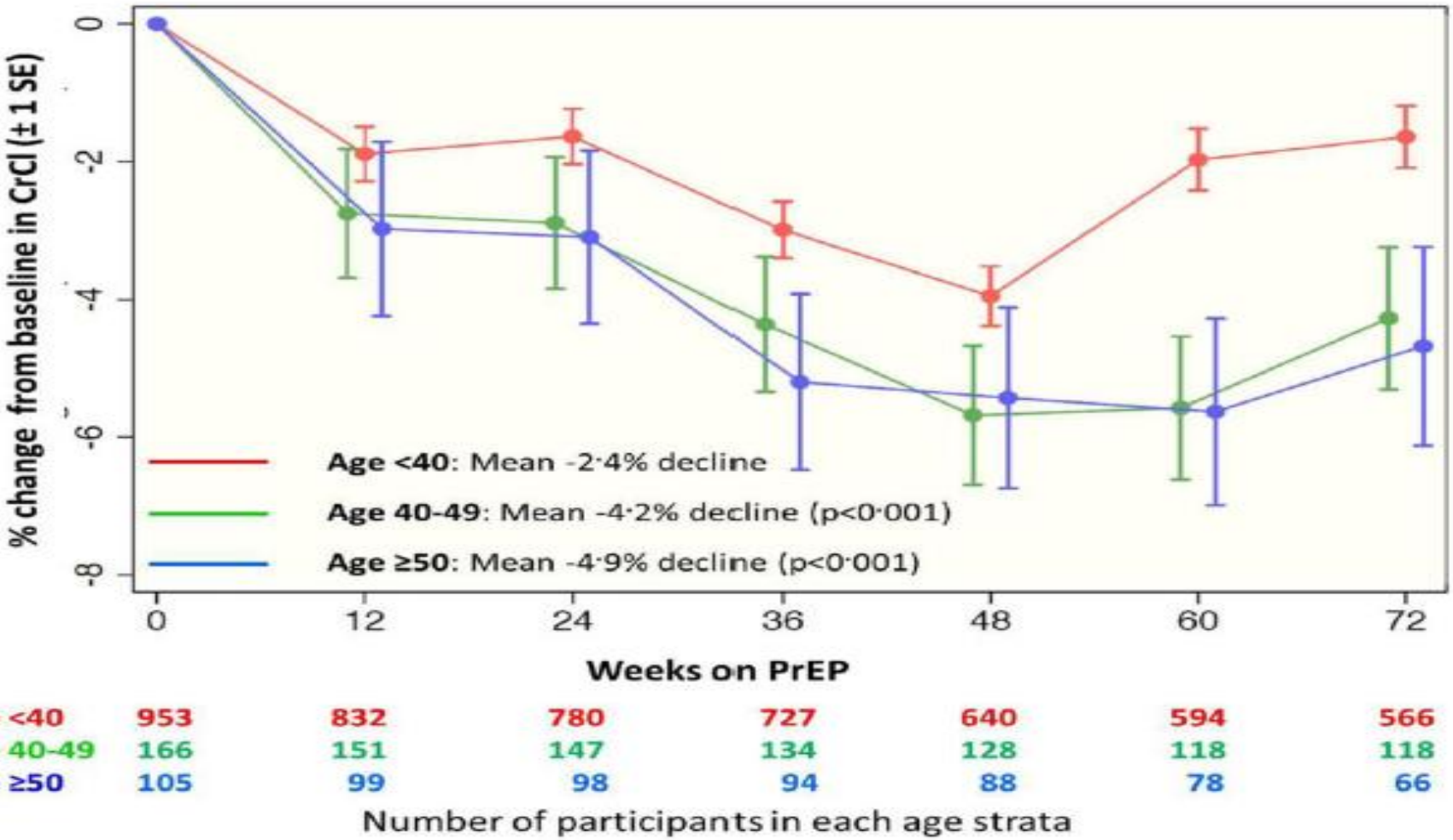


Figure 1.
Change in creatinine clearance over time for iPrEx OLE participants, stratified by baseline age

*Models adjusted for age, baseline CrCl and site of enrollment; p-values compare the % decline in the older age strata to that in those < 40 years; S

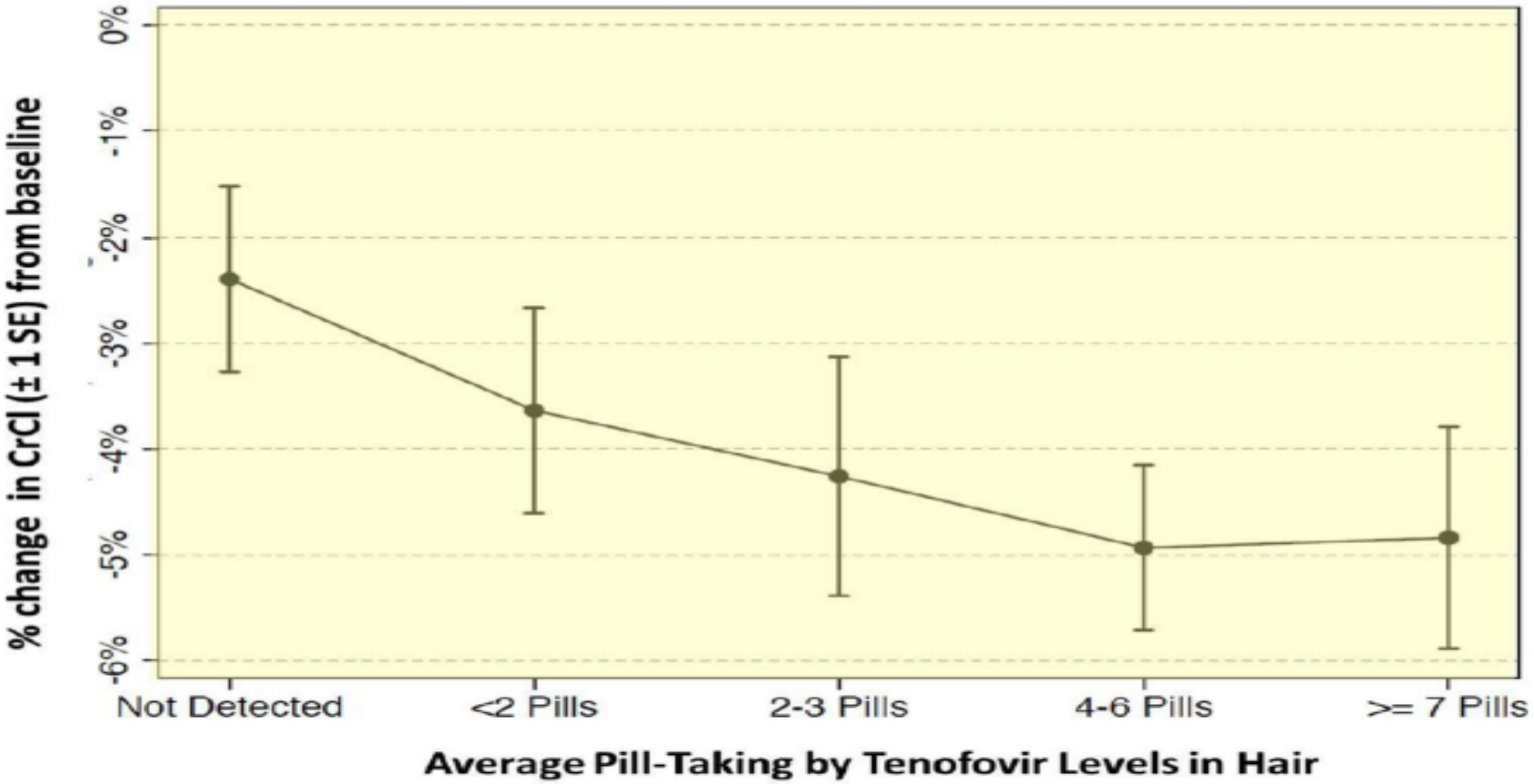
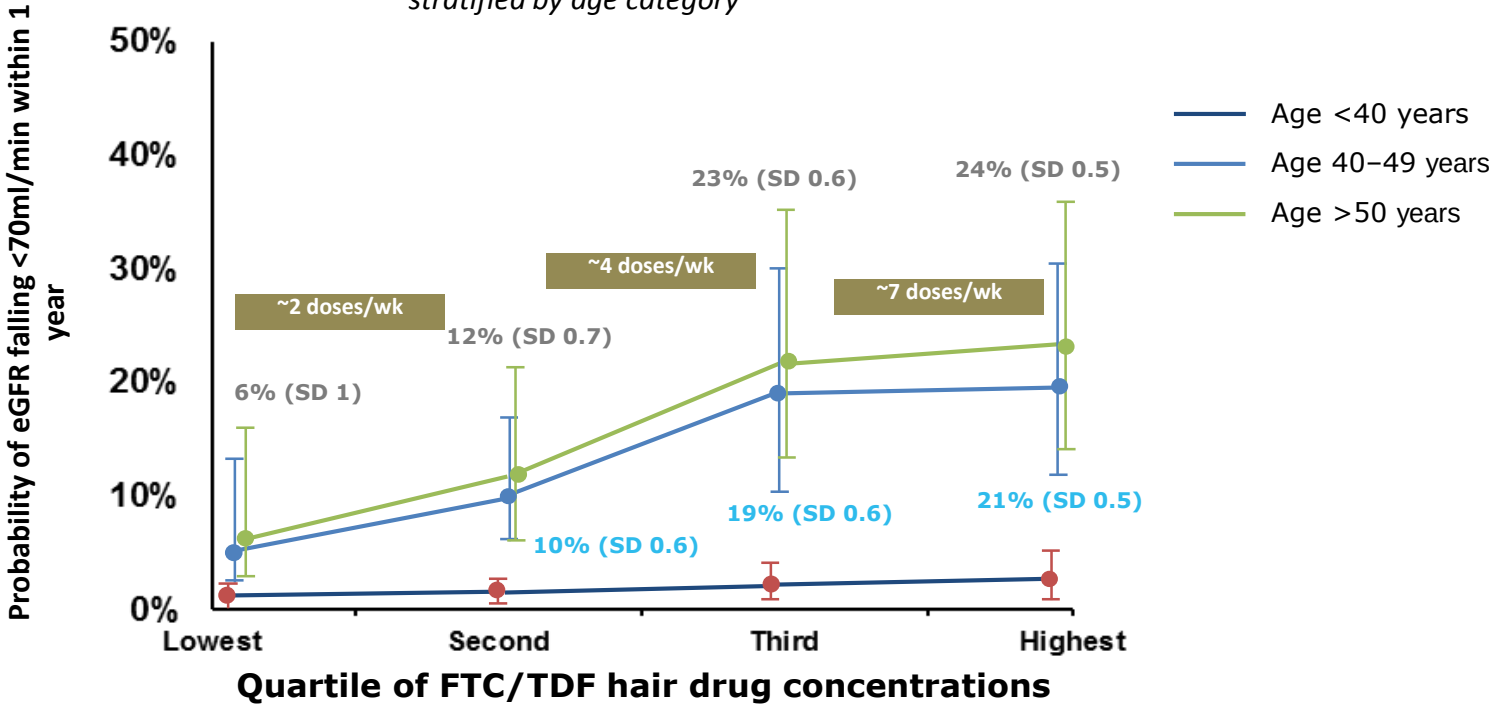


Figure 2.
Relationship between % change in CrCl from baseline and pill taking in iPrEx OLE as determined by hair concentrations
*~ 27% of person-visits had hair levels demonstrating no detectable PrEP use, 16% with <2 pills per week; 9% 2–3 pills per week; 33% 4–6 pills per week; and 16% with daily dosing

iPrEx OLE
Renal safety data: eGFR iprex OLE

Study of 1,225 HIV-negative MSM and TGWMSM individuals evaluated FTC/TDF levels in hair, and renal function

Probability of eGFR falling to <70ml/min by TDF hair quartile (12 weeks) within 1 year, stratified by age category



- **A significant relationship was established between increase in FTC/TDF levels in hair and decreasing renal function over time for FTC (p=0.006) and TDF (p=0.008)**
- **Clinically significant decreases in eGFR to <70ml/min were more common in those with baseline eGFR <90ml/min (27% probability) or aged >40 years (19–24% probability)**

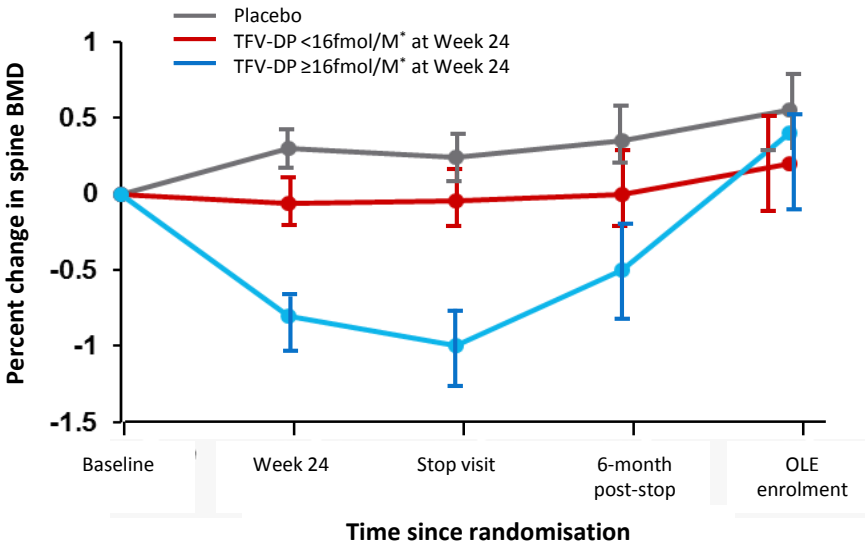
eGFR, estimated glomerular filtration rate; FTC, emtricitabine; MSM, men who have sex with men; OLE, open label extension; PrEP, pre-exposure prophylaxis; SD, standard deviation; TDF, tenofovir disoproxil fumarate; TGWMSM, transgender women who have sex with men; wk, week

Gandhi M et al. CROI 2016. Boston, MA. #866

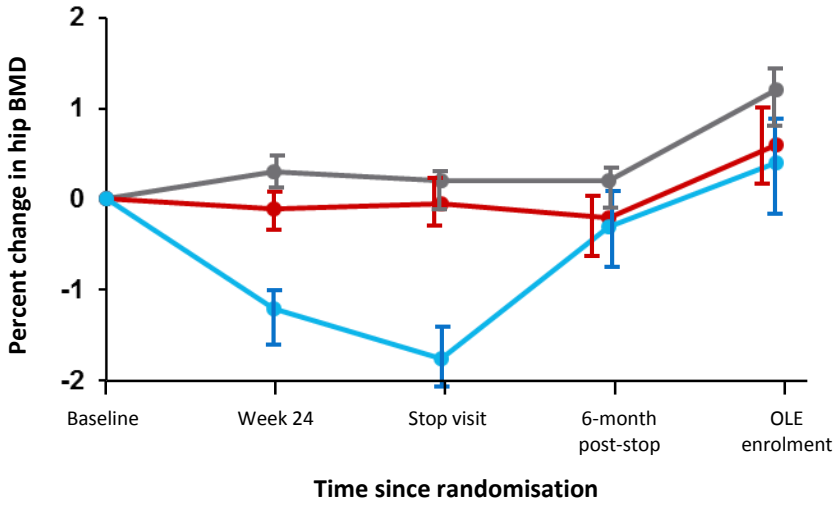
iPrEx/iPrEx OLE
Bone mineral density (BMD)

DEXA sub-study of 498 MSM and TGWMSM individuals, during which BMD was measured every 24 weeks during the iPrEx study, 24 weeks after stopping PrEP, and at the beginning of the iPrEx OLE
(individuals with protective FTC/TDF levels vs without protective levels vs placebo[1])

Change in spine BMD from iPrEx enrolment



Change in hip BMD from iPrEx enrolment



- **BMD recovered completely (to placebo levels) by 6 months in spine**
- **BMD recovered completely by enrolment in iPrEx OLE (median 73 weeks) in both spine and hip**

* Drug concentration in PBMCs to evaluate adherence (fmol/M viable PBMCs); 16fmol/M viable PBMCs is the TDF concentration associated with a 90% reduction in HIV infection risk (EC_{90})

BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; FTC, emtricitabine; MSM, men who have sex with men; OLE, open label extension; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate; TGWMSM, transgender women who have sex with men

Grant R et al. CROI 2016. Boston, MA. #48LB: http://betablog.org/9038-2/ (accessed June 2016)

Drug Saf
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REVIEW ARTICLE

Pre-Exposure Prophylaxis for HIV Prevention: Safety Concerns

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Table 1 Abstract on clinical trials on pre-exposure prophylactic agents (tenofovir and emtricitabine)

Study	Year	Study design	Study population	Sample size	Agent used	Objective	Outcome/results
iPrEx trial [16]	2010	Placebo-controlled RCT	MSM	2499	TDF/FTC	Effectiveness	44%
						Safety	Nausea; ↑serum creatinine
						Adherence	51%
TDF2 [17]	2012	Placebo-controlled RCT	Heterosexual adults	1219	TDF/FTC	Effectiveness	62%
						Safety	Dizziness; nausea; vomiting; ↓bone mineral density
						Adherence	84%
Partners PrEP [14]	2012	Placebo-controlled RCT	Heterosexual couples	1013	TDF vs. TDF/FTC	Effectiveness	67% (TDF); 75% (TDF/FTC)
						Safety	GIT; fatigue; neutropaenia; ↑serum creatinine; ↓phosphorous
						Adherence	82%
VOICE [27]	2015	Placebo-controlled RCT	Women of reproductive age	3019	TDF vs. TDF/FTC	Effectiveness	−49% (TDF); −4% (TDF/FTC)
						Safety	↑Serum creatinine
						Adherence	28–29%
FEM-PrEP [28]	2012	Placebo-controlled RCT	High-risk women	2120	TDF/FTC	Effectiveness	6%
						Safety	Nausea; vomiting; ↑ALT; hepatic and renal abnormalities
						Adherence	37%
PROUD [29]	2016	Placebo-controlled RCT	MSM	545	TDF/FTC	Effectiveness	86%
						Safety	Nausea; diarrhoea; abdominal pains; fatigue; headache; flu-like illness; sleep disturbance; ↑creatinine clearance
						Adherence	86%
Ipergay [5]	2015	Placebo-controlled RCT	MSM	400	TDF/FTC	Effectiveness	86%
						Safety	Abdominal pains; nausea; vomiting; diarrhoea
						Adherence	43% optimal use; 25% suboptimal use by ACASI

Drug Saf
DOI 10.1007/s40264-017-0505-6

REVIEW ARTICLE

Pre-Exposure Prophylaxis for HIV Prevention: Safety Concerns

Raymond A. Tetteh[1,2] · Barbara A. Yankey[3] · Edmund T. Nartey[4,5] · Margaret Lartey[6] · Hubert G. M. Leufkens[3,7] · Alexander N. O. Dodoo[4]

ADAPT [45]	2015	Placebo-controlled RCT	MSM; TGW	179	TDF/FTC	Effectiveness	NR
						Safety	Nausea; unintentional weight loss; ↑serum creatinine
						Adherence	Daily, 79%; time driven, 63%; event driven, 53%
The Bangkok Tenofovir study [30]	2013	Placebo-controlled RCT	Drug injectors	2413	TDF	Effectiveness	48.9%
						Safety	Nausea; vomiting
						Adherence	83.8%
CAPRISA 004 trial [18]	2013	Placebo-controlled RCT	Women of reproductive age	889	TDF	Effectiveness	39%
						Safety	↑Serum creatinine; anaemia; diarrhoea
						Adherence	NR
PrEP safety trial [31]	2013	Placebo-controlled RCT	MSM	400	TDF	Effectiveness	NR
						Safety	Back pain; ↓in bone mass density; Hypophosphatemia
						Adherence	92% (pill count); 77% (MEMS)

ACASI Audio Computer-Assisted Self-Interview Software, *ADAPT* Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking, *ALT* alanine transaminase, *CAPRISA* Centre for AIDS program of Research in South Africa, *FEM PrEP* Preexposure Prophylaxis Trial for HIV Prevention among African Women, *FTC* emtricitabine, *Ipergay* Intervention Preventive de l'Exposition aux Risques avec Risques avec et pour les Gays, *iPrEX* Iniciativa Profilaxis Pre-Exposicion, *MEMS* medication event monitoring system, *MSM* men who have sex with men, *NR* not reported, *PrEP* pre-exposure prophylaxis, *PROUD* Pre-exposure Prophylaxis to Prevent the Acquisition of HIV-1 Infection, *RCT* randomised controlled trial, *TDF* tenofovir, *TGW* trans-gender women, *VOICE* Vaginal and Oral Interventions to Control the Epidemic, ↑ increased, ↓ decreased

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REVIEW ARTICLE

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shows a favourable pattern of adverse events for PrEP among eligible populations. Side effects can lead to a lack of compliance, resulting in low levels of adherence (frequency of medicine intake) to pill use. Some reported symptoms associated with the start of PrEP gradually resolve. Generally, even for some side effects listed as serious, such as kidney dysfunction, observed increases in the serum creatinine level return to normal after the discontinuation of PrEP. Tubular renal toxicity from PrEP is rare and active screening is not recommended. The same applies to the reduction of BMD after cessation in the use of TDF and therefore current evidence does not support constant X-ray monitoring at baseline before initiating PrEP and while taking TDF/FTC.

Clin Infect Dis. 2017 Feb 1;64(3):317-325. doi: 10.1093/cid/ciw765. Epub 2016 Nov 15.

Decline in Bone Mass With Tenofovir Disoproxil Fumarate/Emtricitabine Is Associated With Hormonal Changes in the Absence of Renal Impairment When Used by HIV-Uninfected Adolescent Boys and Young Men for HIV Preexposure Prophylaxis.

Havens PL[1], Stephensen CB[2], Van Loan MD[2], Schuster GU[3], Woodhouse LR[2], Flynn PM[4], Gordon CM[5], Pan CG[6], Rutledge B[7], Liu N[7], Wilson CM[8], Hazra R[9], Hosek SG[10], Anderson PL[11], Seifert SM[11], Kapogiannis BG[9], Mulligan K[12]; Adolescent Medicine Trials Network for HIV/AIDS Interventions 117 study team.

⊕ Author information

Abstract

BACKGROUND: We aimed to define the relative importance of renal and endocrine changes in tenofovir disoproxil fumarate (TDF)-related bone toxicity.

METHODS: In a study of daily TDF/emtricitabine (FTC) preexposure prophylaxis (PrEP) in human immunodeficiency virus (HIV)-uninfected young men who have sex with men, we measured changes from baseline in blood and urine markers of the parathyroid hormone (PTH)-vitamin D-fibroblast growth factor 23 (FGF23) axis, creatinine, and renal tubular reabsorption of phosphate (TRP). We explored the relationship of those variables to changes in bone mineral density (BMD). Tenofovir-diphosphate (TFV-DP) in red blood cells was used to categorize participants into high and low drug exposure groups.

RESULTS: There were 101 participants, median age 20 years (range 15 to 22). Compared with low drug exposure, high-exposure participants showed increase from baseline in PTH and decline in FGF23 by study week 4, with no differences in creatinine, phosphate, or TRP. At 48 weeks, the median (interquartile range) percent decline in total hip BMD was greater in those with high- compared to low- exposure (-1.59 [2.77] vs +1.54 [3.34] %, respectively; P = .001); in high-exposure participants, this correlated with week 4 TFV-DP (inversely; r = -0.60, P = .002) and FGF23 (directly; r = 0.42; P = .039) but not other variables.

CONCLUSIONS: These findings support the short-term renal safety of TDF/FTC PrEP in HIV-seronegative young men and suggest that endocrine disruption (PTH-FGF23) is a primary contributor to TDF-associated BMD decline in this age group.

J Acquir Immune Defic Syndr. 2016 Dec 15;73(5):540-546.

Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation.

Marcus JL[1], Hurley LB, Hare CB, Nguyen DP, Phengrasamy T, Silverberg MJ, Stoltey JE, Volk JE.

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Abstract

BACKGROUND: Placebo-controlled and open-label studies have demonstrated the safety and efficacy of daily oral preexposure prophylaxis (PrEP) in preventing HIV infection, but data are limited on real-world PrEP use.

METHODS: We conducted a cohort study from July 2012 through June 2015 of Kaiser Permanente Northern California members initiating PrEP. We assessed pharmacy refill adherence and discontinuation, decreases in estimated glomerular filtration rate (eGFR), and sexually transmitted infection (STI)/HIV incidence.

RESULTS: Overall, 972 individuals initiated PrEP, accumulating 850 person-years of PrEP use. Mean adherence was 92% overall. Black race/ethnicity [adjusted risk ratio (aRR) 3.0; 95% confidence interval: 1.7 to 5.1, P < 0.001], higher copayments (aRR 2.0; 1.2 to 3.3, P = 0.005), and smoking (aRR 1.6; 1.1 to 2.3, P = 0.025) were associated with <80% adherence. PrEP was discontinued by 219 (22.5%); female sex (aRR 2.6; 1.5 to 4.6, P < 0.001) and drug/alcohol abuse (aRR 1.8; 1.3 to 2.6, P = 0.002) were associated with discontinuation. Among 909 with follow-up creatinine testing, 141 (15.5%) had an eGFR <70 mL·min·1.73 m and 5 (0.6%) stopped PrEP because of low eGFR. Quarterly STI positivity was high and increased over time for rectal chlamydia (P < 0.001) and urethral gonorrhea (P = 0.012). No HIV seroconversions occurred during PrEP use; however, 2 occurred in individuals who discontinued PrEP after losing insurance coverage.

CONCLUSIONS: PrEP adherence was high in clinical practice, consistent with the lack of HIV seroconversions during PrEP use. Discontinuation because of renal toxicity was rare. STI screening every 6 months, as recommended by current guidelines, may be inadequate. Strategies are needed to increase PrEP access during gaps in insurance coverage.

Bone Changes With TDF-containing and Non-TDF-containing Prep in U.S. Men and Women

Todd T Brown[1], Tim Wilkin[2], Kenneth H Mayer[3], Raphael J Landovitz[4], Ying Q Chen[5], Jing Wang[5], Alicia Young[6], Mark A Marzinke[7], Wairimu Chege[7], Merybeth McCauley[8], Roy M Gulick[3]

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HPTN HIV Prevention Trials Network

ACTG AIDS CLINICAL TRIALS GROUP

BACKGROUND

- Pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) is highly effective in reducing incident HIV infection in high risk populations.
- While generally well-tolerated, TDF-containing PrEP has been associated with decreases in bone mineral density (BMD) in men and women.
- The magnitude of the bone loss with TDF-containing PrEP is dependent on PrEP adherence.
- Due to long-term toxicities of TDF-containing PrEP regimens, the development of non-TDF PrEP alternatives is warranted. However, BMD effects of non-TDF-containing PrEP regimens have not been reported.
- HPTN 069/ACTG 5305 showed similar tolerability of four different daily PrEP regimens: (1) maraviroc 300 mg (MVC); 2) MVC 300 mg plus FTC 200 mg; (3) MVC 300 mg plus TDF 300 mg; or (4) TDF 300 mg plus FTC 200 mg.
- Here, we report the BMD results of HPTN 069/ACTG 5305 and explore factors that are associated with BMD loss in those randomized to TDF-containing PrEP.

RESULTS

Table 1: Baseline Characteristics of Study Population with DXA (N=307)

	Men/TGW		Total	Women		Total
	TDF	Non-TDF	Total	TDF	Non-TDF	Total
N	88	84	172	71	64	135
Age (years) Mean (SD)	34 (10.8)	32 (10.1)	33 (10.5)	39 (11.2)	37 (11.2)	38 (11.2)
Race: Black (%)	24%	30%	27%	66%	63%	64%
BMI Mean (SD)	27 (5.8)	27 (4.9)	27 (5.3)	32 (8.1)	31 (7.1)	31 (7.6)
Lumbar spine Z-score						
Median	-0.6	-0.4	-0.5	0.2	0.3	0.2
(Q1,Q3)	(-1.5, 0.4)	(-1.1, 0.6)	(-1.3, 0.4)	(-0.5, 1.3)	(-0.5, 1.1)	(-0.5, 1.2)
Total hip Z-score						
Median	-0.3	-0.4	-0.3	0.4	0.2	0.3
(Q1,Q3)	(-0.9, 0.4)	(-1.1, 0.2)	(-0.9, 0.3)	(-0.7, 1.2)	(-0.3, 1.1)	(-0.5, 1.1)
Femoral neck Z-score						
Median	-0.1	-0.4	-0.3	0.2	0.0	0.1
(Q1,Q3)	(-0.8, 0.5)	(-1.0, 0.5)	(-0.9, 0.5)	(-0.8, 1.0)	(-0.7, 0.8)	(-0.7, 0.9)

- Women were older, more likely to be Black, and had a higher BMI than men.
- Men, but not women had a low BMD at baseline (Z-scores < 0).

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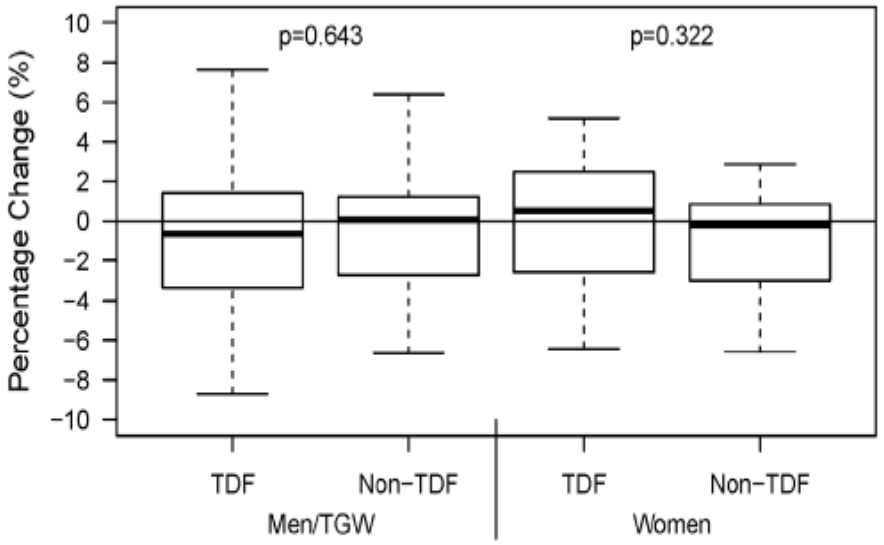
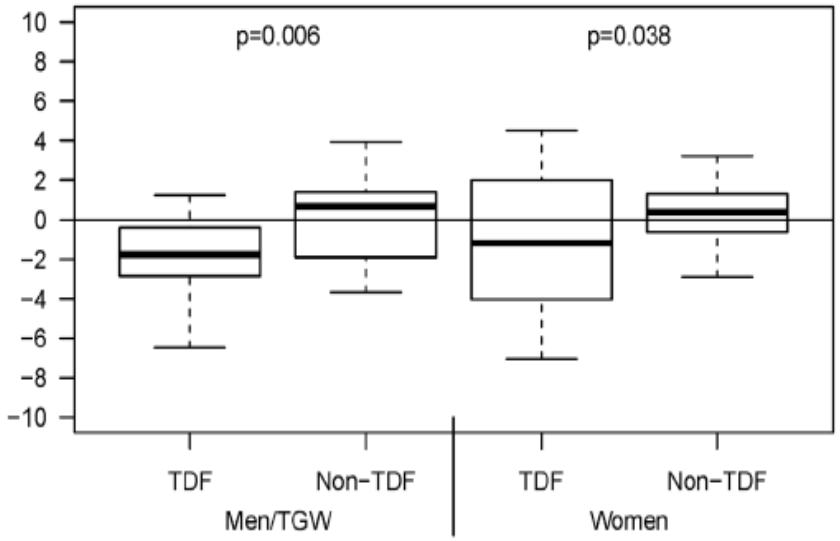
Figure 1. Changes in Spine BMD over 48 weeks with TDF and Non-TDF PrEP: Adherence Subset



- At the lumbar spine, median (Q1, Q3) of BMD change was -0.11% (-2.91%, 2.02%) in the TDF arm and was -0.15% (-2.74%, 1.22%) in the Non-TDF arm (between arm p=0.73).
- Results were similar in men and women (Figure 1).
- Results were similar in the mITT population (data not shown).

Figure 2. Changes in Hip BMD over 48 weeks with TDF and Non-TDF PrEP: Adherence Subset



- At the total hip, median (Q1,Q3) of BMD change was -1.46% (-3.28%, 0.52%) in the TDF arm and was 0.52% (-1.40%, 1.37%) in Non-TDF arm (between arm p=0.0006).
- Results were similar in men and women (Figure 2).
- Results were similar in the mITT population (data not shown).

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Bone Changes With TDF-containing and Non-TDF-containing Prep in U.S. Men and Women

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CONCLUSIONS

- TDF-containing PrEP was associated with significantly greater bone loss at the hip, but not the lumbar spine, compared to non-TDF PrEP (MVC alone and MVC+FTC arms).
- No differences were observed between the effect of TDF on BMD in men and women, although baseline BMD was lower in men.
- Vitamin D deficiency at baseline or hypophosphatemia on treatment were not associated with bone changes in those randomized to TDF-containing PrEP.
- MVC±FTC PrEP may have better bone safety compared to TDF-containing PrEP.

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Older Age Associated with both Adherence and Renal Decline in the PrEP Demo Project

Monica Gandhi[1], Peter Bacchetti[2], Catherine A. Koss[1], Chengshi Jin[2], Howard Horng[3], Richard Elion[4], Michael Kolber[5], Stephanie Cohen[6], Susan Buchbinder[7], Albert Liu[7]

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METHODS

- **Study population**: The U.S. PrEP Demonstration Project (PrEP Demo) provided open-label PrEP to a diverse population of men-who-have-sex-with-men (MSM) and transgender women (TGW) in San Francisco, Miami and Washington DC (N=557) from Oct 2012-Jan 2014[12]
- Hair samples were collected every 12 weeks in a subset of participants in PrEP Demo who opted into the "Enhancing PrEP in Community" (EPIC) Hair Study
- Creatinine (Cr) measured every 12 weeks and eGFR estimated by the MDRD equation[13]
- Hair TFV and FTC concentrations measured via validated liquid chromatography/tandem mass spectrometry-methods in the UCSF Hair Analytical Laboratory (HAL)
- Data from STRAND, where HIV-noninfected volunteers were provided directly observed TDF at 2, 4 and 7 doses/week, provided estimates for TFV levels in hair consistent with different dosing patterns[14] for this analysis
- Factors associated with "good TFV hair levels" (≥ 4 doses per week, seen to be protective in iPrEx OLE[15]) assessed via multivariate logistic regression models
- Relationship between hair TFV levels and changes in eGFR (adjusted for baseline) estimated by linear mixed models

Characteristic (N=280)		Distribution
Age at study entry (years)	Median (range)	34 (19-65)
Risk factor	MSM Transgender female (TGW)	276 (99%) 4 (1%)
Race/ethnicity (self-report)	White, Black Latino Other (Asian, Native, etc.)	219 (78%) 15 (5%) 65 (23%) 56 (20%)
Receptive condomless anal intercourse (last 3 months)	N (%) Median episodes (range)	199 (71%) 3 (0-115)
Any recreational drug use (last 3 months)	N (%)	217 (60%)
Amphetamine use (last 3 months)	N (%)	35 (13%)
Baseline eGFR (ml/min/1.73m^2)	Median (range)	98 (51-72)
"Good adherence" ≥ 4 doses/wk*	N (%) of person-visits (876 person visits)	718 (82%)
Distribution of doses/week	13 (4.6%) < 2 doses/week; 20 (7.1%) 2-3; 103 (36.8%) 4-6 doses/wk; 87 (31%) daily	

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Table 2: Predictors of "good adherence" (n=876 person-visits)

Factor (timeframe)	OR (95% CI)*	p-value
Per decade of age (at baseline)	1.42 (1.00-2.00)	p= 0.05
Condomless receptive anal sex with HIV+ ptr (in past 3 months) No (reference) Yes	 1.0 2.35 (1.22-4.50)	 p= 0.01
Amphetamine use (in past 3 months) No (reference) Yes	 1.0 2.46 (0.93-6.5)	 p= 0.07

*Odds ratio (OR); Confidence interval (CI)

Table 3: Predictors of eGFR drop to <70 (4% person-visits)

Factor	OR (95% CI)*	p-value
Every unit of GFR above 70 at baseline*	0.85 (0.79-0.90)	p<0.001
Age >45 years	3.38 (1.15-9.9)	p= 0.027
"Good" TFV hair level†	1.33 (0.36-5.5)	p= 0.67

*Odds of eGFR dropping below 70 decrease by 15% for each additional single point higher above GFR of 70 ml/min/1.73m^2 the participant was at baseline.

†TFV hair level ≥0.023ng/mg

Older Age Associated with both Adherence and Renal Decline in the PrEP Demo Project

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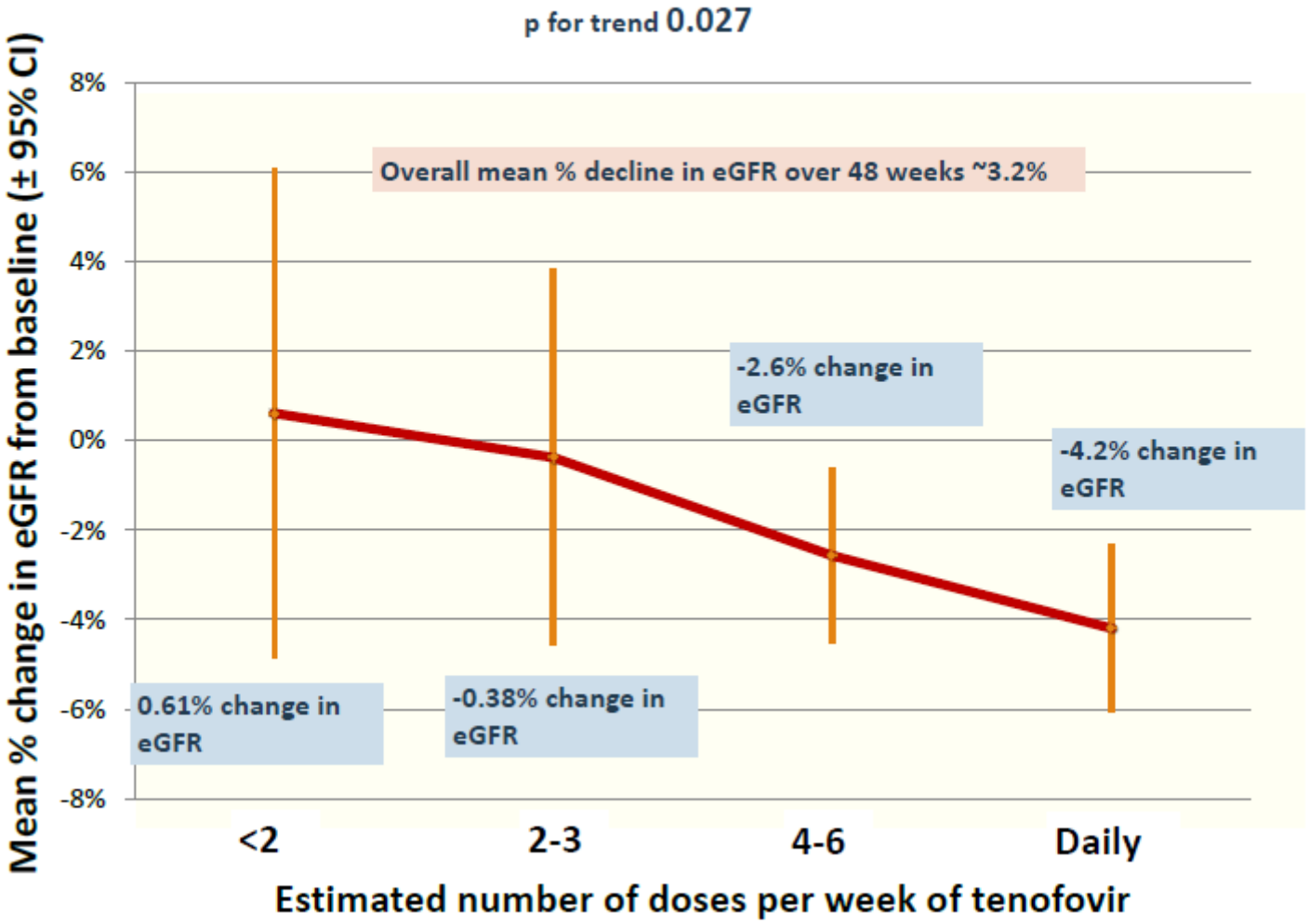
Figure 1: Relationship between hair concentration of TFV and mean % change in eGFR from baseline (using all post-baseline observations) over duration of study (up to 48 weeks)



PrEP Used in Pregnancy Does Not Increase Poor Birth Outcomes

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Kampala, Uganda: Elly Katabira, Nulu Bukya
Kisumu, Kenya: Elizabeth Bukusi, Josephine Odoyo
Thika, Kenya: Nelly Mugo, Kenneth Ngure

Partners PrEP Study site PIs:
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Kabwohe, Uganda: Elioda Tumwesigye
Jinja, Uganda: Patrick Ndase, Elly Katabira
Kampala, Uganda: Elly Katabira, Allan Ronald
Kisumu, Kenya: Elizabeth Bukusi, Craig Cohen
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Thika, Kenya: Nelly Mugo
Tororo, Uganda: James Campbell, Jordan Tappero, Jonathan Wangisi

Data management: DF/Net Research
Study drug was provided by Gilead

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Poster #934. For more information, please contact Renee Heffron: rheffron@uw.edu

Background

- Safety data from women using PrEP throughout pregnancy are very limited.
- Current recommendations for women using PrEP who become pregnant include counseling with the choice to continue or discontinue PrEP.

Methods

Interventional study population (PrEP-exposed):

- Partners Demonstration Project women (n=334) who became pregnant while using PrEP (n=30)
- Open-label FTC/TDF provided to participants at 4 research sites in Kenya and Uganda

Comparison group (PrEP unexposed):

- Partners PrEP Study women randomized to placebo (n=621) who became pregnant (n=79)
- Placebo-controlled trial at 9 research sites in Kenya and Uganda

Study procedures & statistical methods

- Monthly study visits during pregnancy for both groups; quarterly visits for infants after birth
- Pregnancy outcomes compared using generalized estimating equations – pregnancies with duration <8 weeks excluded
- Sex and age-adjusted z-scores calculated using WHO growth standards and a two-sample t-test was used to test for differences at each point in follow up

Participant characteristics

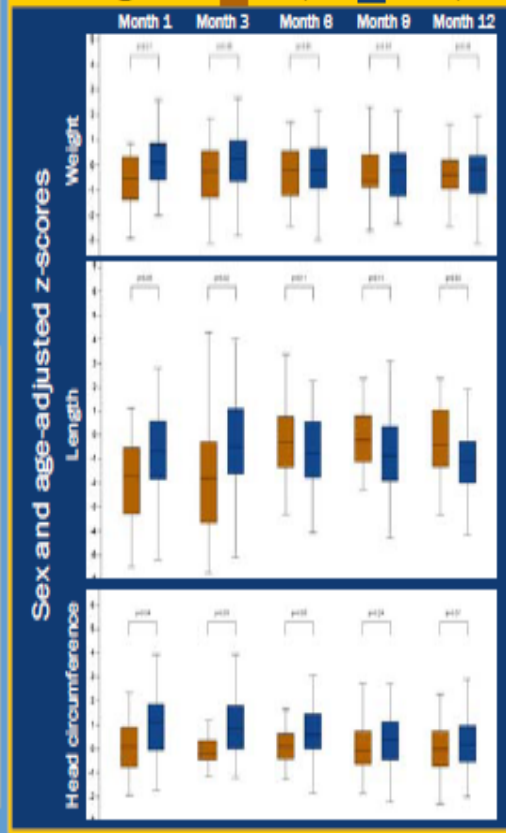
PrEP exposed	PrEP unexposed
• N=30 pregnancies, 30 women	• N=85 pregnancies, 79 women
• Median age: 25 (IQR 21-28)	• Median age: 28 (IQR 24-33)
• Median prior children: 2 (IQR 1-2)	• Median prior children: 2 (IQR 1-4)

Pregnancy outcomes

	PrEP-exposed	PrEP-unexposed	OR (95%CI)* p-value
Preterm delivery	0	5 (7.7%)	0.4 (0-2.3) p=0.4
Pregnancy loss	5 (16.7%)	20 (23.5%)	0.8 (0.3-2.5) p=0.7
Congenital anomaly	0	5 (7.7%)	Fisher's exact p=0.3

*Adjusted for maternal age at study enrollment

Infant growth



Conclusions

- Pregnancy loss and preterm delivery similar in PrEP-exposed and unexposed pregnancies
- Infant growth characteristics were similar at 12 months; early detriments in PrEP-exposed babies appear to have caught up by 12 months

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REVIEW ARTICLE

WILEY Liver INTERNATIONAL

Hepatitis B virus long-term impact of antiviral therapy nucleot(s)ide analogues (NUCs)

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Abstract

The goal of antiviral therapy is to improve the quality of life and survival of patients with chronic hepatitis B (CHB) by halting the progression to cirrhosis, end-stage liver disease or hepatocellular carcinoma (HCC), thus preventing anticipated liver-related death. Oral administration of potent and less resistance-prone nucleot(s)ide analogues (NUCs), such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) has become the most popular treatment strategy worldwide because of their excellent efficacy and safety profile as well as easy management confirmed in both registration trials and in clinical practice studies. Long-term administration of ETV or TDF suppresses HBV replication in >95% of patients, resulting in biochemical remission, histological improvement including the regression of cirrhosis and prevention or reversal of clinical decompensation but not the development of HCC, particularly in patients with cirrhosis. Moreover, NUCs can be administered to all patients including those with severe liver disease, the elderly and in those who do not respond, are unwilling to take or have contraindications to interferon. The need for long-term, perhaps indefinite, treatment is the main limitation of NUCs therapy with the associated costs, unknown long-term safety and the low rates of hepatitis B surface antigen (HBsAg) seroclearance, which is still the best stopping rule for NUCs-treated patients with cirrhosis.

KEYWORDS
cirrhosis, hepatitis B, hepatocellular carcinoma, nucleot(s)ides analogues

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REVIEW ARTICLE

WILEY Liver INTERNATIONAL

Hepatitis B virus long-term impact of antiviral therapy nucleot(s)ide analogues (NUCs)

8.1 | Nephrotoxicity

Ten cases of TDF-associated Fanconi syndrome, an acute and severe form of proximal tubular toxicity, have been described, while no cases have been linked to the administration of ETV.[47–49] A TDF to ETV switch is the current recommended strategy as a rescue protocol for

In nine real-life studies evaluating changes in renal function in 1310 NUC-naïve patients treated with ETV and 1287 with TDF, nephrotoxicity was mainly observed with TDF.[47] In 664 NUC-experienced patients enrolled in five real-life studies, the impact of TDF on renal function varied between studies. Possible reasons for the observed discrepancies include the use of different definitions and cut-offs for reporting renal toxicity, and differences in patient populations (i.e. excluding patients with comorbidities). A significant association was found, in particular for older age, pre-existing renal insufficiency, comorbidities and prior long-term use of ADV.[47]

To prevent and/or reduce the risk of renal complications, monitoring of glomerular function and tubular function to define the optimal dose and identify the few cases with kidney impairment, respectively, is currently recommended.[2-4] TAF could represent a new therapeutic option for NUC-experienced patients with a low eGFR and/or chronic tubular damage, but these studies are still ongoing.

8.2 | Reduced bone mineral density (BMD)

Three studies have specifically assessed changes in BMD during NUC therapy.[47] In a US study, 106 adolescents did not reach the endpoint of a decrease of at least 6% from baseline in lumbar spine BMD over 72 weeks. An Italian study assessed BMD in 60 CHB patients who switched from LMV+ADV to TDF. The proportion of patients with reduced BMD was 53% at baseline, 73% at month 6 and 53% after 12 months of TDF treatment. In a UK cohort including 170 patients, a reduction in BMD during TDF was limited to one anatomical site. Age, smoking, a lower BMI and TDF exposure were independent predictors of low BMD in univariate and multivariate analysis. Because the real impact of NUC on BMD has not been confirmed, current guidelines and reviews do not recommend determining bone density at baseline and during NUC therapy in HBV patients.[2–4,47]

Therapeutic Advances in Musculoskeletal Disease

SAGE

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Bone health in HIV and hepatitis B or C infections

Emmanuel Biver, Alexandra Calmy, and René Rizzoli

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Oral nucleoside or nucleotide analogs are also widely used long-term to treat chronic hepatitis B. Few data are available on the bone safety profile of these treatments in a non-HIV related context. TDF-exposed patients with chronic hepatitis B have reduced BMD at total hip compared with non-TDF-exposed patients with chronic hepatitis B [Gill *et al.* 2015]. In studies of cohorts with chronic hepatitis B, the incidence of hip fracture is low and does not differ between treated and untreated patients [Porcelli *et al.* 2014; Wong *et al.* 2015]. However, exposure to nucleotide analogues increased the risk of hip fracture compared with nucleoside analogs [hazard ratio (HR) = 5.69; 95% CI: 1.98–16.39; $p = 0.001$], suggesting that tenofovir-containing treatments may also slightly increase the risk of hip frac
hepatitis B [Wong *et al.* 2015].

US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

MANAGING SIDE EFFECTS

Patients taking PrEP should be informed of side effects among HIV-uninfected participants in clinical trials (see Table 5). In these trials, side effects were uncommon and usually resolved within the first month of taking PrEP ("start-up syndrome"). Clinicians should discuss the use of over-the-counter medications for headache, nausea, and flatulence should they occur. Patients should also be counseled about signs or symptoms that indicate a need for urgent evaluation (e.g., those suggesting possible acute renal injury or acute HIV infection).

All patients receiving PrEP should be seen as follows:

- **At least every 3 months to**
  - Repeat HIV testing and assess for signs or symptoms of acute infection to document that patients are still HIV negative (see Figure)
  - Repeat pregnancy testing for women who may become pregnant
  - Provide a prescription or refill authorization of daily TDF/FTC for no more than 90 days (until the next HIV test)
  - Assess side effects, adherence, and HIV acquisition risk behaviors
  - Provide support for medication adherence and risk-reduction behaviors
  - Respond to new questions and provide any new information about PrEP use
- **At least every 6 months to**
  - Monitor eCrCl
    - If other threats to renal safety are present (e.g., hypertension, diabetes), renal function may require more frequent monitoring or may need to include additional tests (e.g., urinalysis for proteinuria)
    - A rise in serum creatinine is not a reason to withhold treatment if eCrCl remains ≥60 ml/min.
    - If eCrCl is declining steadily (but still ≥60 ml/min), consultation with a nephrologist or other evaluation of possible threats to renal health may be indicated.
  - Conduct STI testing recommended for sexually active adolescents and adults (i.e., syphilis, gonorrhea, chlamydia)[83]

- Evaluate the need to continue PrEP as a component of HIV prevention

Optional Assessments

Bone Health

Decreases in bone mineral density (BMD) have been observed in HIV-infected persons treated with combination antiretroviral therapy (including TDF-containing regimes)[84,85]. However, it is unclear whether this 3%-4% decline would be seen in HIV-uninfected persons taking fewer antiretroviral medications for PrEP. The iPrEx trial (TDF/FTC) and the CDC PrEP safety trial in MSM (TDF) conducted serial dual-emission x-ray absorptiometry (DEXA) scans on a subset of MSM in the trials and determined that a small (~1%) decline in BMD that occurred during the first few months of PrEP either stabilized or returned to normal[20,86] . There was no increase in fragility (atraumatic) fractures over the 1-2 years of observation in these studies comparing those persons randomized to receive PrEP medication and those randomized to receive placebo.

Therefore, DEXA scans or other assessments of bone health are not recommended before the initiation of PrEP or for the monitoring of persons while taking PrEP. However, any person being considered for PrEP who has a history of pathologic or fragility bone fractures or who has significant risk factors for osteoporosis should be referred for appropriate consultation and management.

BHIVA–BASHH Position Statement on PrEP in UK

Appendix 1: Practical guidance for healthcare workers

Sheena McCormack, Sarah Fidler, Laura Waters, Yusef Azad, Tristan Barber, Gus Cairns, Valentina Cambiano, Dan Clutterbuck, Monica Desai, David Dunn, Julie Fox, Yvonne Gilleece, Margaret Kingston, Charles Lacey, Heather Leake Date, Fabiola Martin, Alan McOwan, Anthony Nardone, Koh-Jun Ong, Roger Pebody, Andrew Phillips, Mags Portman, Killian Quinn, Iain Reeves, Ann Sullivan, George Valiotis

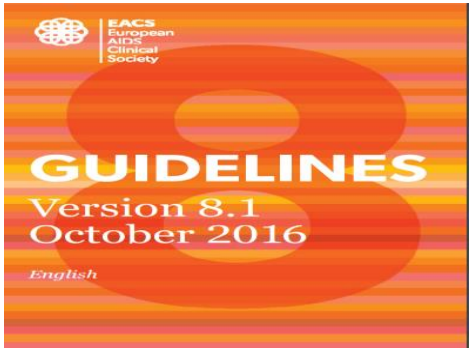
Recommended tests

- Before or at time of starting PrEP:
  - 4th generation venous blood HIV test
  - Consider POCT and start PrEP same day if negative
  - HBV surface antigen (and start vaccination if immunity unknown; on-demand Truvada is not recommended in chronic hepatitis B infection and if continuous PrEP is started, hepatology review is required before cessation)
  - Serum creatinine and eGFR
  - Urinalysis
- On PrEP:
  - 3-monthly 4th generation venous blood HIV test +/- POCT
  - 3-monthly STI screen for MSM [*as per BASHH 2014 MSM guidance*]; STI screen as appropriate for heterosexuals
  - Urinalysis every visit (further investigation if protein 1+ or more)
  - Annual creatinine/eGFR (more frequent if abnormal at baseline or proteinuria or >50 or on concomitant medications that are relevant to renal function)

Note: POCT useful on the day of starting, and at any visit if risks were taken during a period when PrEP was not as per national guidelines on HIV testing.

Purpose of the update and appendix

This update follows the NHS England update on the commissioning and provision of pre-exposure prophylaxis (PrEP) for HIV prevention (https://www.england.nhs.uk/2016/03/prep). The Appendix contains practical guidance for healthcare workers.



Pre-exposure Prophylaxis (PrEP)

1. PrEP should be used in adults at high-risk of acquiring HIV infection when condoms are not used consistently. Before PrEP is initiated, HBV serology status should be documented.

- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals when condoms are not used consistently with casual partners or with HIV-positive partners who are not on treatment. A recent STD, use of post-exposure prophylaxis or chemsex may be markers of increased risk for HIV acquisition.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment.

2. PrEP is a medical intervention that provides a high level of protection against HIV acquisition but does not protect against other STDs and should be used in combination with other preventive interventions. PrEP should be supervised by a doctor, experienced with sexual health and use of HIV medicines, possibly as part of a shared care arrangement.

The following procedures are recommended:

- Documented negative fourth generation HIV test prior to starting PrEP. During PrEP, this test should be repeated every 3 months, and PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit.
- Before PrEP is initiated, HBV serology status should be documented. If HBsAg positive, see Clinical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons.
- Counsel that PrEP does not prevent other types of STDs; screen for STD (including HCV) when starting PrEP and regularly during use of PrEP.
- Counsel that PrEP may impact renal and bone health, see page 47 and 43. Check renal function before starting PrEP and check renal function and bone mineral density during PrEP according to guidelines on TDF use.
- Counsel that PrEP, like other prevention methods, only works when it is taken. Adherence counselling is recommended.
- Counsel that PrEP can be prescribed long-term but that each consecutive PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring.

3. PrEP regimen

- TDF/FTC 300*/200 mg 1 tablet qd. For MSM with high-risk sexual behavior PrEP may be dosed 'on demand' (double dose of TDF/FTC 2-24 hours before each sexual intercourse, followed by two single doses of TDF/FTC, 24 and 48 hours after the first drug intake). If dosed 'on demand', the total dose per week should not exceed 7 tablets.
- Use of generic formulations of TDF/FTC, if and where available, may help to improve the cost-effectiveness of PrEP, which is essential for its use as public health approach.
- There are not currently clinical data on the use of 3TC or TAF for PrEP.

* In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate).

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Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

22 Novembre 2016

Valutazione iniziale della persona con indicazione alla PrEP	• Effettuare un test HIV Ab/Ag (almeno 4° generazione) per escludere la presenza dell'infezione ed una visita con raccolta accurata dell'anamnesi per identificare presenza o storia recente di eventuali segni o sintomi di infezione acuta. • Effettuare HBsAg, HBsAb e HBcAb per valutare lo stato sierologico della persona nei confronti dell'epatite B. • Effettuare una sierologia per epatite C (HCV Ab o Ag) ed epatite A. • Suggerire vaccinazione contro epatite A e HPV. • Effettuare una determinazione della creatinina sierica e calcolare la clearance della creatinina tramite Cockcroft-Gault (CrCl>60 mL/min). • Effettuare un test di gravidanza. • Acquisire l'accettazione dell'aderenza al follow-up clinico. • Effettuare uno screening per IST.	[AII]	[8,9]
Prescrizione della PrEP	• prescrivere TDF/FTC in quantità sufficiente per 1 mese alla prima visita e successivamente per un periodo non superiore a 3 mesi, con il seguente schema: - 1 dose/die	[AI]	[1-5]
	OPPURE		
	- solo per gli MSM: "on demand" 2 dosi da 2 a 24 ore prima dei rapporti sessuali, seguite da una terza 24 ore dopo la prima assunzione e una quarta dose 24 ore dopo. In caso di più rapporti in giorni consecutivi o con pause inferiori ai tre giorni, una dose/die fino all'ultimo rapporto seguita dalle due dosi post esposizione.	[AI]	[6,7]

Follow-up della persona in PrEP	• **Dopo 1 mese, ed in seguito ogni 3 mesi:** - Test HIV Ab/Ag - Test di gravidanza (nelle donne che NON stiano tentando un concepimento programmato) - Supporto per la riduzione del rischio sessuale e iniettivo - Counselling per l'aderenza e valutazione degli effetti collaterali (vedi sotto) - Prescrizione di una nuova scorta di farmaco • **Ogni 6 mesi:** - determinazione della creatininemia e stima della clearance (la prima volta al 3° mese, poi ogni 6 mesi) - screening per IST • **Ogni 12 mesi:** - Rivalutazione dei comportamenti e dell'esistenza di fattori che comportino un rischio di acquisizione dell'infezione da HIV e quindi della necessità di continuare ad assumere la PrEP.	[All]	[1-9]

MSM: Maschi che fanno Sesso con Maschi; IST: Infezioni Sessualmente Trasmesse; PEP: profilassi post-esposizione; PrEP: Profilassi pre-esposizione; SERT: Servizi per le tossicodipendenze.

How Does a PrEP Ambulatory Clinic Work in Paris?

Dr Alexandre ASLAN, MD

Infectious diseases hospital practitioner

Clinical Psychopathology - Psychotherapist

Sexual Health

Infectious Diseases Unit University Hospital Saint Louis, Paris

Baseline Characteristics (Jan 2016- June 2016)

Pts Characteristics (Median, IQR) or (%)	N= 867
Age, years	38 (30-44)
French	87%
Male	96.4%
Female	0.6% (n=6)
Transgender	0.3% (n=3)
MSM	96.4%
Use of psychoactive drugs	20.8%
STIs in prior 12 months	30%
PEP use in last 12 months	11.9%
On Demand PrEP	65.2%

Dosing Regimens and Follow-up

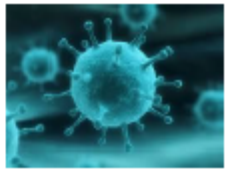
- **Dosing Schedule**
  - **Daily** (1 pill a day) or **On demand** (only for MSM – Ipergay dosing regimen)

- **Patients follow-up : Consultation and Blood samples**
  - 70 % paid by Social Security
  - 30 % paid by patient or private insurance

- **Global Sexual Health approach**
  - Referrals for psychiatry, addiction, proctology, sex therapy…

Who is Not Eligible for Truvada

- HIV Serologic assay positive or unknown



- Signs or symptoms of primary HIV-infection
- Creatinine clearance < 50 ml/mn

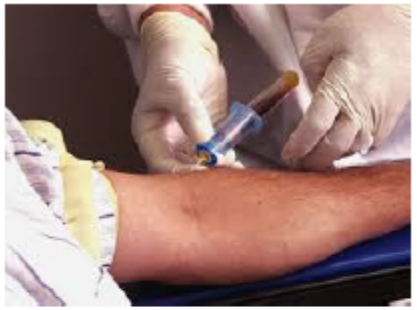
- Chronic HBV infection if PrEP used On Demand

- Breast-feeding

- Hypersensitivity to TDF or FTC or excipients

Study and Data Manager Nurse

- Biological screening sent to the patient :
  - HIV 1 and 2 serology (Elisa 4th generation)
  - Creatinemia and clearance MDRD
  - Urine dipstick for glycosuria and proteinuria
  - Hepatitis B and C and A serology
  - Syphilis serology
  - Liver enzymes
  - PCR Chlamydia and gonococcia on 3 sites : throat / anal and urines
  - Pregnancy tested if needed



Medical follow up

- At each visit (every 3 months) : M 1 / 3 / 6 / 9 / 12
  - Assess/support adherence
  - Risk reduction counseling
  - Provide condoms
  - HIV & STI test
  - Renal function

HIV/AIDS – Research and Palliative Care

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REVIEW

Profile of cabotegravir and its potential in the treatment and prevention of HIV-1 infection: evidence to date

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Abstract: Modern antiretroviral therapy has demonstrated effectiveness in preexposure prophylaxis (PrEP) and treatment of HIV infection. There is a demand for prevention and treatment regimens that could overcome challenges of improving adherence, toxicity, and dosing convenience. Cabotegravir is an integrase strand transfer inhibitor and an analog of dolutegravir. Unlike dolutegravir, cabotegravir has a long half-life and can be formulated into a long-acting nanosuspension for parenteral administration. Initial pharmokinetic studies in humans have demonstrated adequate drug levels with intramuscular (IM) administration at 4 weekly and 8 weekly intervals, with few interactions with commonly used concomitant medications. Preliminary animal PrEP studies have shown that IM cabotegravir can prevent simian/HIV acquisition from rectal, vaginal, and intravenous challenge. Currently, there are two ongoing Phase II studies assessing cabotegravir as a PrEP agent in humans: ÉCLAIR and HPTN077. Cabotegravir has been studied in combination with rilpivirine as long-acting IM maintenance therapy. The Long-Acting Antiretroviral Treatment Enabling study demonstrated that those switching to oral cabotegravir/rilpivirine once virologically suppressed were more likely to maintain suppression than those continuing standard efavirenz-based therapy (82% vs 71% at 24 weeks). Initial results of the Long-Acting Antiretroviral Treatment Enabling-2 study of parenteral regimens found that 12 weeks after randomization to parenteral or oral regimens, there was no difference in proportions virologically suppressed on cabotegravir/rilpivirine daily orally vs IM every 4 weeks or 8 weeks (91% vs 94% vs 95%). The injections were well tolerated as, although they caused injection site pain in most recipients, most participants reported satisfaction with parenteral therapy. Cabotegravir offers a new member of the integrase strand transfer inhibitor class with potential for alternative mode of delivery. We await Phase III studies to define its efficacy and real-world experience to learn which patient groups stand to benefit most from the novel mode of delivery of treatment and PrEP.

Keywords: integrase inhibitor, long-acting antiretroviral therapy, preexposure prophylaxis

MTN-020/ASPIRE

- Phase III, **dapivirine vaginal ring** worn for a month at a time
- With or without levonorgestrel: provides also lasting but reversible contraception.

- 2,629 women ages 18 to 45, who are randomly assigned in equal numbers to use either the dapivirine ring or a placebo ring. Women use their assigned ring for at least one year, some for m

- from 15 clinical research sites in Malawi, South Africa, Uganda and Zimbabwe.

- **Primary endpoint**: HIV seroconversion
- **Secondary endpoint**: long-term safety of the ring and acceptability


Andrew Loxely

http://www.mtnstopshiv.org/news/studies/mtn020

Pregnancy Incidence and Outcomes Among Women Using the Dapivirine Vaginal Ring

Bonus Makanani[1], Jennifer E. Balkus[2], Thesla Palanee-Philips[3], Yamikani Mbilizi[1], Jeanna Piper [4], Kenneth Kintu[5], Tchangani Tembo[6], Lisa Noguchi [7], Helen Rees[3], Jared M. Baeten[8], for the MTN-020/ASPIRE Team

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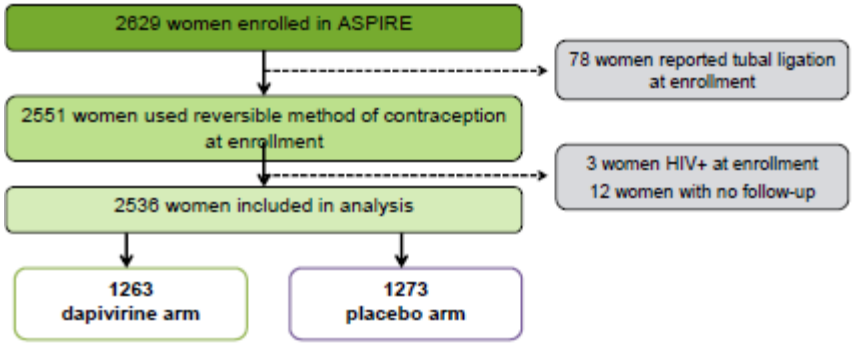
Background

- Monthly use of the dapivirine vaginal ring has been shown to be safe and effective for HIV-1 prevention
- Dapivirine is a novel NNRTI but data are limited on the safety of dapivirine use during pregnancy
- Understanding the safety of exposure during pregnancy is important for the potential roll-out of the dapivirine ring for HIV-1 prevention
- In MTN-020/ASPIRE, use of a highly effective contraceptive method was a criterion for study participation and highly effective methods were offered to study participants; however, pregnancies occurred, resulting in short-term exposure to study product during the periconception period

Objective: To compare pregnancy incidence and outcomes by study arm among women who participated in MTN-020/ASPIRE

Results

Figure 1. Analysis Population



- 169 women became pregnant during follow-up, resulting in 179 incident pregnancies and 180 pregnancy outcomes (1 set of twins)
- No difference in pregnancy incidence by study arm was observed (Table 1) (Hazard ratio = 0.93; 95% CI 0.68-1.26)

Table 3. Pregnancy outcomes by arm

	Dapivirine N=86		Placebo N=94	
Full term live birth	52	(60%)	53	(56%)
Preterm birth	0	(0%)	9	(10%)
Stillbirth/Intrauterine fetal demise	2	(2%)	2	(2%)
Spontaneous abortion	18	(21%)	21	(22%)
Therapeutic/elective abortion	13	(15%)	8	(9%)
Ectopic pregnancy	1	(1%)	1	(1%)

Table 4. Congenital anomalies by arm[1]

	Dapivirine N=48	Placebo N=59
Any anomaly	4 (8%)	4 (7%)
Physical defect	1 (2%)	3 (5%)
Cranio-facial	1 (2%)	0
Other	2 (4%)	1 (2%)

[1]Data available for 107 of 114 live births

- The distribution of pregnancy outcomes appears similar by study arm (Table 3)
- No difference noted in frequency or pattern of potential congenital anomalies by arm (Table 4)

CROI 2017
Abstract# 935

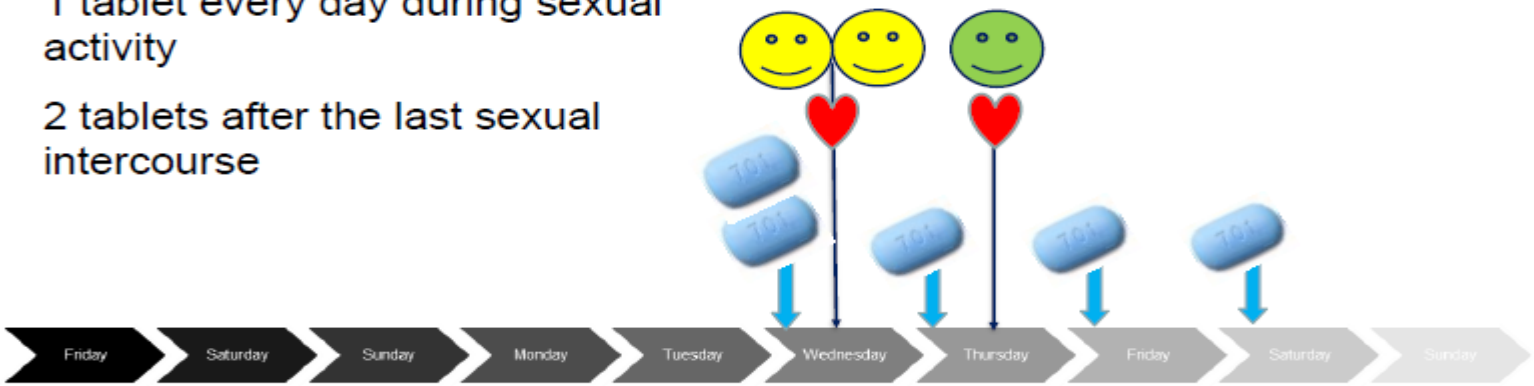
Truvada daily ?

Truvada on demand ?

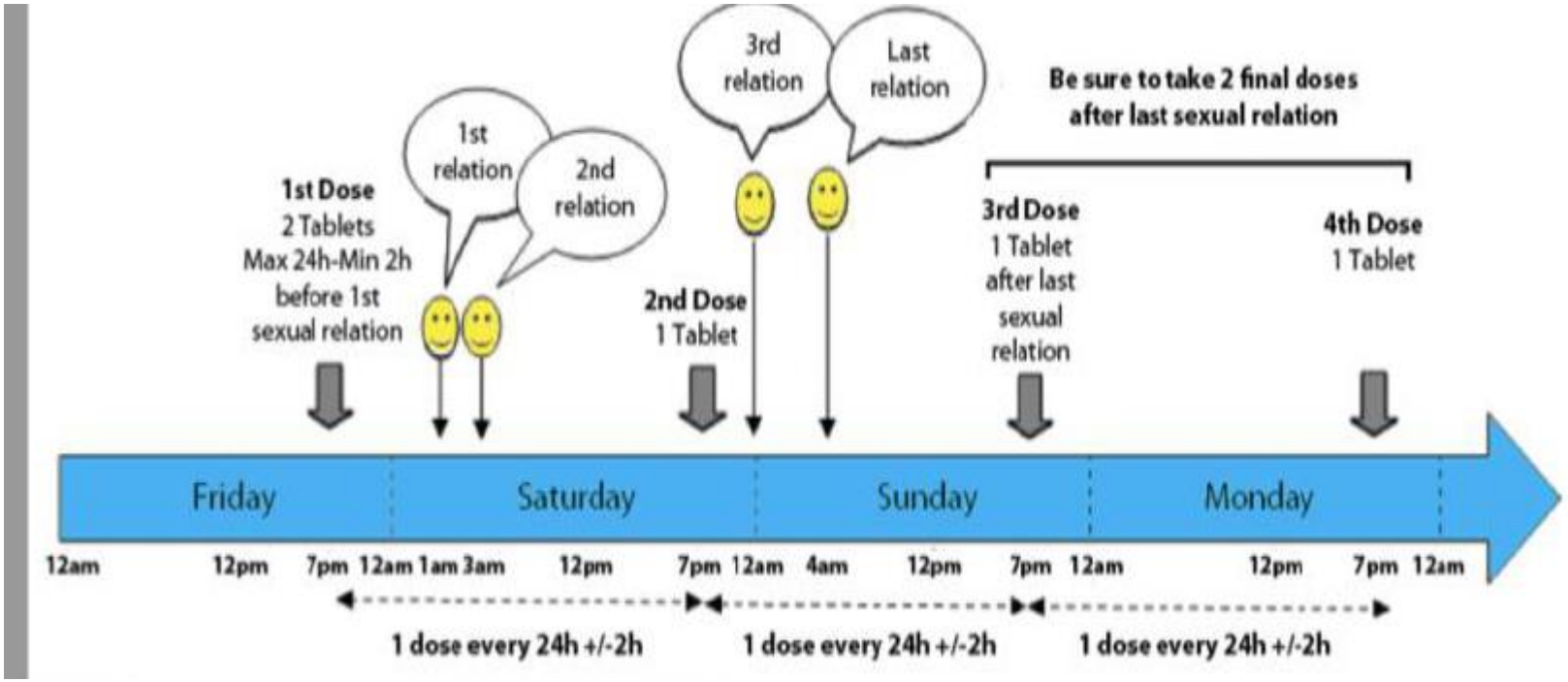
2 tablets 2-24 hours before sex

1 tablet every day during sexual activity

2 tablets after the last sexual intercourse



On demand PrEP tells you **How to Start and How to Stop PrEP**



Quali screening tossicità nel paziente candidato alla PREP?

- Screening : funzionalità renale, esame urine, GFR (CKDEPI), FRAX con calcemia , FA e fosforemia . FR per osteoporosi valutare se DEXA

- Follow-up : ogni sei mesi funzionalità renale, GFR (CKDEPI). Osso se fattori di rischio

- Chi paga la PREP?

- Chi paga gli esami di controllo?

……with love