Mettre fin à l'épidémie de HIV: quels sont les moyens de prévention de l'infection en 2018?

13/12/2018

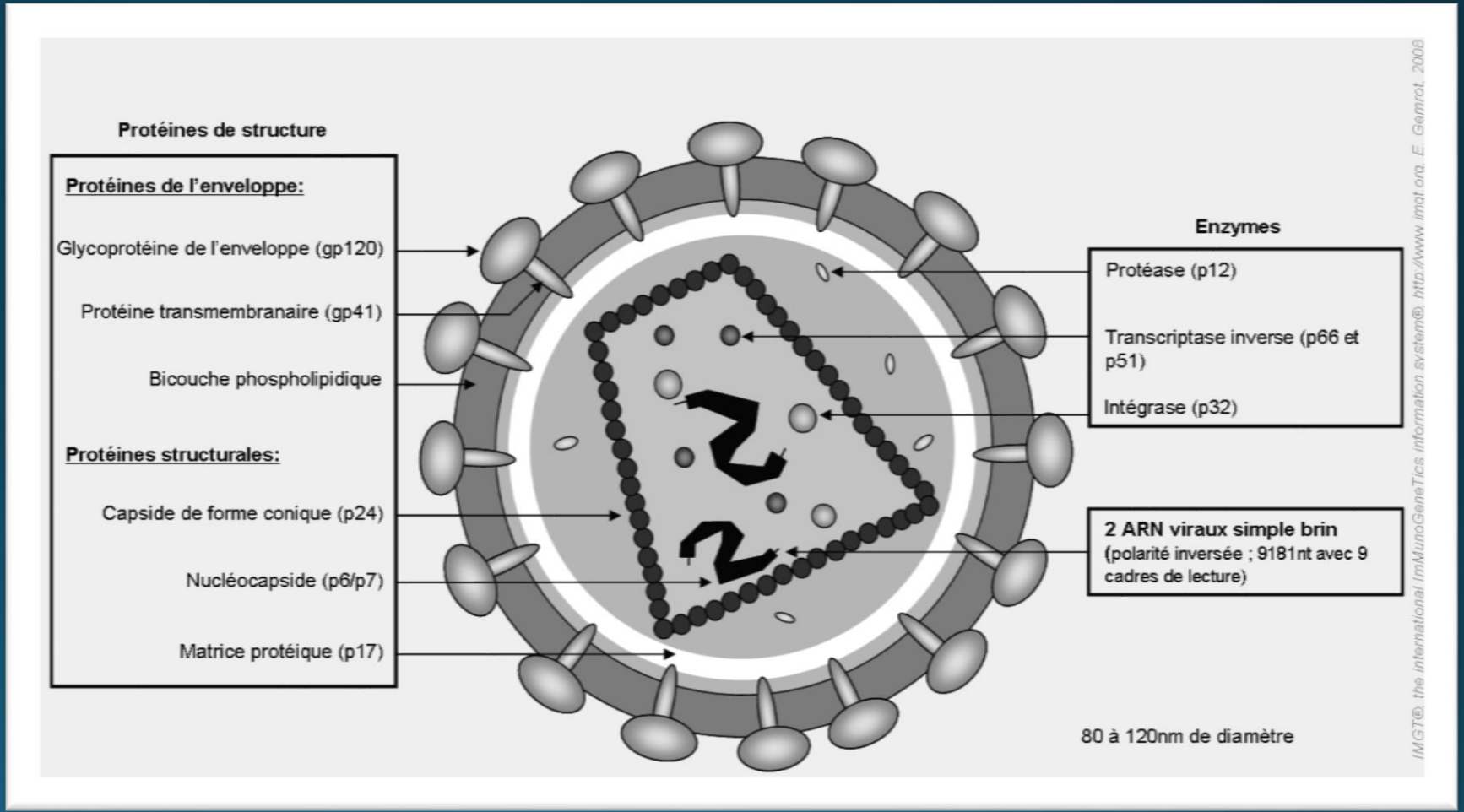
Dr AS Sauvage, Service de Médecine interne générale et Maladies infectieuses

CHU de Liège, Centre de Référence SIDA

Petits rappels sur le VIH

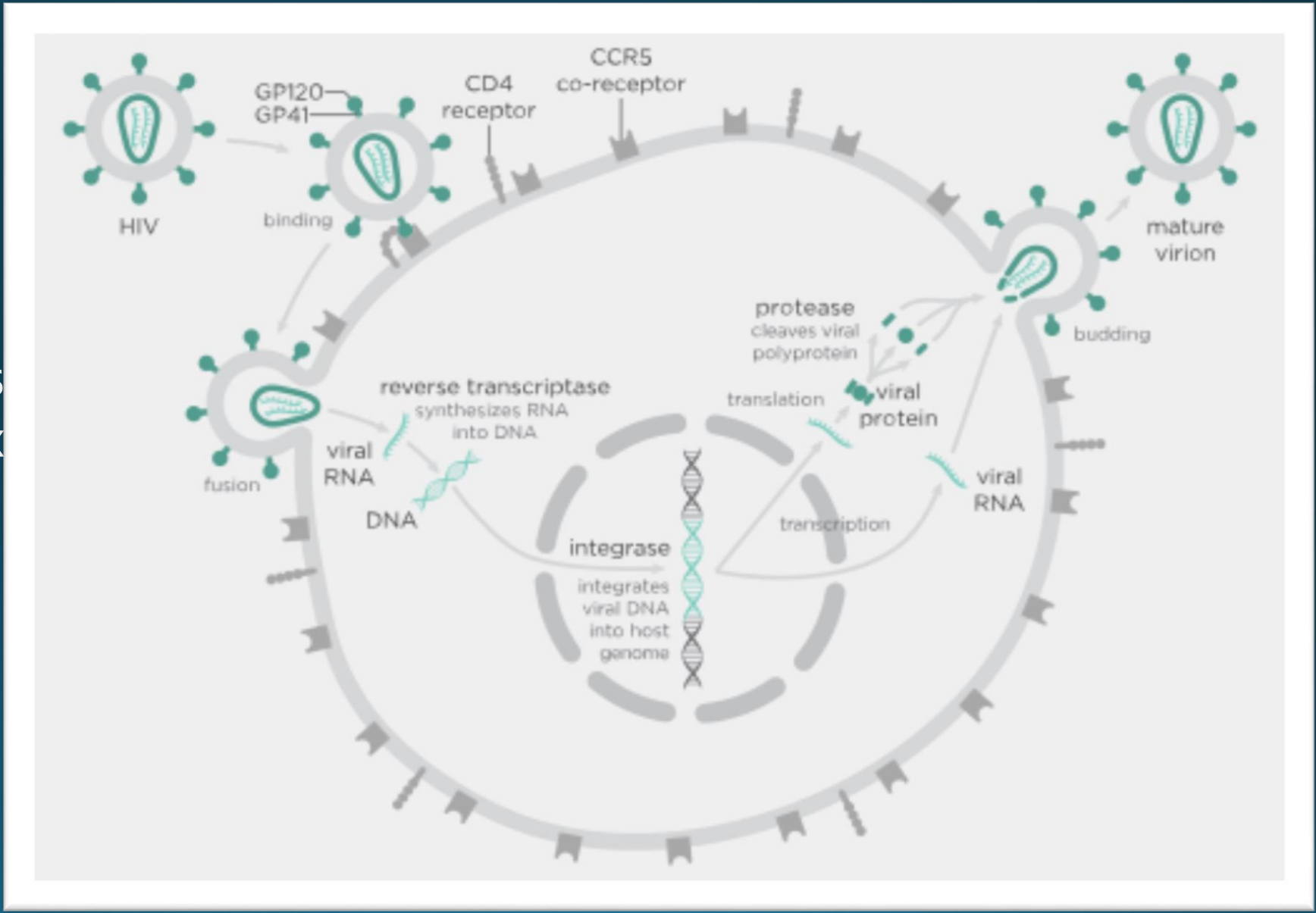
- Virus à ARN

  -> Nécessite une cellule de l'hôte pour se multiplier
- Peut rester en stand-by dans les lymphocytes
- Est secrété dans divers fluides corporels : sang, sécrétions vaginales, sperme, liquide pré-éjaculatoire, lait maternel



- Cycle de réplication intracellulaire
- Intervention de différentes enzymes

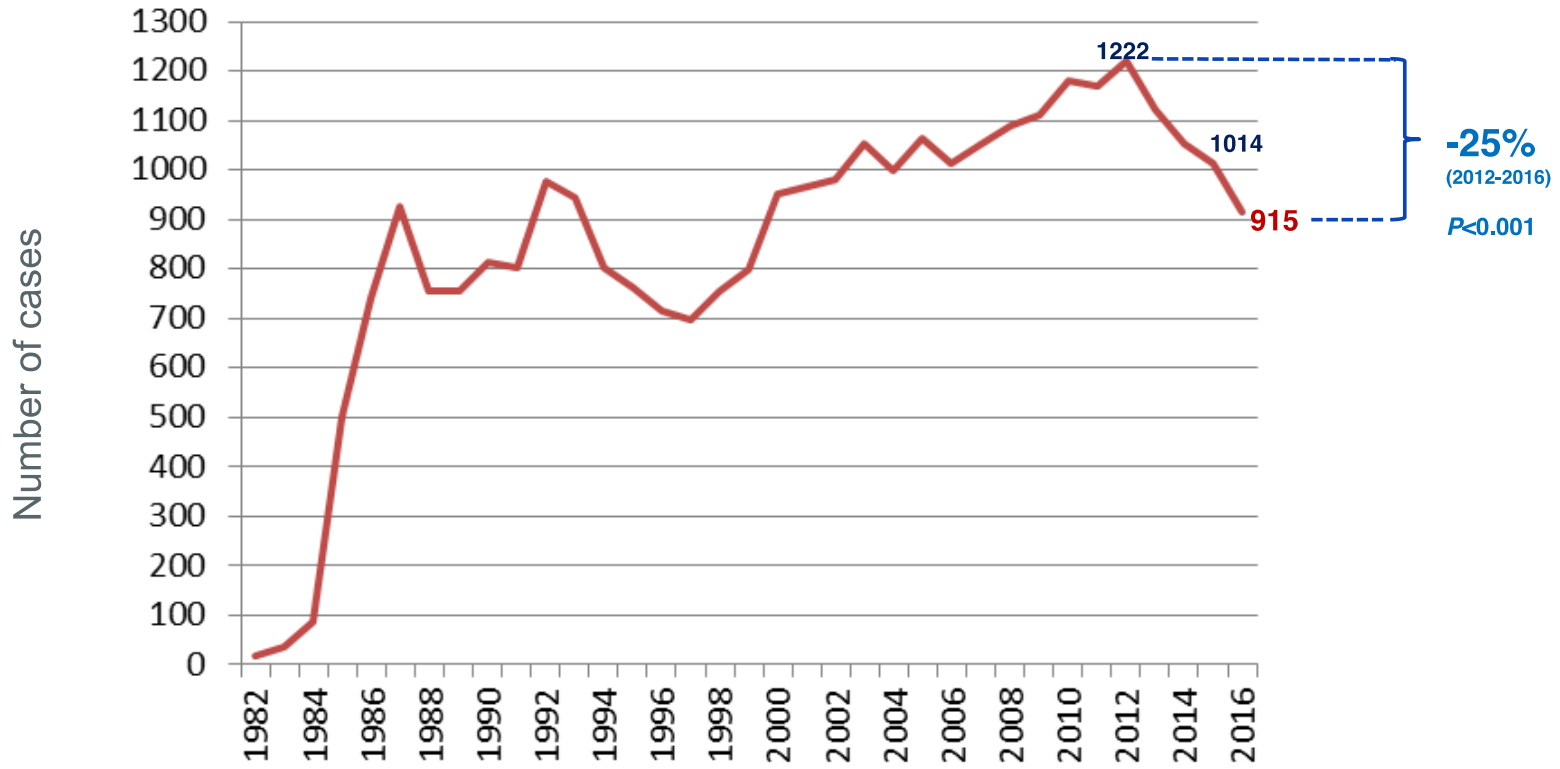
  -> cibles des agents antirétroviraux



Epidémie de SIDA: quelques chiffres

- En 2017, 36,7 millions de personnes vivant avec le HIV dans le monde
- 1,8 millions de nouvelles infections
- 1 million de morts liés au HIV

Number of new HIV diagnoses per year, Belgium, 1982 - 2016



Objectifs

- Mettre fin à l'épidémie en 2030

- 90 – 90 – 90 en 2020

  - 90% des patients porteurs du HIV diagnostiqués
  - 90% sous traitement
  - 90% de contrôle virologique

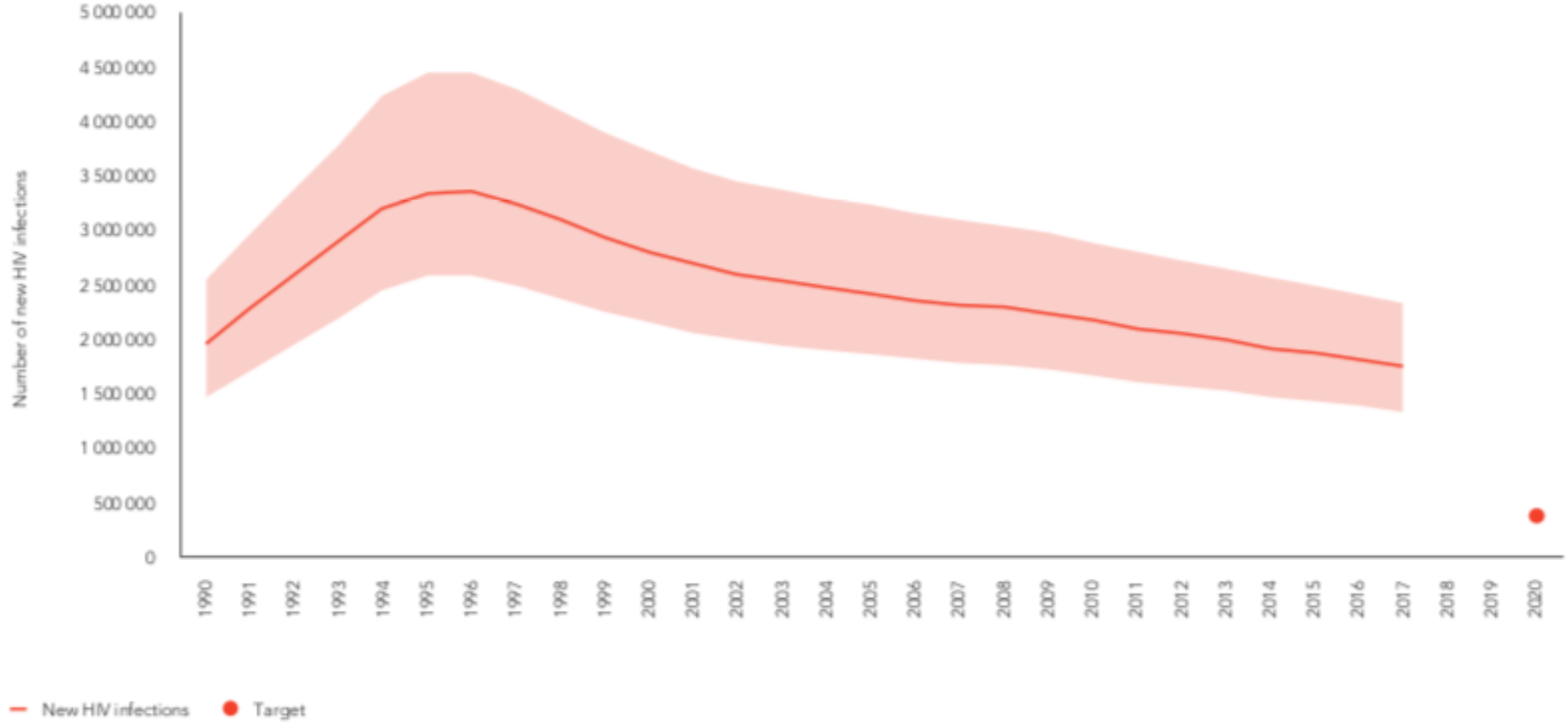
Bilan en 2017…

- 75% des patients vivant avec le HIV (75%) connaissaient leur statut.
- Parmi les patients qui connaissent leur statut, 79% ont accès au traitement.
- Parmi les patients ayant accès au traitement, 81% ont une suppression virologique.

  - 47% de tous les patients vivant avec le VIH ont une suppression virologique.

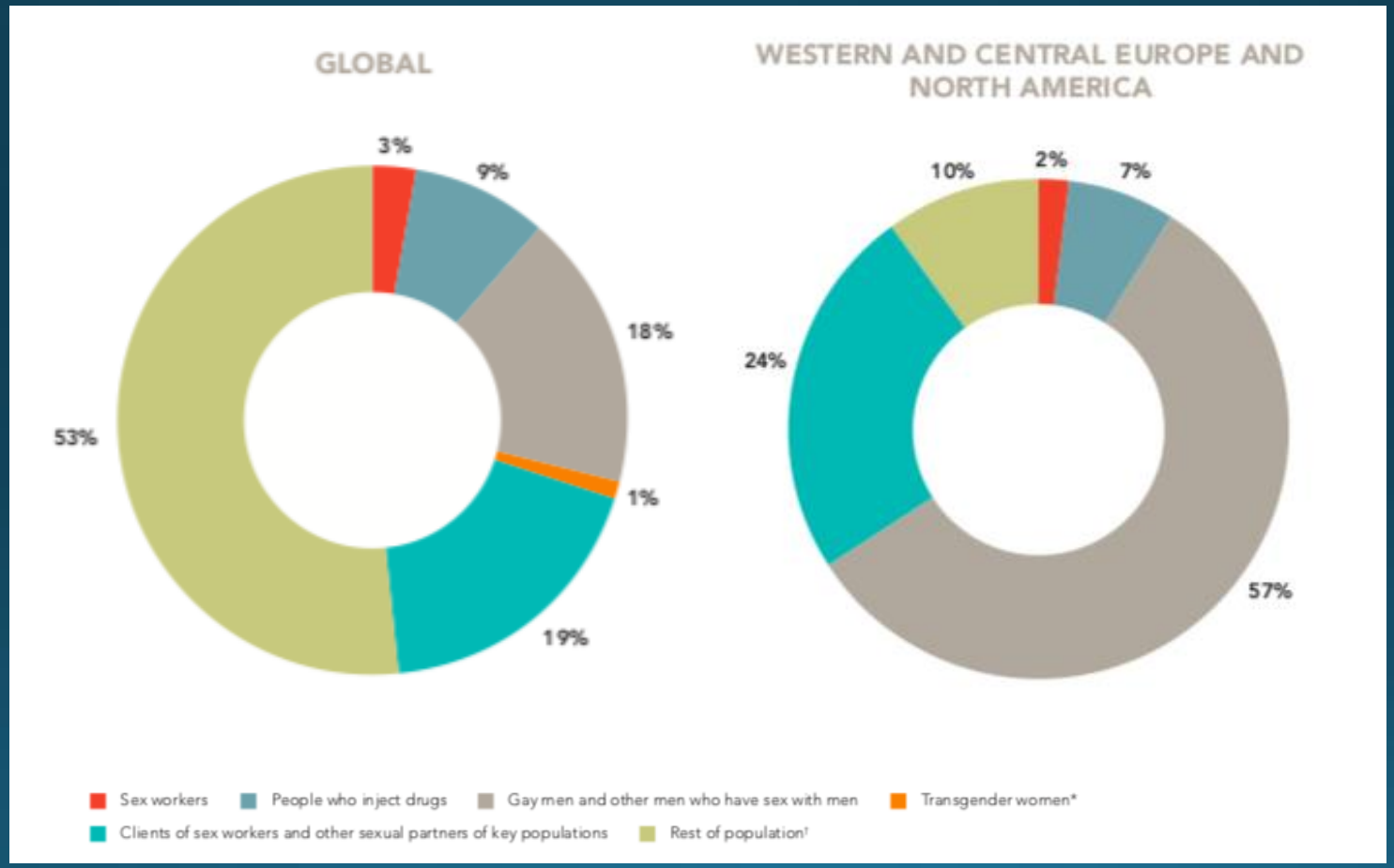
Insufficient progress on prevention

Number of new HIV infections, global, 1990–2017 and 2020 target



Source: UNAIDS 2018 estimates.

Populations à risque en fonction des régions en 2017



Source: ONUSIDA 2018

Populations à risque

- Risque d'acquisition du HIV est :
  - 27 fois plus important chez les HSH
  - 23 plus fréquent chez les personnes qui s'injectent des drogues
  - 13 fois plus fréquent chez les femmes travailleuses du sexe
  - 13 fois plus élevé chez les femmes transgenres

Rapport à risque ?

Table 1. Risk of HIV transmission per exposure from a known HIV-positive not on ART.

Type of exposure	Estimated risk of HIV transmission per exposure from a known HIV-positive individual not on ART	References
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Human bite	< 1 in 10,000	(25, 26)

Extraits des guidelines belges pour NONOPEP

Estimated HIV prevalence in Belgium:

- MSM: 5% in general gay venues in Flanders, 9% in Brussels, 14.5% in high risk venues (cruising) [3]
- Female sex workers: <1% in Western Europe, 1-2% in Central Europe, 2.5-8% in Eastern Europe.
- Male sex workers: 14% (reported from 27 countries)
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- Prevalence in the general population (outside high risk group) estimated between 0.01 to 0.02%.

HIV prevalence in other countries can be found in the UNAIDS 2014 Gap report: http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport

BOX 1 Factors increasing the risk of HIV transmission:

1. A high plasma VL in the source, particularly during primary HIV infection
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3. Menstruation or other bleeding (theoretical risk only)
4. Sexually Transmitted Infection
5. Ejaculation
6. Non-circumcision

Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here?

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Lancet 2013; 382: 1515-24
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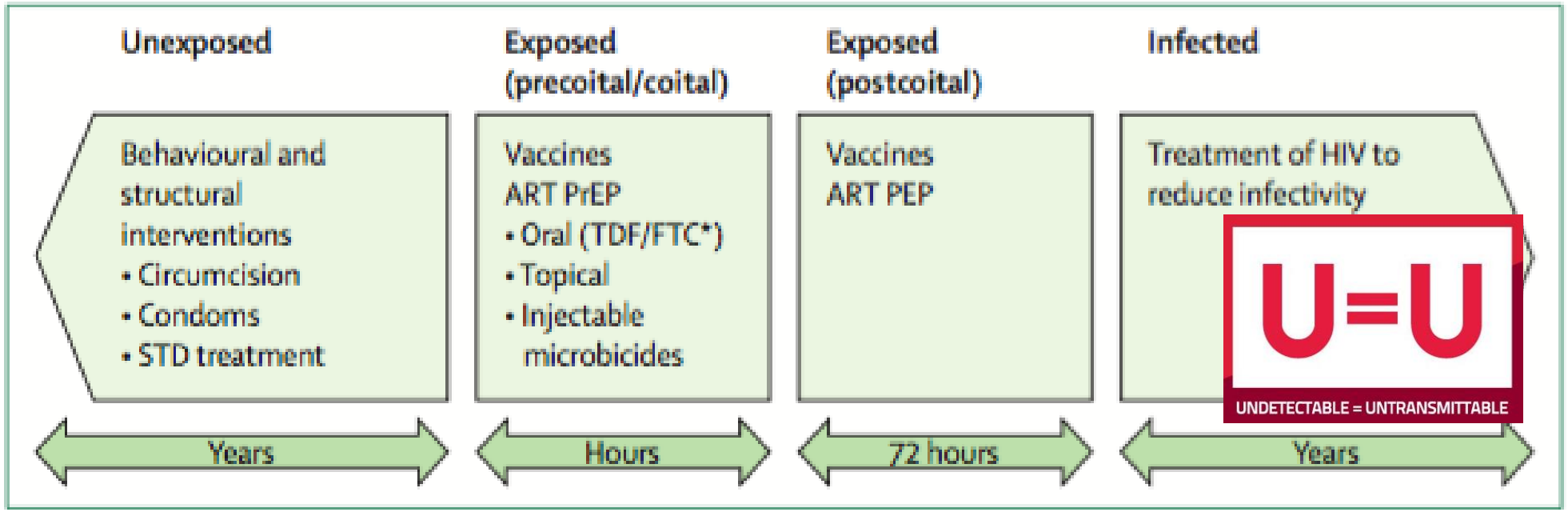

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Cohen MS, et al. Lancet, 2013

Cochrane Library

Cochrane Database of Systematic Reviews

Condom effectiveness in reducing heterosexual HIV transmission (Review)

Weller SC, Davis-Beaty K

Main results

Of the 4709 references that were initially identified, 14 were included in the final analysis. There were 13 cohorts of "always" users that yielded an homogeneous HIV incidence estimate of 1.14 [95% C.I.: .56, 2.04] per 100 person-years. There were 10 cohorts of "never" users that appeared to be heterogeneous. The studies with the longest follow-up time, consisting mainly of studies of partners of hemophiliac and transfusion patients, yielded an HIV incidence estimate of 5.75 [95% C.I.: 3.16, 9.66] per 100 person-years. Overall effectiveness, the proportionate reduction in HIV seroconversion with condom use, is approximately 80%.

Authors' conclusions

This review indicates that consistent use of condoms results in 80% reduction in HIV incidence. Consistent use is defined as using a condom for all acts of penetrative vaginal intercourse. Because the studies used in this review did not report on the "correctness" of use, namely whether condoms were used correctly and perfectly for each and every act of intercourse, effectiveness and not efficacy is estimated. Also, this estimate refers in general to the male condom and not specifically to the latex condom, since studies also tended not to specify the type of condom that was used. Thus, condom effectiveness is similar to, although lower than, that for contraception.

BMJ. 2000 Jun 10; 320(7249): 1592–1594.

PMCID: PMC1127372

PMID: 10845974

How does male circumcision protect against HIV infection?

Robert Szabo, medical resident[a] and Roger V Short, professor[b]

- Diminue de 2 à 8x le risque d'infection par le HIV
- Effet direct: surface interne du prépuce contient des cellules de Langerhans qui ont des récepteurs et corecepteur CCR-5=> probable cibles responsables de la primoinfection via le penis chez l'homme
- Diminue le risque d'autres IST

Vaccins

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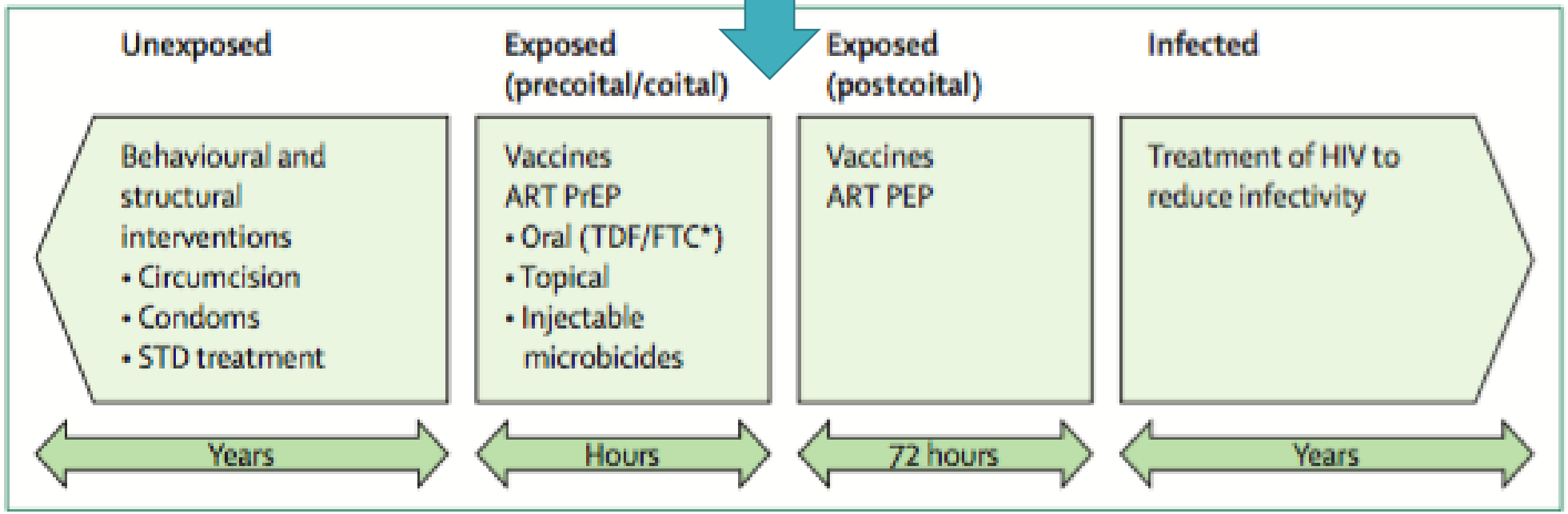

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Cohen MS, et al. Lancet, 2013

Table 1. Summary of HIV-1 vaccine efficacy trials

Study	Vaccines	Study population	Immune response to vaccine	Efficacy	Correlates of risks	Immune pressure	References
Vax 003	AIDSVAX B/E gp120 in alum	Injecting drug users in Thailand	NAb to HIV-1MN and Non-nAb to gp120	No	None		29
Vax 004	AIDSVAX B/B gp120 in alum	MSM and high risk women in north America and the Netherlands	NAb to HIV-1MN and Non-nAb to gp120	No	Higher nAb to HIV-1MN, CD4 blocking Ab and/or ADCVI levels were inversely correlated with risk		30,31,32
STEP HVTN502	MRKAd5 clade B gag/pol/nef	MSM and high risk heterosexual men and women in the Americas and Australia	Interferon-γ-secreting T-cell responses by ELISPOT	No	Uncircumcised men, men with pre-existing Ad5 Ab	Yes on sieve analysis	39,40,41
Phambili HVTN503	MRKAd5 clade B gag/pol/nef	Heterosexual men and women in South Africa	Interferon-γ-secreting T-cell responses by ELISPOT	No			42
RV144	ALVAC-HIV [vCP1521] and AIDSVAX B/E gp120 in alum	Community risk men and women in Thailand	Env-Specific-CD4 T cells, lymphocyte proliferation to HIV antigens, binding Ab to gp120	31%	IgG to V1V2 was correlated inversely with risk. IgA to Env correlated directly with risk but there was no vaccine enhancement of infection. In the presence of low vaccine induced Env IgA, avidity of IgG for Env, ADCC, nAb and Env-sp CD4+ T cells were inversely correlated with the risk of infection	Yes on sieve analysis	43,48,53
HVTN505	DNA (clade B Gag, Pol, Nef and clade A, B, C Env) and rAd5 (Clade B Gag-Pol and Clade A, B, C Env)	MSM with Ad5 Ab <1:18 in the USA	HIV-specific CD4+ and CD8+ T cells and non-nAb	No			66

MSM, men who have sex with men. rAd 5, recombinant adenovirus 5. NAb, neutralizing antibodies. ADCVI, antibody dependent cell-mediated viral inhibition. ADCC, antibody dependent cytotoxicity.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 5, 1018–1030
http://dx.doi.org/10.1080/21645515.2016.1276138

Taylor & Francis
Taylor & Francis Group

REVIEW

Progress in HIV vaccine development

Denise C. Hsu[a,b,c] and Robert J. O'Connell[a,b]

[a]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; [b]US Military HIV Research Program, Silver Spring, MD, USA; [c]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA

- 7 Vaccins testés, 2 efficaces:
  - 2003, Thailande, RV 144:
    - vecteur recombinant CanaryPox + protéine d'enveloppe gp120
    - réduction de 31% du risque d'infection
  - 2018, Boston, étude phase 1, HVTN705:
    - Mosaic Ad26 prime, Ad26 plus gp140
    - 67% de protection chez les macaques
    - => Phase 2b en cours en Afrique du Sud
- Broadly neutralizing antibody (bnAb):
  - Anticorps capable de neutraliser diverses souches circulantes de virus
  - HIV Env protein, composed of 3 gp120 and 3 gp41 monomers
  - Une perfusion induit immunisation passive et protège de l'infection par le SHIV
  - Instillation 1x/semaine intrarectal prévient transmission du SHIV

Treatment as prevention (TasP)

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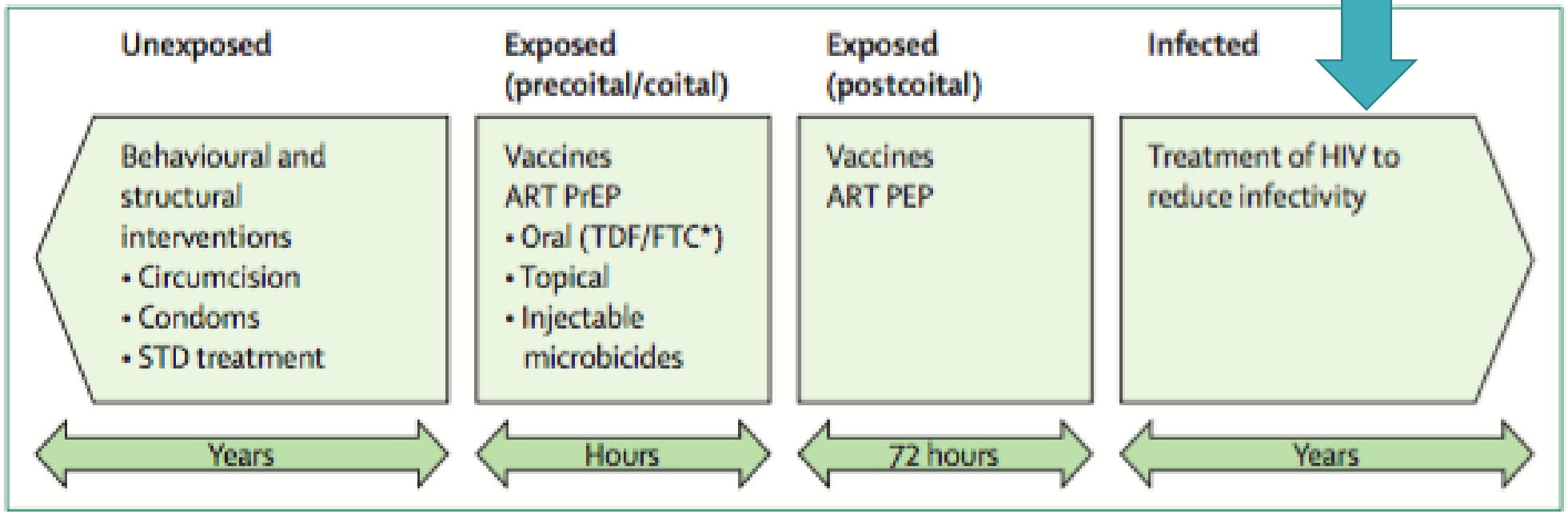

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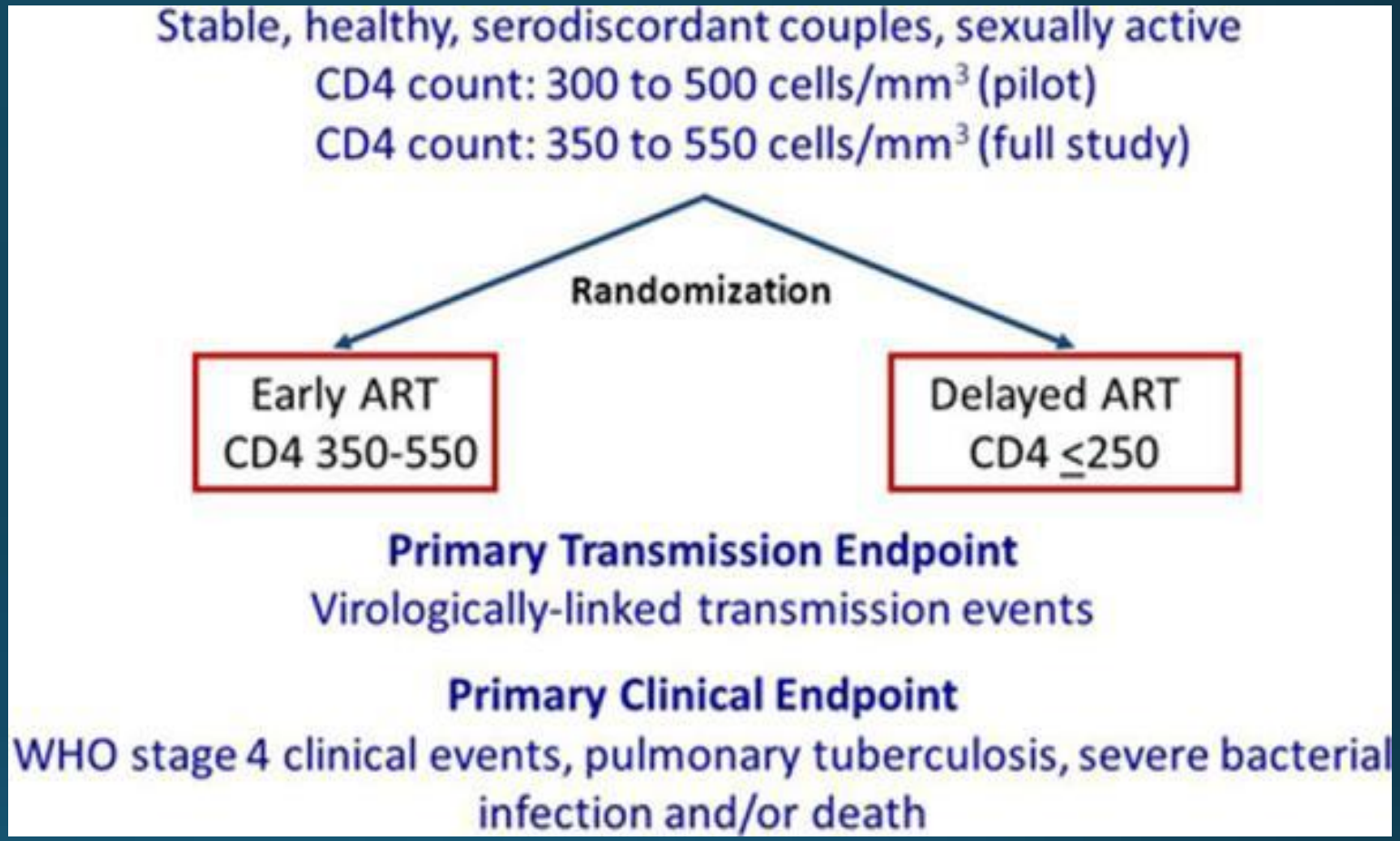
Prevention access campaign 2016

HPTN 052

- Prospective
- Début en avril 2005
- 13 sites en Afrique, Asie et Amériques
- 1763 couples
- 5 ans de suivi
- Counseling pour diminuer les risques et inciter à l'usage de préservatifs



- 877 couples dans le groupe différé
- 27 transmissions prouvées dans le groupe différé vs 1 dans le groupe immédiat
- 10 nouvelles acquisitions mais non liées au virus du partenaire malgré le counseling
- Bénéfice clinique observé pour les traitements précoces

M. Cohen et al, HIV treatment as prevention and HPTN 052, Curr Opin HIV AIDS. 2012 Mar; 7(2): 99–105

Original Investigation FREE

July 12, 2016

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

Alison J. Rodger, MD[1]; Valentina Cambiano, PhD[1]; Tina Bruun, RN[2]; et al

» Author Affiliations | Article Information

JAMA. 2016;316(2):171-181. doi:10.1001/jama.2016.5148

- Étude prospective
- 75 sites dans 14 pays d'Europe
- 1166 HIV serodifferent couples
- Rapports non protégés
- Charge virale inférieure à 200 copies/m

A total of 11 of the originally HIV-negative partners were observed to acquire HIV during eligible follow-up, but there were no phylogenetically linked transmissions. Of the 11 people who became infected, 10 were MSM and 1 was heterosexual; of these, 8 (73%) reported that they had had recent condomless sex with others apart from their study partner.

➢ **Aucune transmission au sein des couples sérodiscordants**

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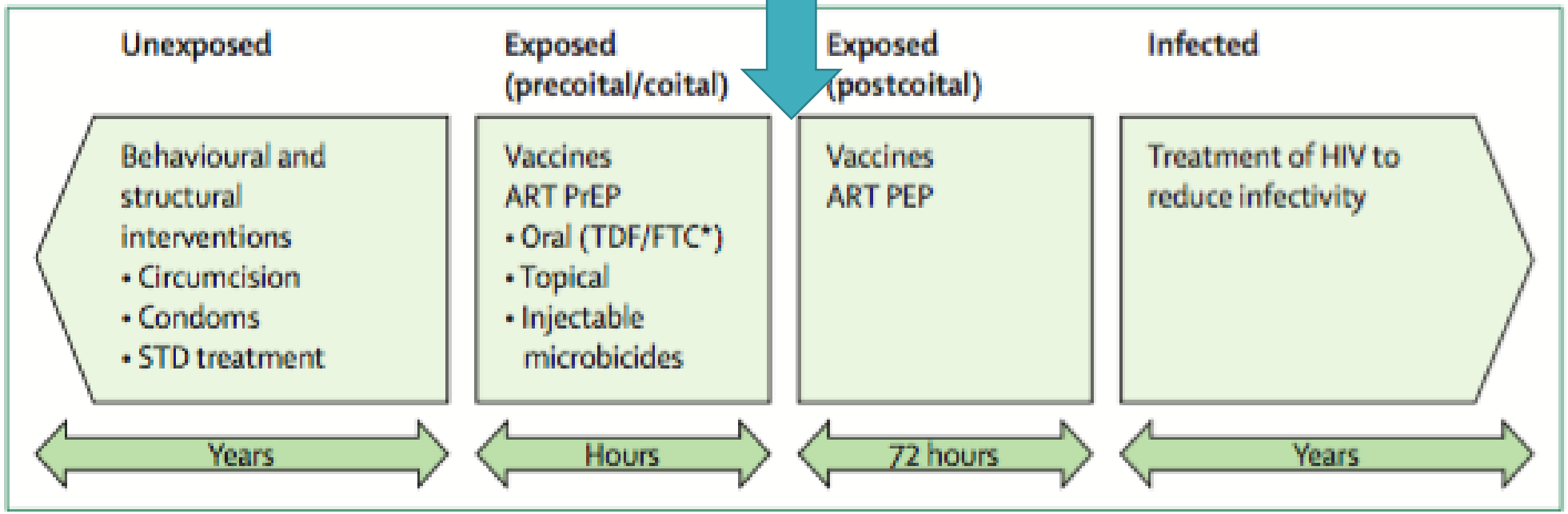
PEP (ou TPE) et PrEP



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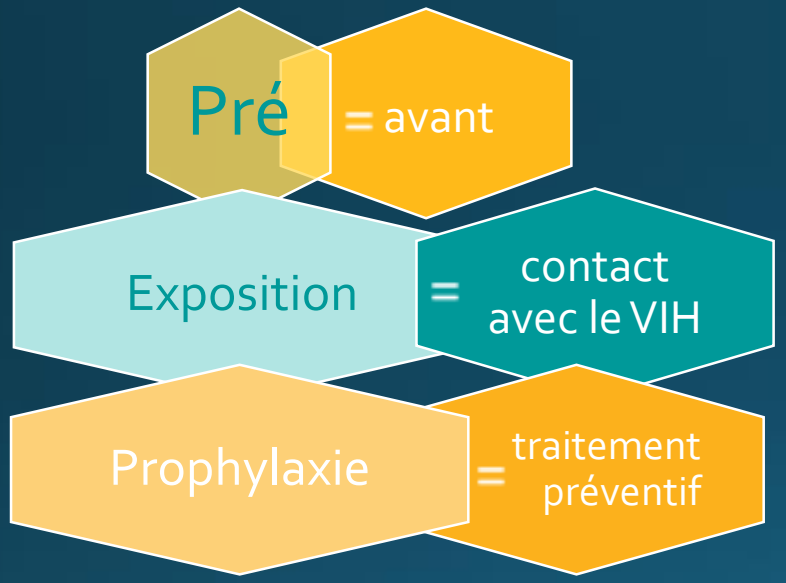
PrEP



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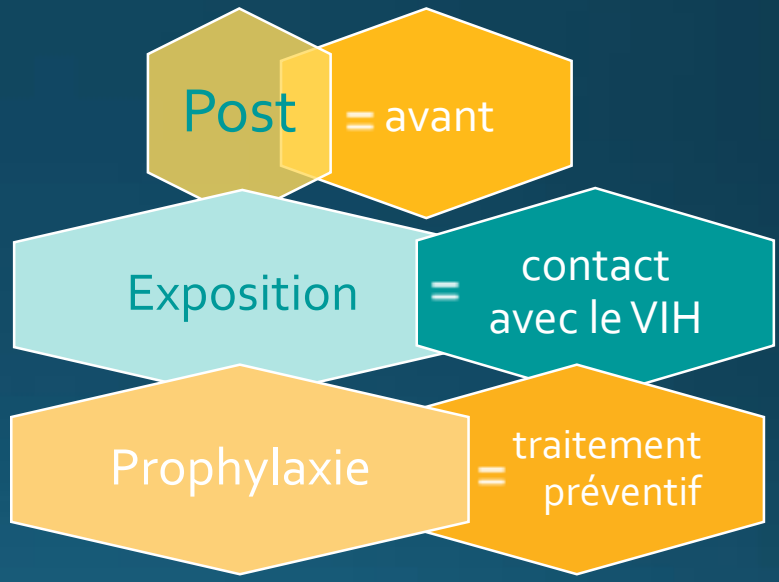

= TPE = Traitement post-exposition

Traitement postexposition non professionnel

- Après avoir traversé la muqueuse ou la peau si lésée, zone de latence de 48 – 72 heures avant de détecter le virus dans les ganglions
- Administrer un traitement dans les 48h, max 72 heures permet de limiter le risque d'infection par le HIV

Efficacité?

- Chez le macaque:
  - max d'efficacité entre 24 et 36h après le contact, décroit au delà
  - Durée de traitement: étude de 3 vs 10 vs 28 jours => meilleure efficacité avec 28 jours
- Pas d'étude randomisée chez l'homme
- Une étude cas-contrôle dans les accidents au sang après piqure: 81% d'efficacité
- Etudes de cohorte:
  - Efficacité dépend surtout de l'adhérence au traitement

Seroconversion Following Nonoccupational Postexposure Prophylaxis against HIV

Michelle E. Roland,[1] Torsten B. Neilands,[2] Melissa R. Krone,[2] Mitchell H. Katz,[1,4] Karena Franses,[1] Robert M. Grant,[5] Michael P. Busch,[6] Frederick M. Hecht,[1] Barbara L. Shacklett,[5a] James O. Kahn,[1] Joshua D. Bamberger,[4] Thomas J. Coates,[2a] Margaret A. Chesney,[2a] and Jeffrey N. Martin[1,2,3]

[1]Positive Health Program at San Francisco General Hospital, [2]Center for AIDS Prevention Studies, and [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, [4]Department of Public Health, [5]Gladstone Institute for Virology and Immunology, and [6]Blood Systems Research Institute, San Francisco, California

- 877 exposed subjects, 702 were evaluable 12 weeks after exposure
- 7 séroconversions dont 3 sans autre facteur de risque après le rapport à risque
- => pas d'efficacité de 100%

Traitement postexposition

Acta Clinica Belgica

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Belgian guidelines for non-occupational HIV post-exposure prophylaxis 2017

Agnès Libois, Eric Florence, Inge Derdelinckx, Jean Cyr Yombi, Sophie Henrard, Françoise Uurlings, Stefaan Vandecasteele, Sabine D. Allard, Rémy Demeester, Filip Van Wanzeele, Nathalie Ausselet & Stéphane De Wit

Recommandé si risque >1/10000

Risque lié à l'acte x la fréquence du HIV dans la population à laquelle appartient le/la partenaire

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Schéma recommandé

- Trithérapie antirétrovirale (anciennement Combivir/Kaletra, actuellement Stribild)
- A débuter le plus tot possible, maximum dans les 72 heures
- Durée de 28 jours
- A prendre à heure fixe en mangeant

- Cout: Stribild 969,98€
  - => prix en charge par la convention HIV TPE
  - => délivré par un Centre de référence SIDA

Effets secondaires

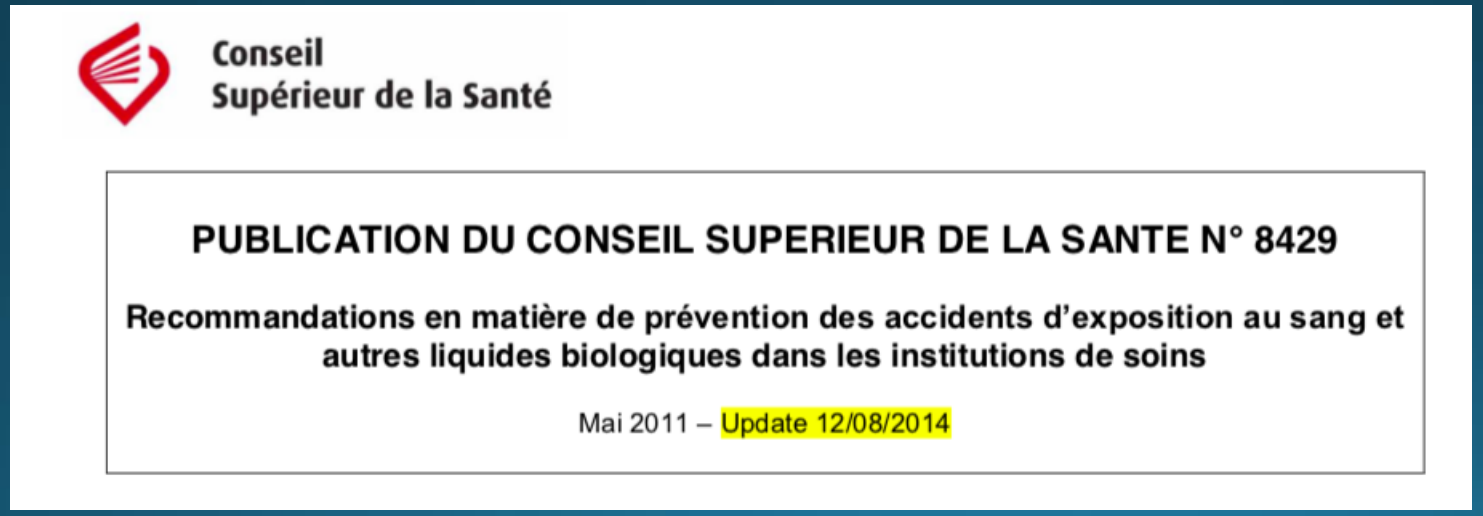
- Digestifs: diarrhées, nausées, vomissements
- Céphalées, sensations vertigineuses, asthénie
- Rash
- Insuffisance rénale (<1%)

- Attention: contient du cobicistat qui est un inhibiteur de cytochrome (P3A4 et C2D6)!

=> Vérifier les interactions avec trithérapie antirétrovirale, https://www.hiv-druginteractions.org

Exposition professionnelle

- Même schéma de 28 jours
- A débuter le plus tot possible, idéalement dans les 2 heures et maximum 72 heures
- Traitement pris en charge par l'organisme assureur



Conseil
Supérieur de la Santé

PUBLICATION DU CONSEIL SUPERIEUR DE LA SANTE N° 8429

Recommandations en matière de prévention des accidents d'exposition au sang et autres liquides biologiques dans les institutions de soins

Mai 2011 – Update 12/08/2014

a- Exposition percutanée à des liquides biologiques présentant des risques élevés.

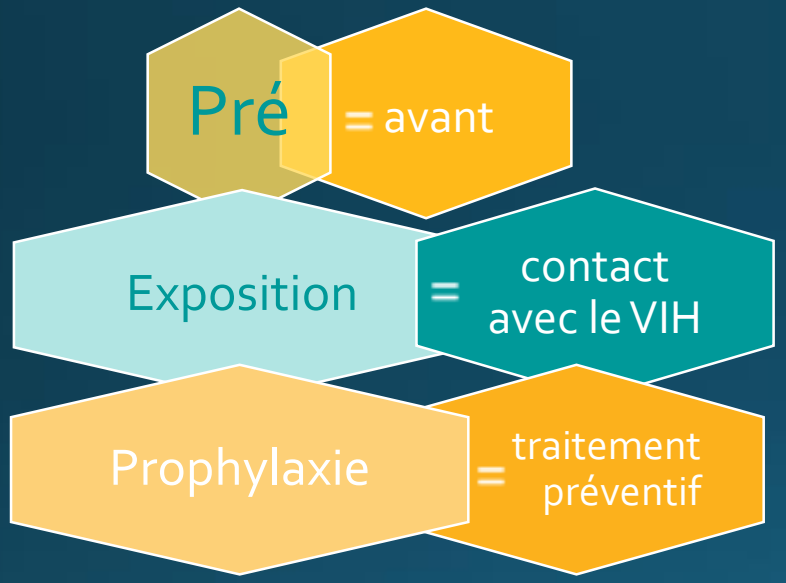
Origine	Type d'exposition		
	A risque élevé : – Aiguille creuse à haut débit – Sang visible sur accessoire – Ponction profonde – Aiguille introduite dans une artère ou une veine	**A risque moyen** : – Aiguille pleine – Scalpel	**A faible risque** : – Ponction superficielle – Autres situations
VIH avec charge virale détectable ou manque d'informations récentes sur la charge virale	Recommandé	Recommandé (3)	A envisager (4)
VIH avec charge virale stable et confirmée indétectable	Recommandé	A envisager (4)	A envisager (4)
Statut VIH inconnu mais appartenant à un groupe (1) / une zone (2) à haute prévalence	Recommandé si un test rapide VIH de la source n'est pas disponible	Recommandé si un test rapide VIH de la source n'est pas disponible	A envisager si un test rapide VIH de la source n'est pas disponible
Statut VIH inconnu et appartenant à un groupe (1) / une zone (2) à prévalence faible ou inconnue	A envisager si un test rapide VIH de la source n'est pas disponible	A envisager si un test rapide VIH de la source n'est pas disponible	Déconseillé
Aiguille abandonnée dans un établissement de soins de santé	A envisager dans les établissements dans lesquels l'exposition à des personnes infectées par le VIH est probable	A envisager dans les établissements dans lesquels l'exposition à des personnes infectées par le VIH est probable	Déconseillé

(1) Groupes à haute prévalence :
- hommes homo- et bisexuels ;
- drogués par voie IV ;
- prostitué(e)s ;
- antécédents d'infection(s) sexuellement transmissibles ;
- partenaires sexuels multiples ;
- relations sexuelles à plusieurs (plus de 3 individus) ;
- (ex) prisonniers.

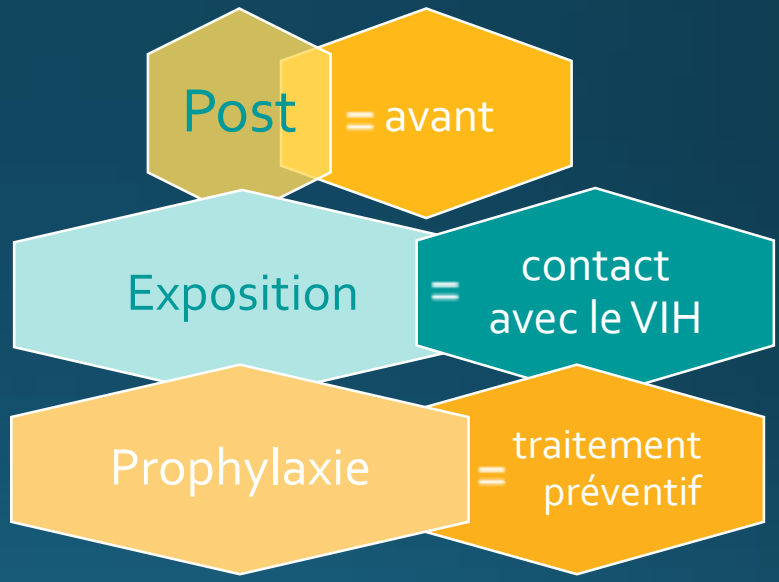
(2) Zone à haute prévalence de VIH : > 2 % dans la population générale (voir http://www.unaids.org/en/dataanalysis/tools/aidsinfo/countryfactsheets/).

(3) Envisager d'arrêter le traitement ou de continuer par une double thérapie INTI en cas de

PrEP



PEP

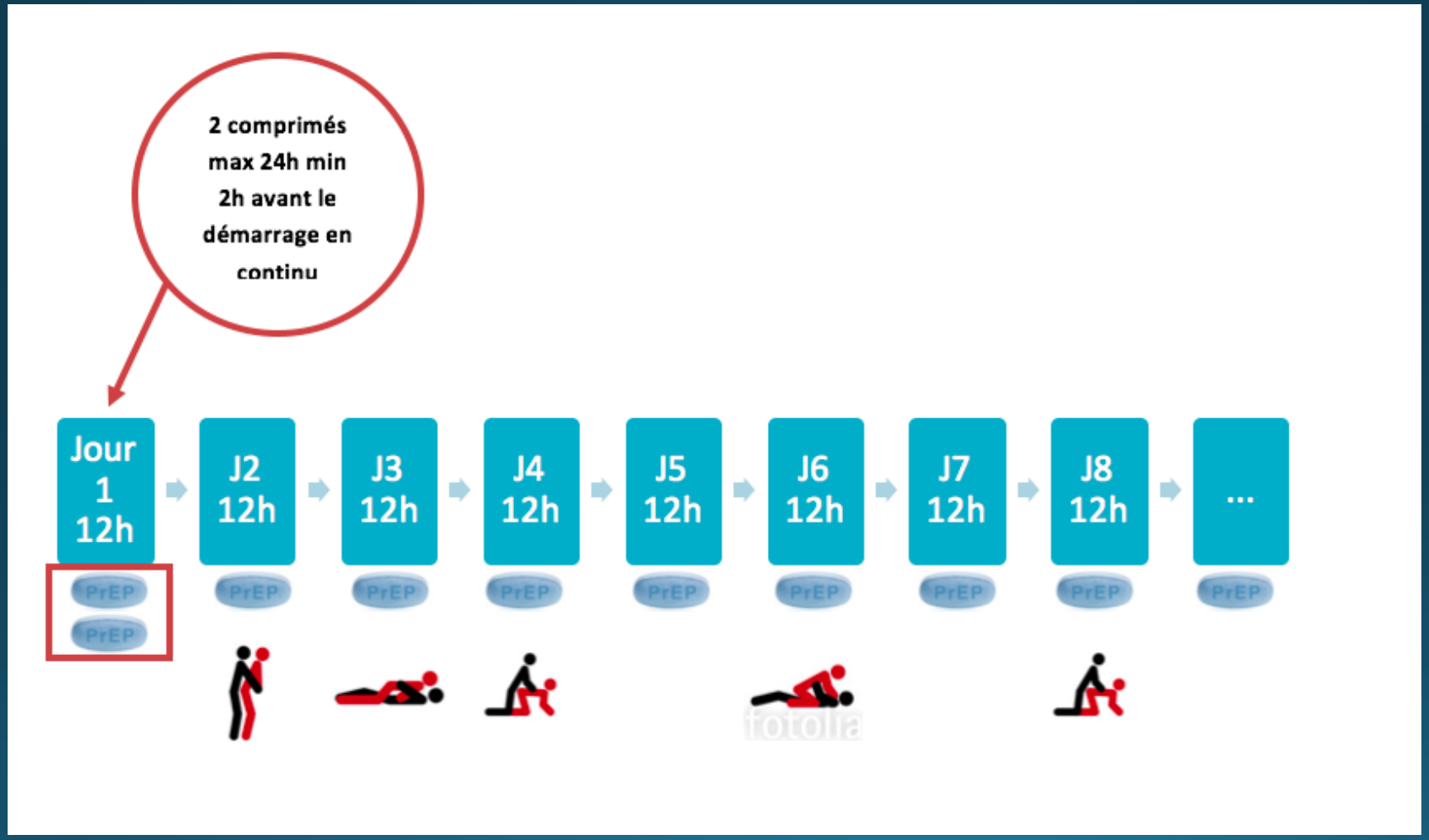


= TPE = Traitement post-exposition

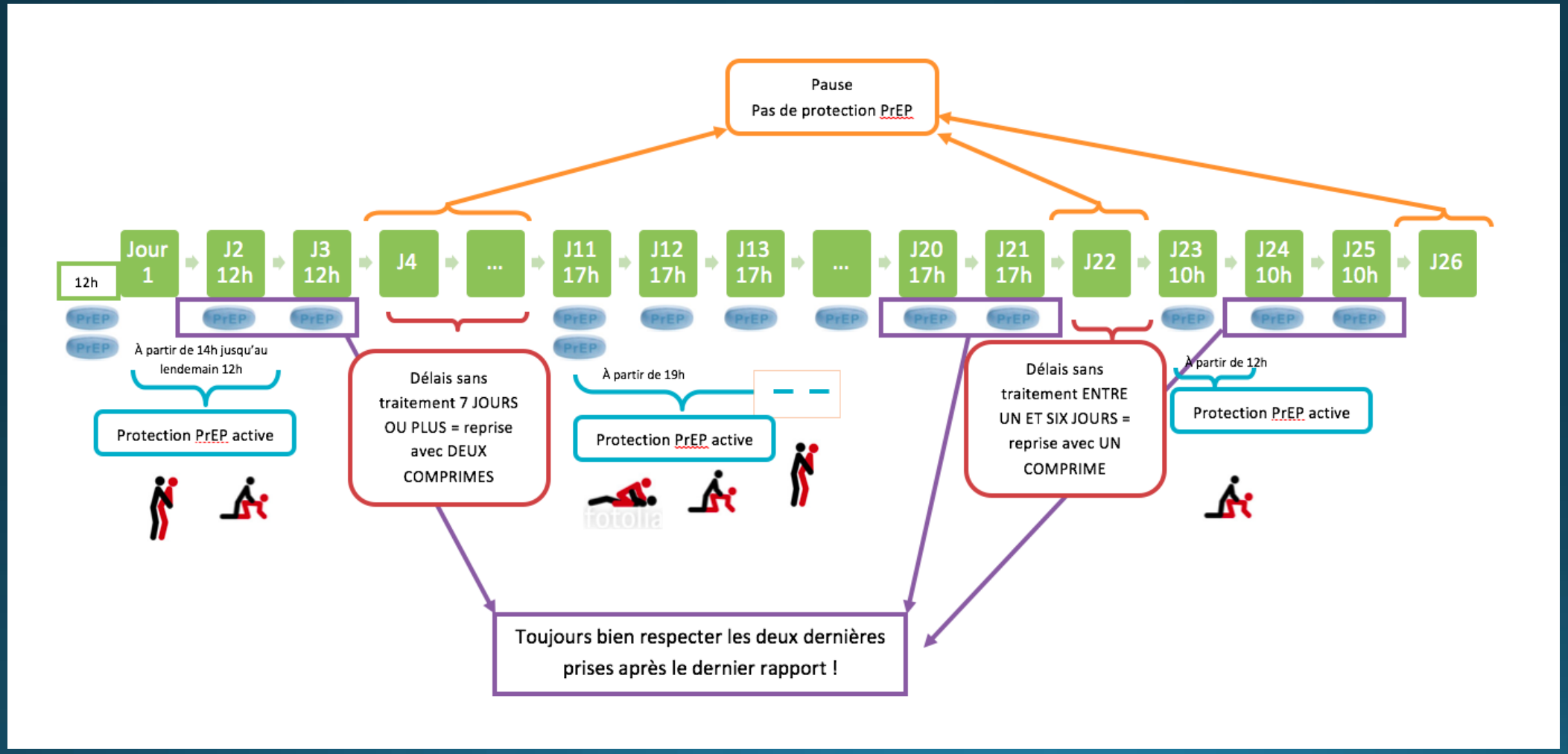
Traitement étudiés

- Prise en continu (tenofovir ou tenofovir+emtricitabine = truvada)
- PREP à la demande (truvada)
- Gel intravaginal (tenofovir)
- Anneau vaginal (dapivirine)
- Injection intramusculaire ou sous-cutanee mensuelle (cabotegravir)

La PrEP en continu (1 comprimé toutes les 24h)



PrEP a l'acte/ à la demande



Exemple…

- Sortie prévue le samedi soir…
  - Prise de 2 comprimés à midi

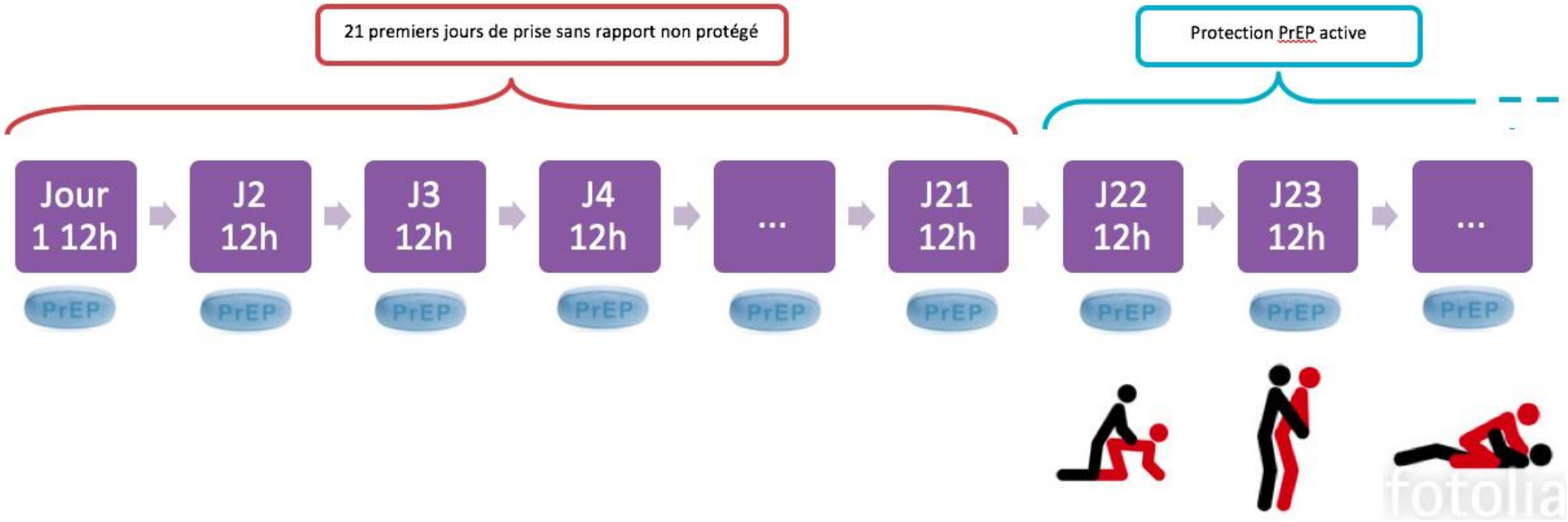
Samedi	Dimanche	Lundi	Mardi

12h 22h 11h 12h 12h 12h



TJS 2 x 1 comprimé après le dernier rapport

Pour les femmes : une seule possibilité



Diffusion des ARV dans les muqueuses

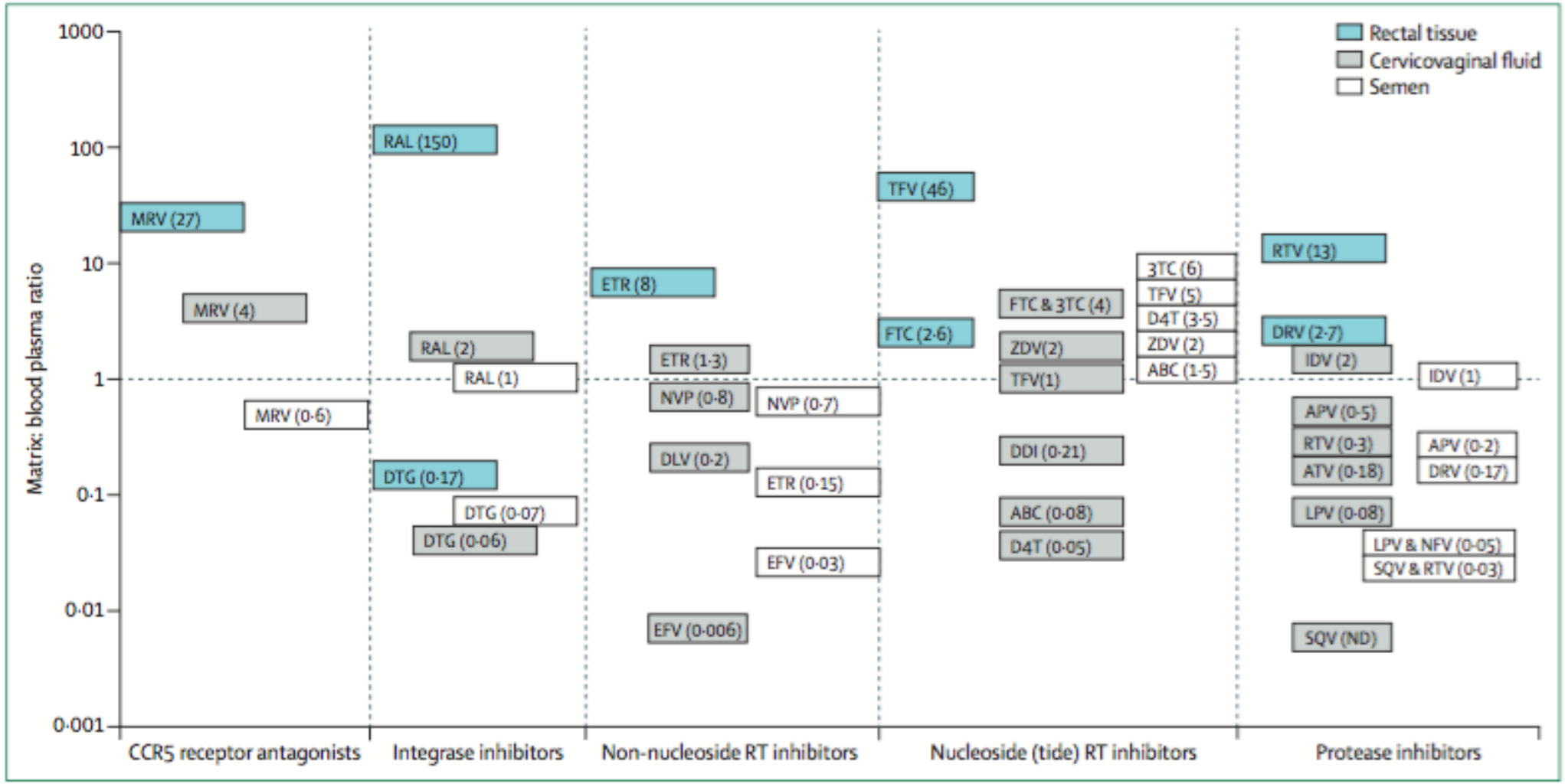


***Figure 2:* Comparison of antiretroviral exposure at mucosal surfaces**

Seminal plasma, cervicovaginal fluid, and colorectal tissue exposure is plotted as a ratio relative to matched blood plasma exposure. The Y axis is on a log scale. Y=1 is the line of unity, at which mucosal surface exposure is similar to blood plasma. Total (protein free plus protein bound) drug concentrations were used to calculate these ratios. Ratios above the line of unity signify that drugs are concentrating at mucosal surfaces, whereas ratios below the line of unity suggest that drug concentrations are lower than blood plasma at mucosal surfaces. Semen concentration ratios are shown in white, cervicovaginal fluid in grey, and rectal tissue in blue. MRV=maraviroc. RAL=raltegravir. DTG=dolutegravir. ETR=etravirine. EFV=efavirenz. NVP=nevirapine. DLV=delavirdine. TFV=tenofovir. FTC=emtricitabine. 3TC=lamivudine. ZDV=zidovudine. ABC=abacavir. DDI=didanosine. D4T=stavudine. RTV=ritonavir. DRV=darunavir. IDV=indinavir. APV=amprenavir. ATV=atazanavir. LPV=lopinavir. NFV=nelfinavir. SQV=saquinavir. ND=not detected. Figure adapted from reference 40.

Cohen MS, et al. Lancet, 2013

4. Efficacite de la prep

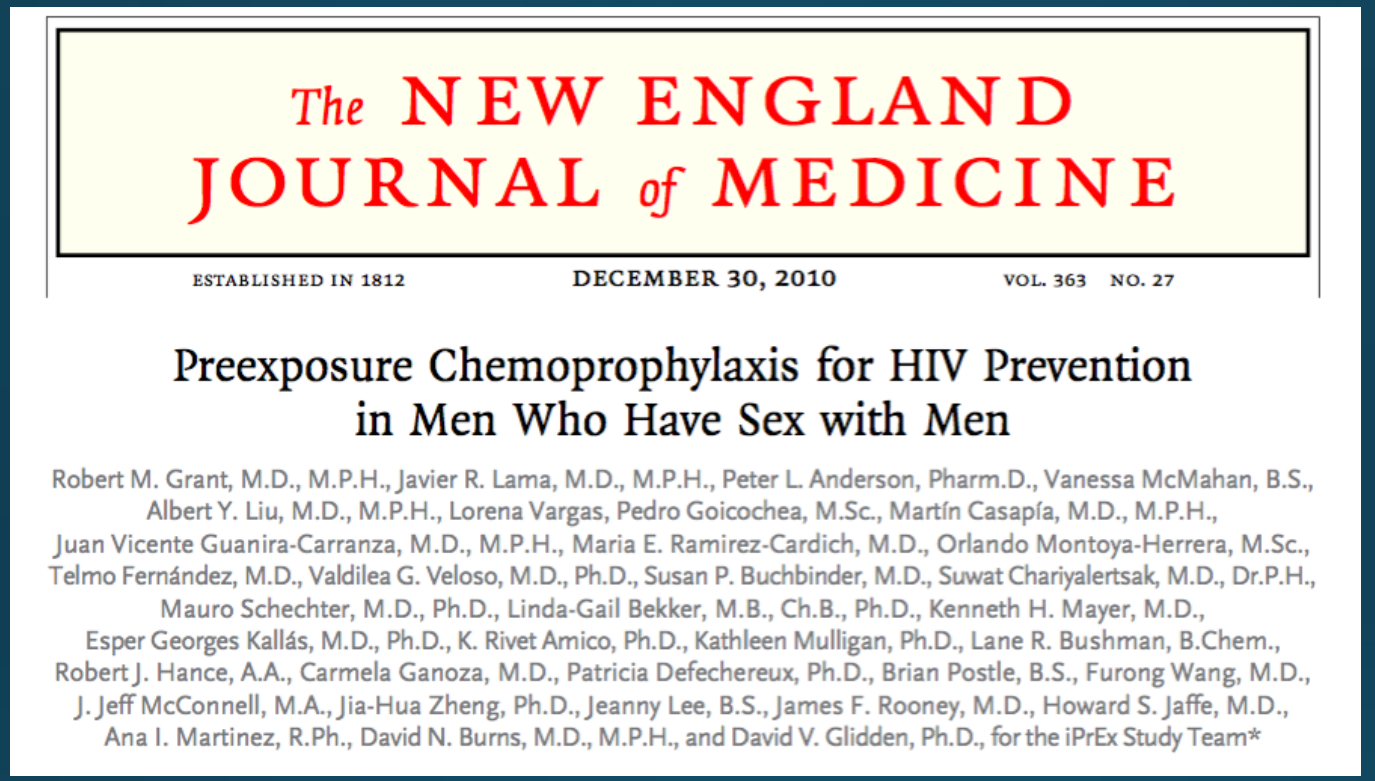
Table 1 Key studies examining efficacy of Tenofovir-based PrEP

Route of exposure	Interventions	Evidence	Positive benefit demonstrated?	
Homosexual men/MSM	Truvada (Tenofovir disoproxil fumarate & Emtricitabine)	$N = 2499$ 44% reduction in the incidence of HIV (95% confidence interval [CI] 15–63; $p = 0.005$) [4]	Y	Etude iPrEX
		$N = 275$ (in immediate PrEP group) Relative reduction 86% (90% CI 64-96, $p = 0-0001$; absolute difference 7-8/100 person-years, 90% CI 4-3–11-3) [3]	Y	Etude PROUD
		$N = 414$ Relative reduction of 86% (95% CI 40–98; $p = 0.002$) [6]	Y	Etude IPERGAY
Injecting drug users	Tenofovir disoproxil fumarate	$N = 1204$ Reduction of 48·9% in incidence (95% CI 9·6–72·2; $p = 0·01$) [2]	Y	
Heterosexual men and women	Tenofovir disproxil fumarate	$N = 1584$ Relative reduction of 67% in incidence of HIV-1 (95% CI 44–81; $p < 0.001$) [1]	Y	
	Truvada (Tenofovir disoproxil fumarate & Emtricitabine)	$N = 1579$ Relative reduction of 75% in incidence of HIV-1 (95% CI 55–87; $p < 0.001$) [1]	Y	
		$N = 611$ Efficacy 62.2% (95% CI 21.5–83.4; $p = 0.03$) [5]	Y	

Women	1% Tenofovir Vaginal Gel	$N = 445$	Y
		Estimated reduction of 39% overall	
		(54% in women with high gel adherence) [7]	
		$N = 2059$ total (gel or placebo)	N
		Incidence rate ratio 1.0 (95% CI 0.7–1.4) [8]	
		$N = 996$	N
		Hazard ratio 0.85 (95% CI 0.61–1.21) [10]	
	Tenofovir disoproxil fumarate	$N = 993$	N
		Hazard ratio 1.49 (95% CI 0.97–2.29) [10]	
	Truvada (Tenofovir disoproxil fumarate & Emtricitabine)	$N = 1062$	N
		Hazard ratio 0.94 (95% CI 0.59–1.52; $p = 0.81$) [9]	
		$N = 985$	N
		Hazard ratio 1.04 (95% CI 0.73–1.49) [10]	

Etude CAPRISA

Effica



The NEW ENGLAND JOURNAL of MEDICINE

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

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

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

- IPREX :
  - première étude, randomisée, en double aveugle, versus placebo, population HSH (et transgenres ayant des relations sexuelles avec des hommes)
  - 2007-2009
  - Truvada en prise quotidienne (emtricitabine+tenofovir)

IPREX

- 2499 patients inclus
  - 1251 Truvada
  - 1258 Placebo

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	FTC–TDF (N = 1251)	Placebo (N = 1248)	P Value
Age group — no. (%)			0.04
18–24 yr	591 (47)	662 (53)	
25–29 yr	274 (22)	241 (19)	
30–39 yr	249 (20)	224 (18)	
≥40 yr	137 (11)	121 (10)	
Education level — no. (%)			0.26
Less than secondary	279 (22)	244 (20)	
No. of alcoholic drinks (on days when subject drank in past month) — no. (%)			0.66
0	206 (16)	184 (15)	
1–4 per day	348 (28)	345 (28)	
≥5 per day	666 (53)	687 (55)	
Sexual risk factors at screening			
No. of partners in past 12 wk	18±35	18±43	0.51
Unprotected receptive anal intercourse in past 12 wk — no. (%)	732 (59)	753 (60)	0.37
Unprotected anal intercourse with partner with positive or unknown HIV status in past 6 mo — no. (%)	992 (79)	1009 (81)	0.34
Transactional sex in past 6 mo — no. (%)	517 (41)	510 (41)	0.84
Sexually transmitted infections diagnosed at screening			
Syphilis seroreactivity — no./total no. (%)	164/1240 (13)	162/1239 (13)	0.95
Serum herpes simplex virus type 2 — no./total no. (%)	458/1241 (37)	430/1243 (35)	0.24
Urine leukocyte esterase positive — no. (%)	23 (2)	22 (2)	1.00
Hepatitis B virus status — no. (%)			0.11
Susceptible	827 (66)	803 (64)	
Immune because of natural infection	247 (20)	222 (18)	
Immune because of previous vaccination	149 (12)	190 (15)	
Current infection with hepatitis B virus	7 (1)	6 (<1)	
Indeterminate	21 (2)	27 (2)	

† Race or ethnic group was self-reported.

IPREX

- 100 séroconversions HIV
  - 36 dans le groupe Truvada
  - 64 dans le groupe placebo

=>Diminution du risque de 44%
MAIS 90% efficacité si adhérence >90% et 92% efficacité si TDF détectable dans le sang

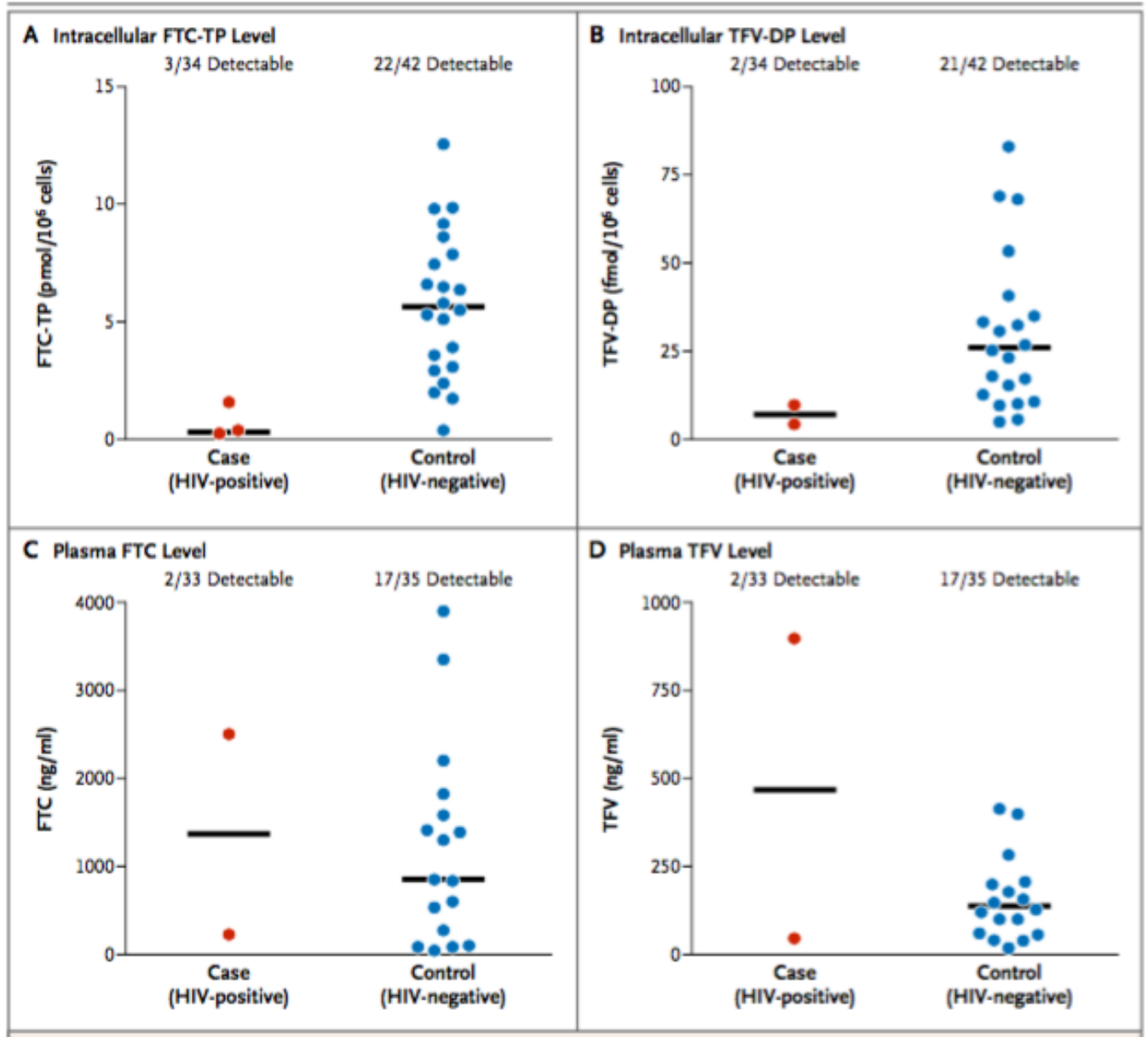
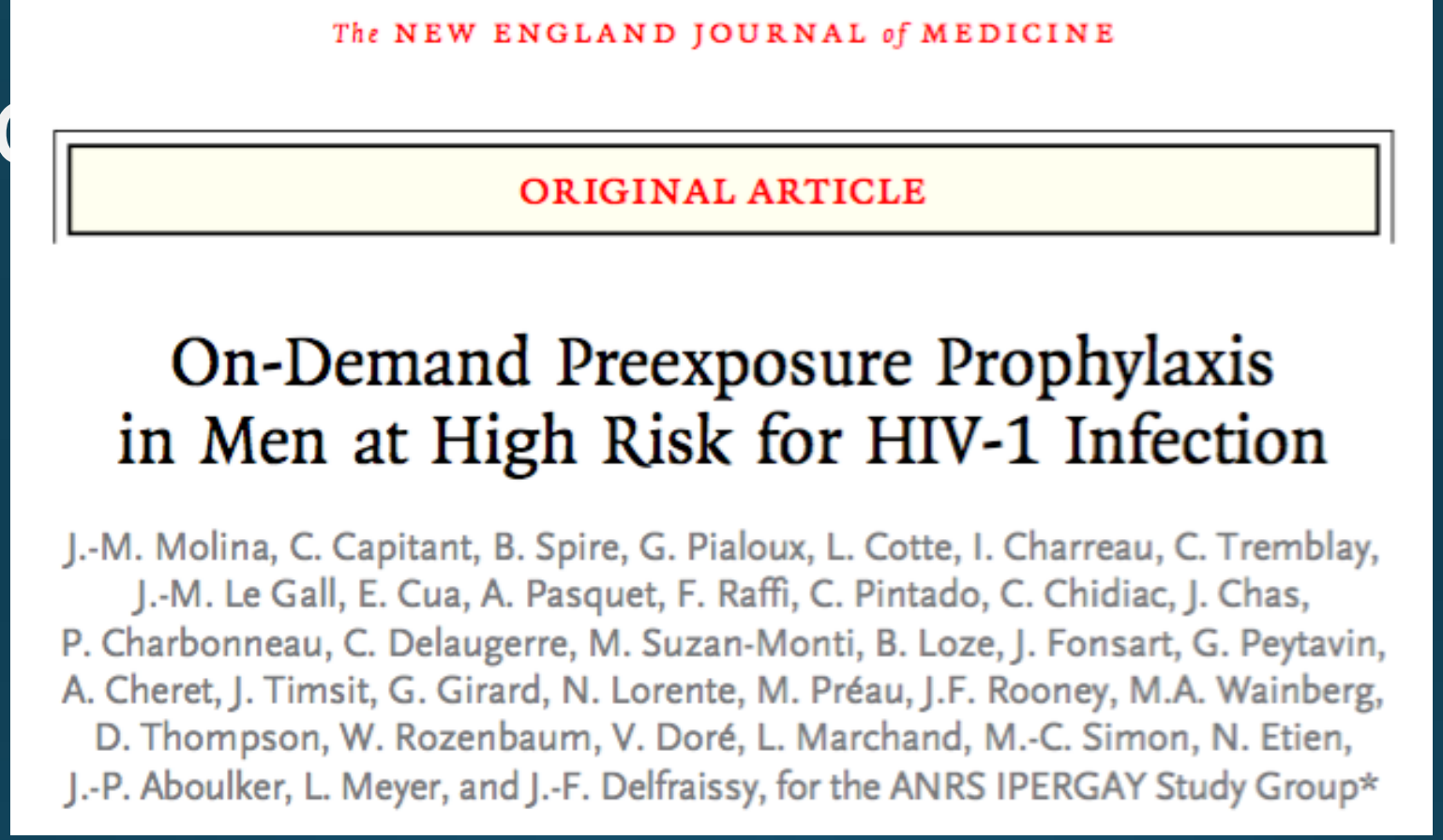


Figure 4. Levels of Study-Drug Components in Blood of Subjects Receiving FTC–TDF, According to HIV Status.
Shown are intracellular levels (Panels A and B) and plasma levels (Panels C and D) of components of emtricitabine and tenofovir disoproxil fumarate (FTC–TDF), quantified in specimens obtained from subjects in the FTC–TDF group. FTC-TP denotes emtricitabine triphosphate, and TFV-DP tenofovir diphosphate. The horizontal lines in each panel indicate medians.

Efficac



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

J.-M. Molina, C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J.-M. Le Gall, E. Cua, A. Pasquet, F. Raffi, C. Pintado, C. Chidiac, J. Chas, P. Charbonneau, C. Delaugerre, M. Suzan-Monti, B. Loze, J. Fonsart, G. Peytavin, A. Cheret, J. Timsit, G. Girard, N. Lorente, M. Préau, J.F. Rooney, M.A. Wainberg, D. Thompson, W. Rozenbaum, V. Doré, L. Marchand, M.-C. Simon, N. Etien, J.-P. Aboulker, L. Meyer, and J.-F. Delfraissy, for the ANRS IPERGAY Study Group*

- IPERGAY :
  - Double aveugle, randomisée, versus placebo, population HSH
  - Truvada en prise intermittente (juste avant et après l'exposition)
  - 2012-2014

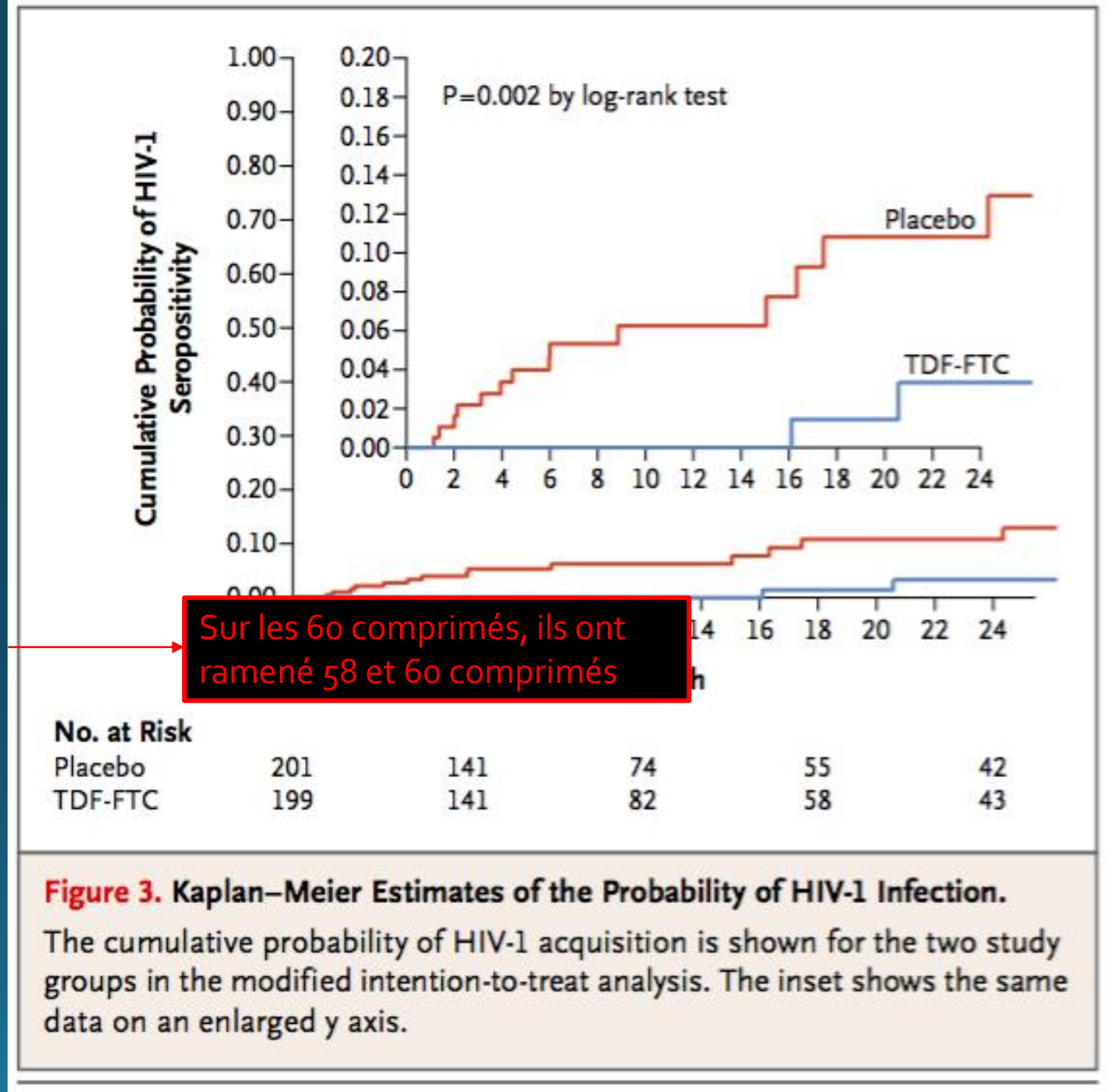
This article was published on December 1, 2015, at NEJM.org.

IPERGAY

- 400 patients inclus
  - 199 Truvada
  - 201 Placebo

- 19 séroconversions HIV
  - 3 entre la randomisation et l'enrollement
  - 16 pendant l'étude
    - 2 dans le groupe Truvada
    - 14 dans le groupe placebo

=> Diminution du risque de 86%



Sur les 60 comprimés, ils ont ramené 58 et 60 comprimés

Figure 3. Kaplan–Meier Estimates of the Probability of HIV-1 Infection.

The cumulative probability of HIV-1 acquisition is shown for the two study groups in the modified intention-to-treat analysis. The inset shows the same data on an enlarged y axis.

Efficacité de la PrEP

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*

Lancet 2016; 387: 53-60

- PROUD :
  - Randomisée open label, prise immédiate ou différée, population HSH
  - Truvada en Prise quotidienne
  - Objectif de démontrer la non majoration du risque
  - 2012-2014

PROUD

	Immediate group (n=273)	Deferred group (n=267)
Age (years)	35 (30–43)	35 (29–42)
Ethnicity		
White	220 (81%)	219 (83%)
Asian	14 (5%)	15 (6%)
Black	11 (4%)	10 (4%)
Other	28 (10%)	21 (8%)
University degree	161 (59%)	166 (62%)
Unemployed	24 (9%)	20 (8%)
Born outside the UK	110 (40%)	107 (40%)
Relationship status		
Partner, living together	87 (32%)	73 (27%)
Partner, living separately	40 (15%)	46 (17%)
No partner	146 (53%)	147 (55%)
Circumcised	77 (28%)	79 (30%)
Chemsex* in past 90 days	115 (43%)	116 (45%)
Sexually transmitted infection diagnosed in past 12 months		
Any	164 (63%)	167 (65%)
Bacterial†	150 (58%)	155 (60%)
Rectal gonorrhoea or chlamydia	89 (34%)	83 (32%)
Number of HIV tests in past 12 months	3 (2–4)	3 (2–4)
Used post-exposure prophylaxis in past 12 months	91 (35%)	93 (37%)

Data are median (IQR) or n (%). Two participants in each group did not return the questionnaire. Data were missing for ethnicity (none in the immediate group vs two in the deferred group), education (one vs none), employment status (none vs two), born outside UK (one vs none), relationship status (none vs one), circumcision status (two vs two), chemsex use (seven vs eight), history of sexually transmitted infection (13 vs ten), previous HIV tests (ten vs ten), and use of postexposure prophylaxis (15 vs 15). *Use of either γ-hydroxybutyrate, 4-methylmethcathinone, or methamphetamine to facilitate or enhance sex. †Gonorrhoea, chlamydia, or syphilis.

Table 1: **Baseline characteristics**

- 540 patients inclus
  - 273 en traitement immédiat
  - 267 en début de traitement différé

- 23 séroconversions HIV
- 20 dans le groupe différé (malgré 174 TPE)
- 3 dans le groupe immédiat
  - Test + à la visite de la 4è semaine -> contamination avant le début de la PrEP

=> Diminution du risque de 90%

Belgian Demonstration project

- *Design*: open-label cohort study
- *Outcomes*: **uptake**, **acceptability** and **feasibility** of PrEP
- *Study drug*: **Truvada**
- *Study population*: 200 HIV (-) MSM "at risk"
- *Study site*: Institute of Tropical Medicine (ITM), Antwerp
- *Follow-up*: 18 months (start Oct 2015)
- Choice between daily and event-driven PrEP

Funding : IWT-TBM

Study drugs donated by Gilead

Be-PrEP-ared

- 300 patients contactés -215 screening - 192 inclus
- 98% men – 2% transwomen
- 78+ daily use – 22% event-driven Prep
- End of the study: June 2018

- 8 diagnostics de séropositivité lors du screening
- Pas de séroconversion durant les 18 mois de suivi

OUI MAIS…

- LES PROBLÈMES, QUESTIONS ET DÉBATS AUTOUR DE LA PrEP
  - Effets secondaires chez un sujet sain
  - Majoration de prise de risque et d'acquisition d'IST
  - Risque d'induire des résistances
  - Cout et Remboursement en période de crise?

1. Effets secondaires du Truvada

- **Etude IPERGAY**: Principalement digestifs (13%) – 1 seul arret
- **Etude PROUD**: 1% d'arrêt de traitement pour effet secondaire digestif

- **Troubles gastro-intestinaux**: nausées, vomissements, diarrhées, douleurs abdominales, flatulences.
- Troubles généraux : maux de tête, vertiges, fatigue, insomnie…
- Troubles rénaux (insuffisance rénale, syndrome de Fanconi,…)
- Affections cutanées
- Réactions allergiques
- Trouble osseux : baisse de la densité minérale osseuse
- Acidose lactique, stéatose hépatique

1. Effets secondaires

- Fonction rénale
  - élévation des taux sériques de créatinine dans 2,2 % des cas
  - 0,1 % d'insuffisance rénale
  - <0,1 % de cas de tubulopathie proximale ou de syndrome de FanconI

Nelson M, Katlama C, Montaner J, et al. the safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults : the first 4 years. AIDS 2007;21: 1273-81.

1. Effets secondaires

- Ostéoporose
  - Démineralisation osseuse accrue avec tous les antiretroviraux mais + Tenofovir
- Pas d'effet sous PrEP

mais recul insuffisant

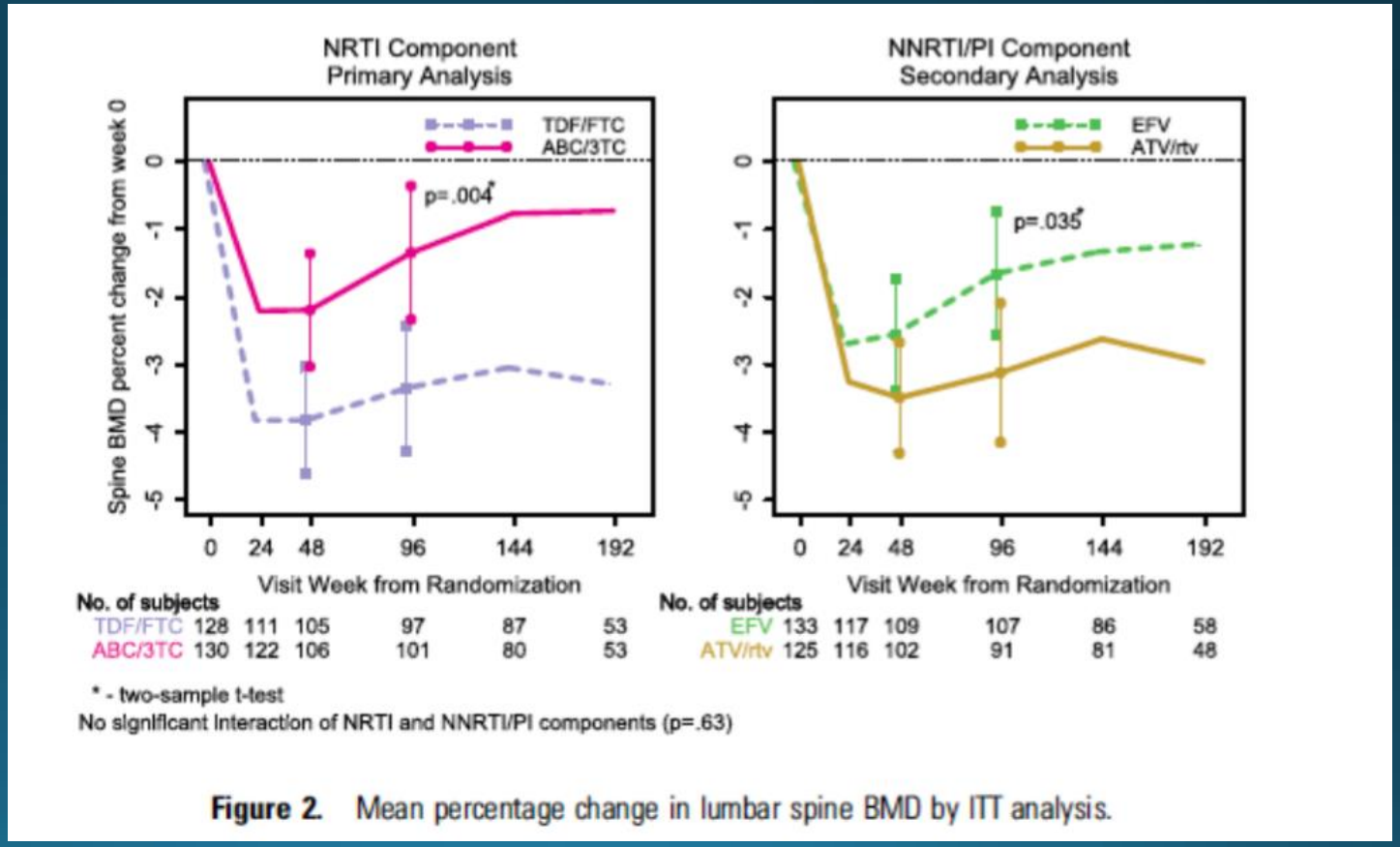


Figure 2. Mean percentage change in lumbar spine BMD by ITT analysis.

IPERGAY

Table 2. Adverse Events.*

Adverse Events	TDF-FTC (N=199)	Placebo (N=201)	P Value
	no. of patients (%)		
Any adverse event	186 (93)	181 (90)	0.21
Any serious adverse event	20 (10)	17 (8)	0.58
Death	0	0	1.00
Any grade 3 or 4 event	19 (10)	15 (7)	0.45
Treatment discontinuation due to adverse event	1 (1)	0	
Gastrointestinal adverse event†	28 (14)	10 (5)	0.002
Nausea	16 (8)	2 (1)	
Vomiting	3 (2)	0	
Abdominal pain	13 (7)	3 (1)	
Diarrhea	8 (4)	6 (3)	
Confirmed laboratory event			
Elevated plasma creatinine			
Any grade	35 (18)	20 (10)	0.03
Grade 1	35 (18)	19 (9)	
Grade 2	0	1 (<1)	
Proteinuria ≥2+	11 (6)	9 (4)	0.63
Glycosuria ≥2+	1 (1)	0	0.50

PROUD

	Weeks since enrolment	Signs and symptoms	Grade*	Relation to study drug*
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**

- 21 patients ont arrêté ou suspendu la prise en raison d'effets indésirables (13 effets ont été considérés en lien avec le traitement)

2. Majoration de la prise de risque et des IST

- Pas de majoration du nombre d'ist entre les groupes traites vs placebo
- etude Proud: open-labe
  - évalue la prep dans le milieu réel
  - Pas de majoration de risque

	Immediate	Deferred	Unadjusted odds ratio	Adjusted odds ratio (90% CI)*	p value
Any	152/265 (57%)	124/247 (50%)	1·33	1·07 (0·78–1·46)	0·74
Gonorrhoea†	103/261 (39%)	89/242 (37%)	1·12	0·86 (0·62–1·20)	0·46
Chlamydia†	77/261 (30%)	54/242 (22%)	1·46	1·27 (0·89–1·80)	0·27
Syphilis	30/263 (11%)	22/247 (9%)	1·32	1·29 (0·79–2·10)	0·39
Rectal gonorrhoea or chlamydia	93/258 (36%)	77/238 (32%)	1·18	1·00 (0·72–1·38)	0·99

Infections diagnosed during deferral phase of follow-up. Analysis based on participants with at least one screen.
*Adjusted for the number of screens for specific infection. †Detected in throat, urethra, or rectum.

Table 3: **Bacterial sexually transmitted infections**

McCormack S, et al. Lancet,

Clinical Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

Article Contents

Abstract

Supplementary data

Comments (0)

ACCEPTED MANUSCRIPT

Effects of Pre-exposure Prophylaxis for the Prevention of HIV Infection on Sexual Risk Behavior in Men Who Have Sex with Men: A Systematic Review and Meta-analysis

Michael W Traeger ✉, Sophia E Schroeder, Edwina
Margaret E Hellard, FRACP PhD, Vincent J Cornelis
Joseph S Doyle, MD FRACP, Mark A Stoové, PhD

Clinical Infectious Diseases, ciy182, https://doi.org/

Published: 02 March 2018 **Article history** ▾

Abstract

Background

Results: Sixteen observational studies and one open-label trial met selection criteria. Eight studies with 4388 participants reported STI prevalence and 13 studies with 5008 participants reported change in condom use. PrEP use was associated with a significant increase in rectal chlamydia (odds ratio [OR]=1.59; 95%CI 1.19-2.13; p=0.002; heterogeneity I^2=23%) and an increase in any STI diagnosis (OR=1.24; 95%CI 0.99-1.54; p=0.059; I^2=50%). The association of PrEP use with STI diagnoses was stronger in later studies. Most studies showed evidence of an increase in condomless sex among PrEP users.

Conclusion: Findings highlight the importance of efforts to minimize STIs among PrEP users and their sexual partners. Monitoring of risk compensation among MSM in the context of PrEP scale-up is needed to assess the impact of PrEP on the sexual health of MSM and to inform preventive strategies.

Trend in reported incidence (/100 000 inh.) of Chlamydia, Gonorrhea and Syphilis, Belgium 2002-2016

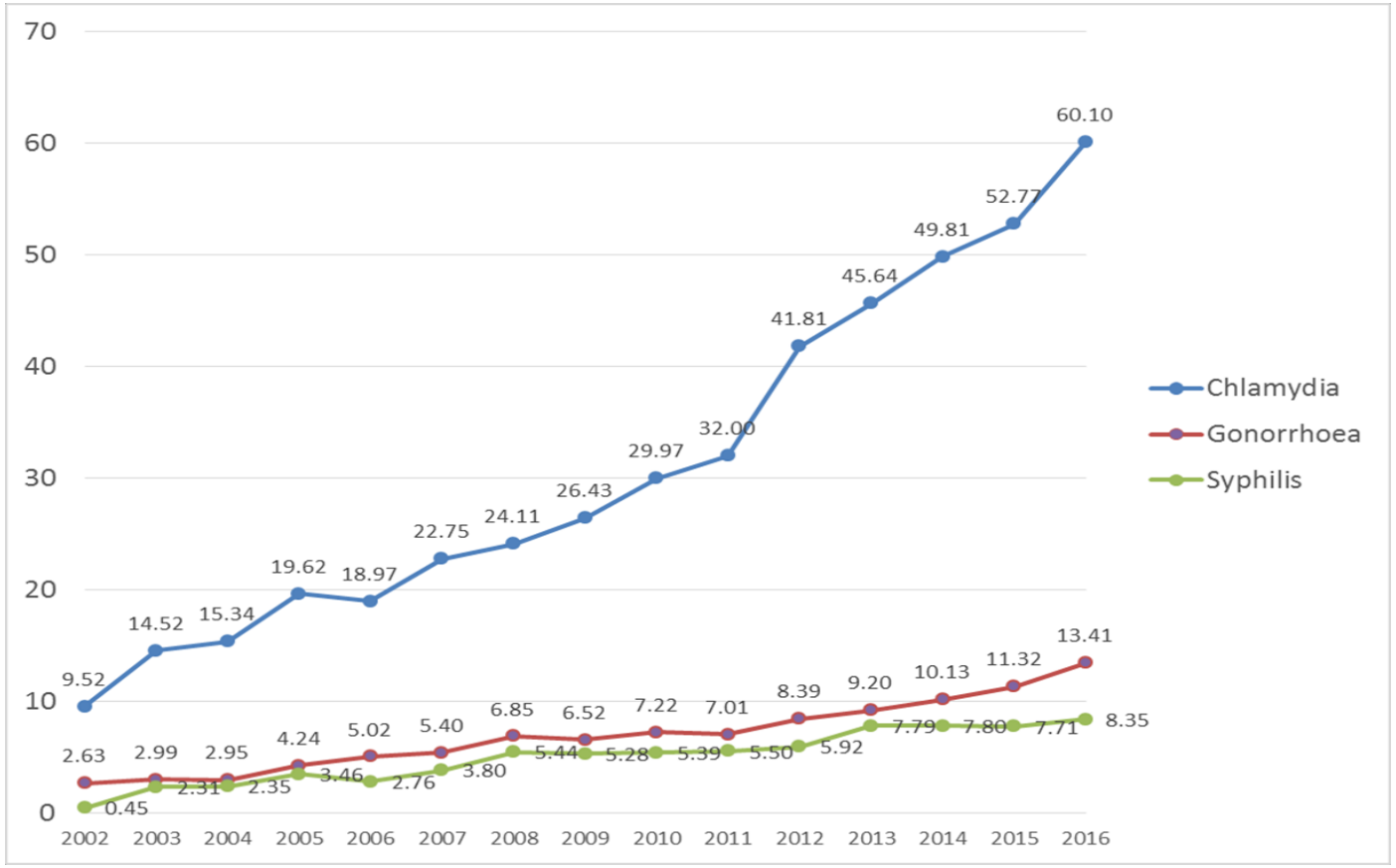


Table 2 Trends in CLAI partners, seroadaptive strategies, and post-exposure prophylaxis (PrEP) use among HIV-negative men who have sex with men (MSM), San Francisco, 2004–2014

	2004 n = 1211		2008 n = 407		2011 n = 371		2014 n = 301		χ^2, p
	Count	%	Count	%	Count	%	Count	%	
Number of CLAI partners									
0	734	60.6	237	58.2	201	54.2	121	40.2	42.2, <0.001
1	341	28.2	116	28.5	110	29.6	94	31.2	1.3, 0.74
2	82	6.8	32	7.9	28	7.5	29	9.6	3, 0.39
3	28	2.3	15	3.7	17	4.6	27	9.0	30, <0.001
4	12	1.0	4	1.0	9	2.4	14	4.7	21.7, <0.001
5	14	1.2	3	0.7	6	1.6	16	5.3	27.9, <0.001
Behavioral strategies WITHOUT PrEP as a category									
No anal intercourse	288	23.8	113	27.8	88	23.7	66	21.9	3.8, 0.28
Consistent condom user	446	36.8	124	30.5	113	30.5	55	18.3	39.7, <0.001
Pure serosorting	285	23.5	100	24.6	110	29.6	120	39.9	35.3, <0.001
Condom serosorting	67	5.5	16	3.9	24	6.5	16	5.3	2.6, 0.46
Seropositioning	71	5.9	24	5.9	27	7.3	23	7.6	2, 0.57
No strategy	54	4.5	30	7.4	9	2.4	21	7.0	13.3, <0.001
Behavioral strategies WITH PrEP as a category									
No anal intercourse	288	23.8	113	27.8	88	23.7	66	21.9	3.8, 0.28
PrEP	0	0	0	0	0	0	29	9.6	194.1, <0.001
Consistent condom user	446	36.8	124	30.5	113	30.5	52	17.3	43.7, <0.001
Pure serosorting	285	23.5	100	24.6	110	29.6	106	35.2	19.9, <0.001
Condom serosorting	67	5.5	16	3.9	24	6.5	15	5.0	2.7, 0.44
Seropositioning	71	5.9	24	5.9	27	7.3	18	6.0	1.1, 0.79
No strategy	54	4.5	30	7.4	9	2.4	15	5.0	10.9, 0.01

CLAI condomless anal intercourse

3. Risque de résistances

- Risque de développer des mutations conférant une résistance au tenofovir ou à l'emtricitabine
  - Proud: 2 cas de mutation liée à l'exposition à l'emtricitabine
- Importance du dépistage
- Importance du respect du schéma

MAIS...

Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis

TO THE EDITOR: Preexposure prophylaxis with emtricitabine (FTC)–tenofovir disoproxil fumarate (TDF) has been shown to be efficacious in preventing human immunodeficiency virus type 1 (HIV-1) infection in men who have sex with men and in whom adherence to treatment is high, as measured by levels of tenofovir diphosphate (TFV-DP) in dried blood spots.[1] We describe a case of HIV-1 infection despite FTC-TDF–based preexposure prophylaxis.[2]

clinical suspicion of HIV acquisition during the patient's reported receptive anal sex with multiple partners without the use of condoms 2 to 6 weeks before day 0.[3] In addition, the infection date estimated by means of viral deep-sequencing analysis (BEAST software, version v1.8.3) was within the exposure period. Details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

Liquid chromatographic–tandem mass spec-

N ENGL J MED 376;5 NEJM.ORG FEBRUARY 2, 2017

Acquisition of wild-type HIV-1 infection in a patient on

	Sept 23, 2015	Oct 19, 2015	Dec 7, 2015	March 7, 2016	May 18, 2016	May 24, 2016	May 30, 2016	June 6, 2016	June 14, 2016	June 23, 2016	July 18, 2016
PrEP use	Start	Yes	Yes	Yes	Yes	Stop	..	..	..	..	..
Sexually transmitted infection diagnosed*	..	..	Anal chlamydia and gonorrhoea	Anal chlamydia and gonorrhoea	Anal lymphogranuloma venereum	..	..	..	..	..	..
Fourth-generation antibody and antigen test	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Reactive†	Reactive†	..	..	..	..	..
Tenofovir diphosphate in dried blood spot (fmol per punch)	..	..	..	2234	..	2258	..	..	..	..	..
HIV RNA qualitative	Negative‡	..	..	..	ND	Negative§	..	..	..	..	..
HIV RNA quantitative¶	..	..	..	..	ND	<40 copies per mL	<40 copies per mL	..	12 882 copies per mL||	101 156 copies per mL	..
Western blot	..	..	..	..	ND	gp120/160 positive	..	..	..	gp120/160 positive; p24 weak positive	gp120/160 positive; p24 positive; p17 positive
HIV cDNA in PBMCs	..	..	..	..	..	..	Negative	..	..	..	..
HIV cDNA in sigmoid biopsies	..	..	..	..	..	..	..	Negative	..	..	..
ART use	..	..	..	..	..	..	..	..	..	Start	Yes

PrEP=pre-exposure prophylaxis. ND=not done. PBMCs=peripheral blood mononuclear cells. ART=combination antiretroviral therapy. *Anal chlamydia and gonorrhoea were also diagnosed and treated in November, 2015. †Antibody positive and antigen negative. ‡Pooled HIV RNA using COBAS Taqscreen MPX version 2.0. §Analysed with the Xpert HIV-1 Qual test. ¶Analysed with the Abbott RealTime HIV-1 Viral Load Assay. ||No resistance mutations detected.

Table 2: **HIV test results and tenofovir diphosphate concentrations in dried blood spot samples of a PrEP user who seroconverted for HIV with high tenofovir diphosphate concentrations**

4. Aspect financier

- Remboursement de la PrEP en période de crise?

COUT-EFFICACITE

- COUT DU MEDICAMENT
- SCHEMA UTILISE (PLUS DE COMPRIMES SI PRISE EN CONTINU)
- Contexte epidemique
- Niveau d'Adhérence au traitement
- PrEP programme coverage
- Stratégie de priorité d'accessibilité au traitement

Gomez GB, Borquez A, Case KK, et al. The cost and impact of scaling up preexposure prophylaxis for HIV prevention: a systematic review of cost- effectiveness modelling studies. PLoS Med 2013; 10:e1001401.

En pratique en Belgique…

Remboursement depuis le 01/06/2017
Demande doit être introduite par un médecin attaché à un Centre Référence SIDA

Critères pour le remboursement:

MSM:
•Pratiques sexuelles anales non protégées avec >1 partenaire (derniers 6 mois)
•Plusieurs IST(derniers 12 mois)
•Recours à la PEP
•Utilisation des substances psycho-actives lors des activités sexuelles (chemsex)

Haut risque individuel:
•Injection de drogue
•Travail dans la prostitution
•Exposition à des pratiques sexuelles non protégées
•Partenaire d'un patient VIH positif sans suppression virale

Extracted from: http://www.inami.fgov.be

Qui?

Les critères d'inclusion:

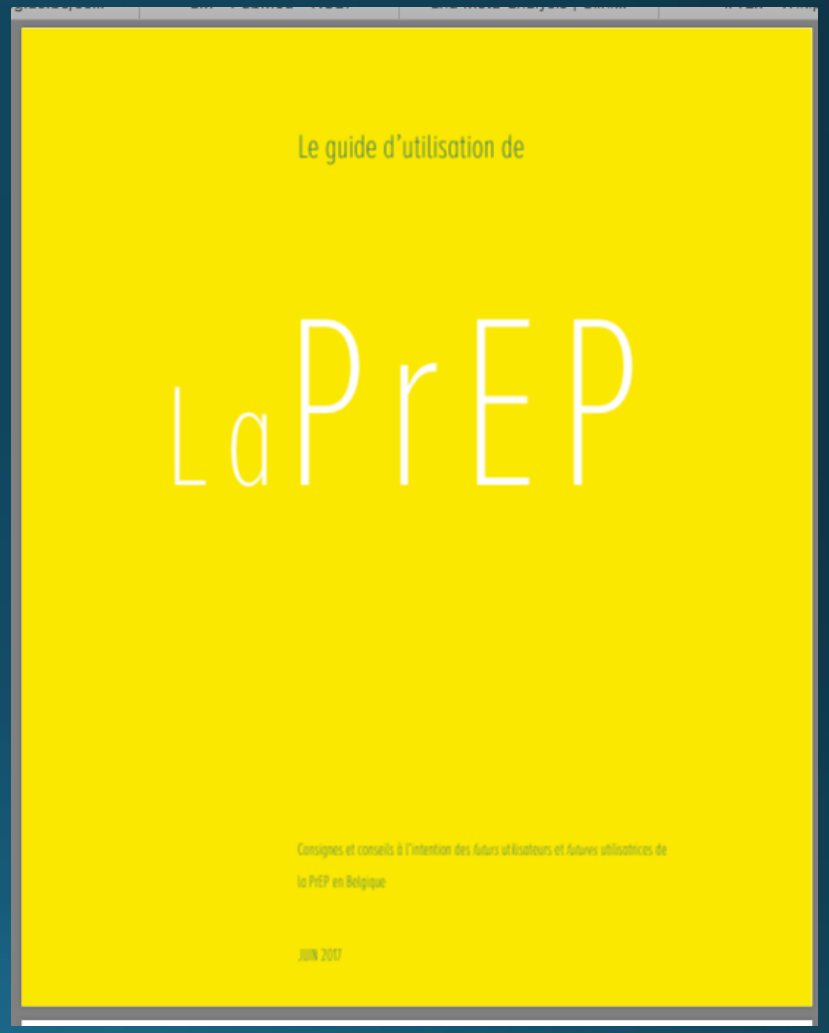
- Adulte de plus de 18ans
- A haut risque d'acquisition du VIH
- Dépistage HIV négatif (test de 4ème génération) dans des délais permettant son interprétation
- Aucun signe de primo-infection

Critères d'exclusion :

- Personnes présentant des symptômes de primo-infection ;
- Personnes ayant eu un test de dépistage positif ou incertain ;
- Personnes vivant avec le VIH (PVVIH).
- Personnes dont la filtration glomérulaire estimée est <60ml/min ;
- Personnes présentant une hypersensibilité à TDF ou au FTC ;
- Personnes ayant une infection HBV chronique (sauf schéma en continu).
- Personnes prenant un traitement post-exposition (TPE) ou des produits médicinaux contenant des substances ayant une activité antirétrovirale
- Traitement en cours avec potentielles interactions médicamenteuses (critère défini par le médecin au cas par cas)
- Sujets faisant partie d'un groupe dont la prévalence du VIH<1%

En pratique…

- Proposition d'encadrement de la prise de PrEP
- Accompagnement médical
- Accompagnement pluridisciplinaire (social, psychologique)
- Accompagnement communautaire



	Jo	J+28	3M	6M	9M	12M
Anamnèse	X	X	X	X	X	X
Examen clinique	X	X	X	X	X	X
Hémogramme	X		X			X
Fonction rénale Tests hépatiques	X		X	X	X	X
Urinaire	X			X		X
Sérologie HIV	X	X	X	X	X	X
Sérologie syphilis, HCV	X	X	X	X	X	X
Prélèvements Chlam/gono	X		X	X	X	X
Vaccination SN						
Prescription PrEP		X	X	X	X	X
Counseling + distribution	X	X	X	X	X	X

CSIRO PUBLISHING

Sexual Health
https://doi.org/10.1071/SH18071

Short report

High uptake of pre-exposure prophylaxis (PrEP) during early roll-out in Belgium: results from surveillance reports

Bea Vuylsteke
Jessika Deblonde
Jean-Christophe
Steven Callens

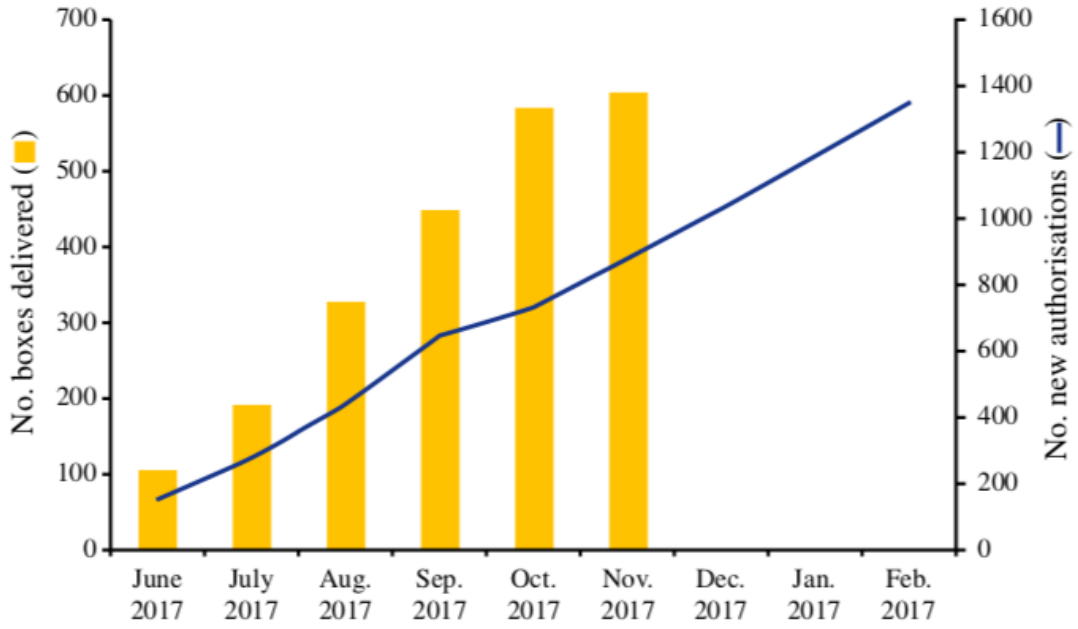


Fig. 1. Cumulative number of new authorisations for reimbursement issued and the number of boxes of Truvada (Gilead Sciences, Cambridge, UK) (30 tablets in each box) delivered in Belgian pharmacies for pre-exposure prophylaxis (PrEP) indication.

Données PrEP à Liège

	Cis
F	2
M	135

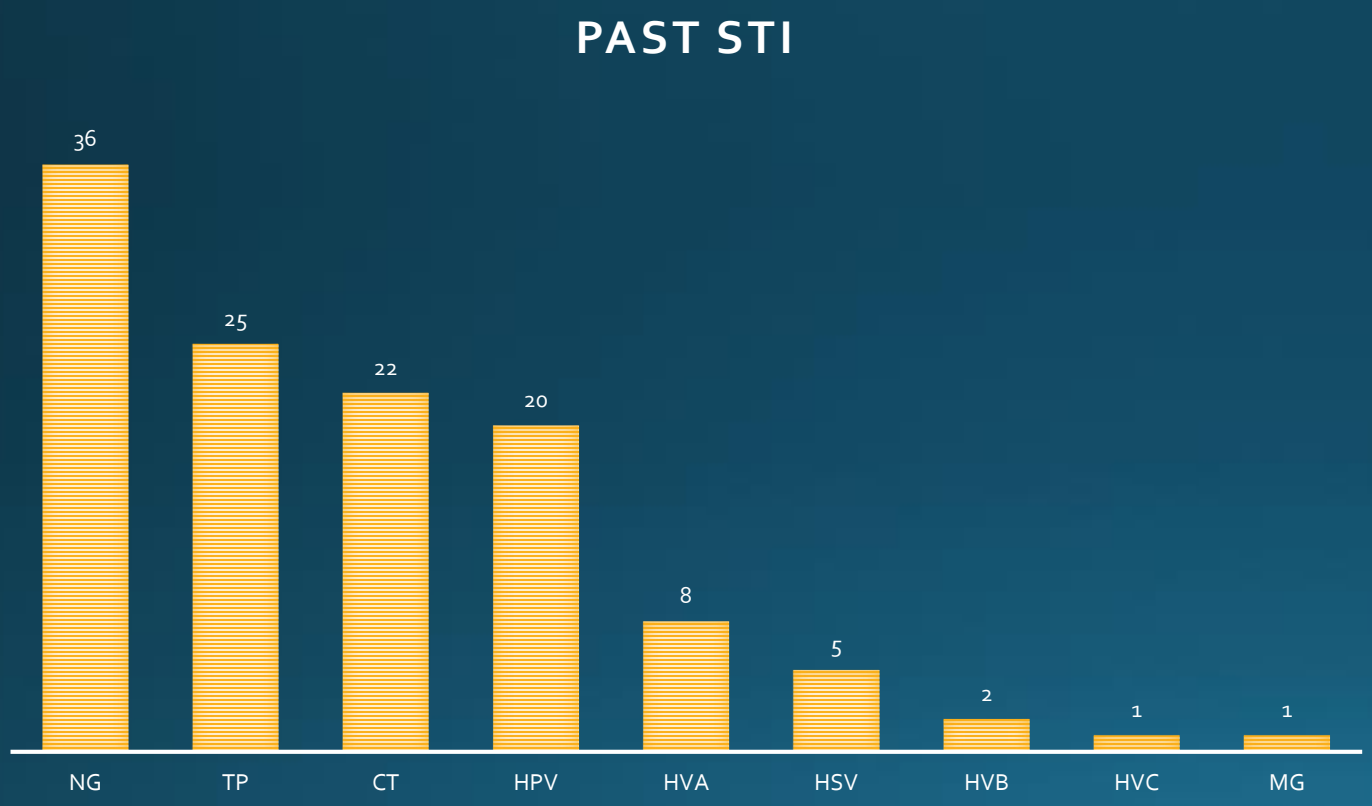
Origin (n=136)	
Belge	77,2 %
Européenne	16,2 %
SAM	1,47 %
Autre	5,15 %

Sexual orientation (n=137)	
Bi	7,30 %
Hétéro	4,38 %
Homo	88,3 %

Chemsex (n=135)	**Prostitution** (n=136)	**N partner** (n=136)	**Past STI** (n=135)	**Past PEP** (n=137)
25,9 %	2,21%	X = 40 M = 20	62,96%	27,0 %

UPS with S/C partners (n=135)	**STI Co** (n=137)
91,1 %	25,5 %

STIs



STI during follow-up 2017 (n=93)
8,60%

STI during follow-up 2018 (n=137)
10,90%

Regimen

Regimen C2 (n=112)	
Daily	22,32%
On demand	77,68%

Refusal, stop or break

Reasons

- Risk decrease / relationship changes
- Confidentiality
- Cost
- Moving abroad
- Not interested
- Cancelation
- Cons-indications
- Seroconversion

Stop/break in 2017 (n=93)	**Stop/break in 2018** (n=44)
19,3 %	4,54 %

Merci de votre attention