

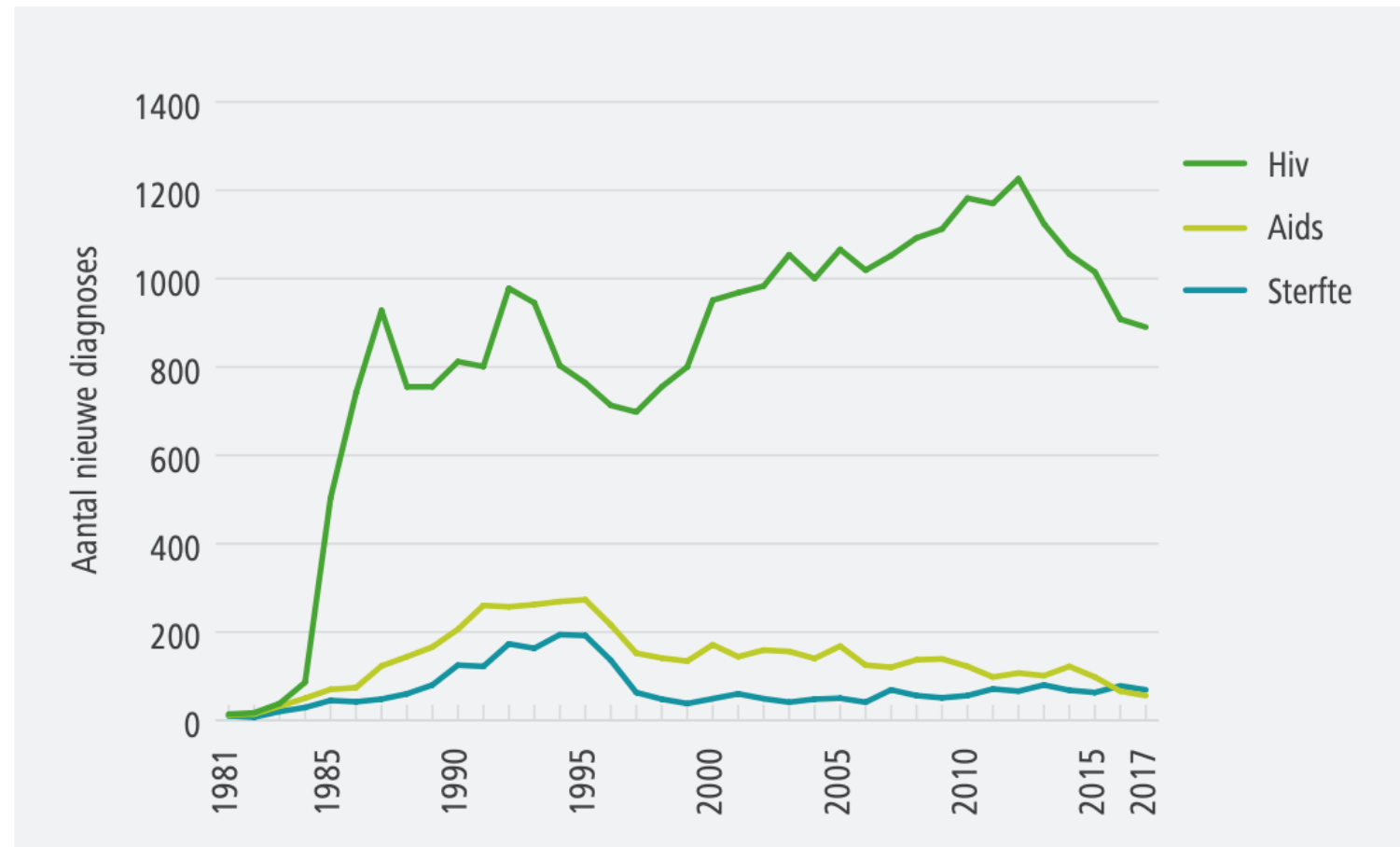
Rol van antiretrovirale therapie in preventie

S. Callens
Dept. Algemene Inwendige Ziekten



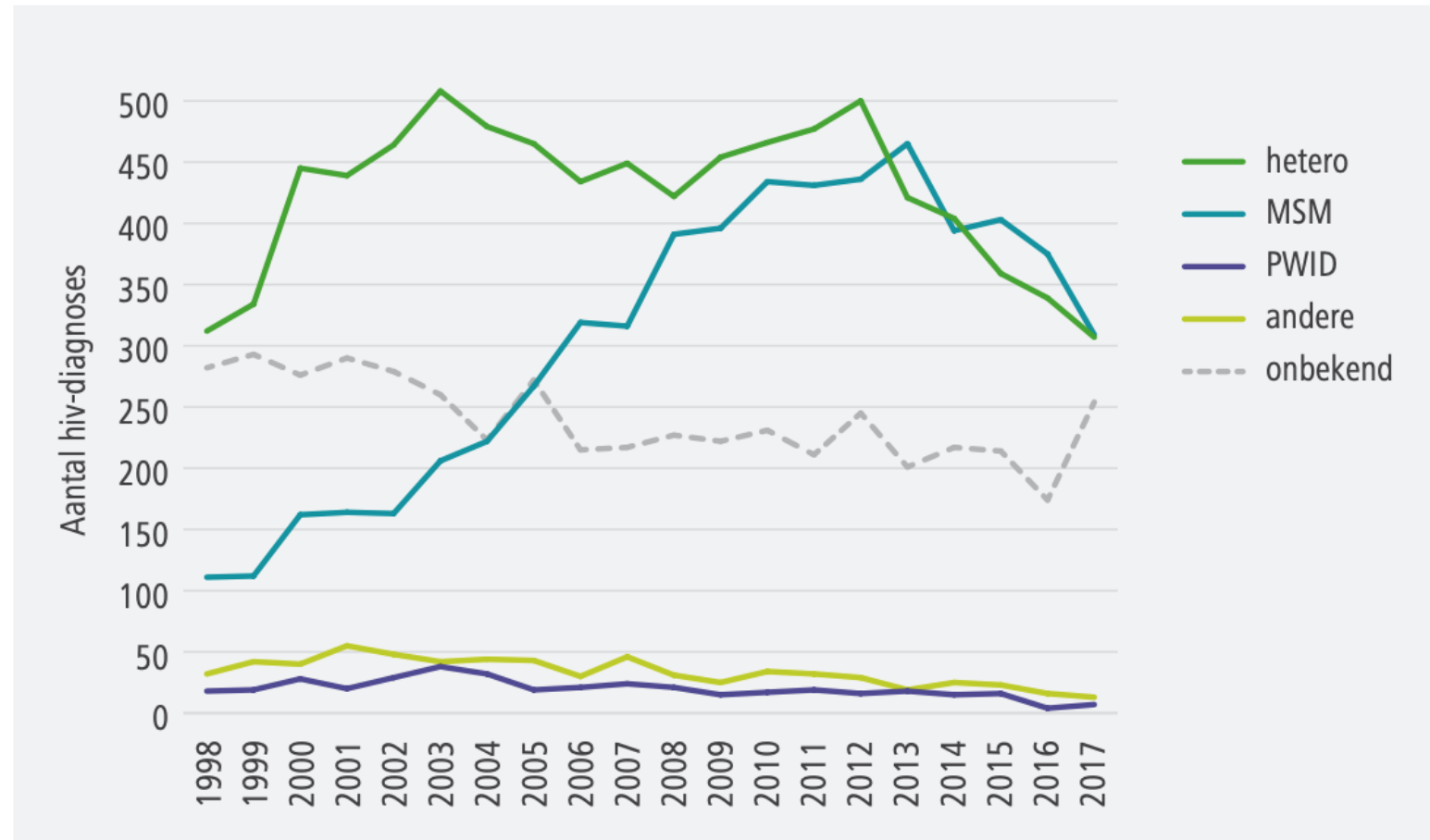
HIV in België

Figuur 1 | Jaarlijks aantal nieuwe hiv- en aids-diagnoses en gerapporteerde sterfte, België 1982-2017



HIV in België

Figuur 5 | Evolutie van het jaarlijks aantal nieuwe diagnoses per overdrachtswijze, België 1998-2017





HIV transmission: Window of (Prevention) Opportunity

Semen

● **NSI HIV (M-tropic)**
● **SI HIV (T-tropic)**

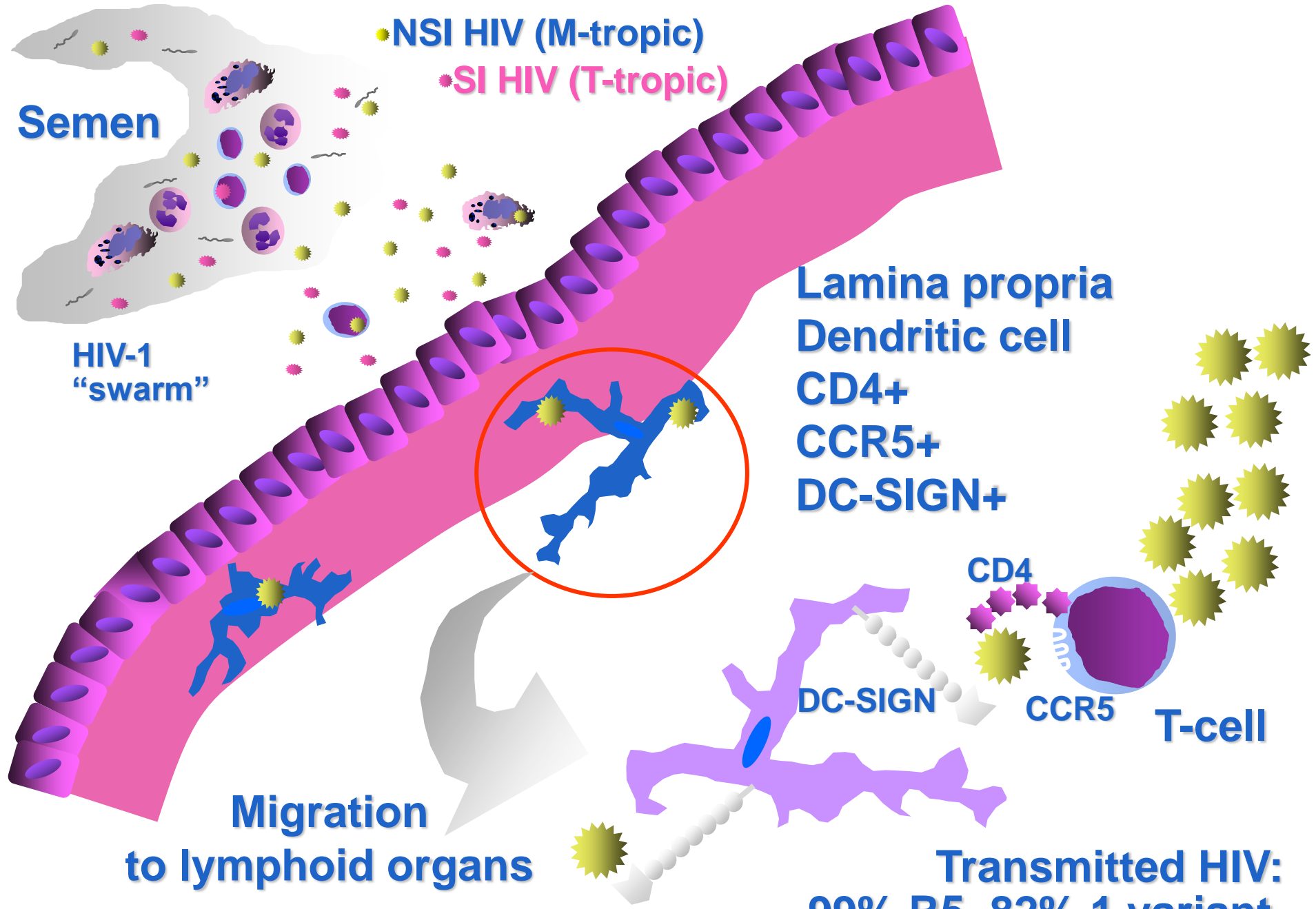
**HIV-1
"swarm"**

**Lamina propria
Dendritic cell
CD4+
CCR5+
DC-SIGN+**

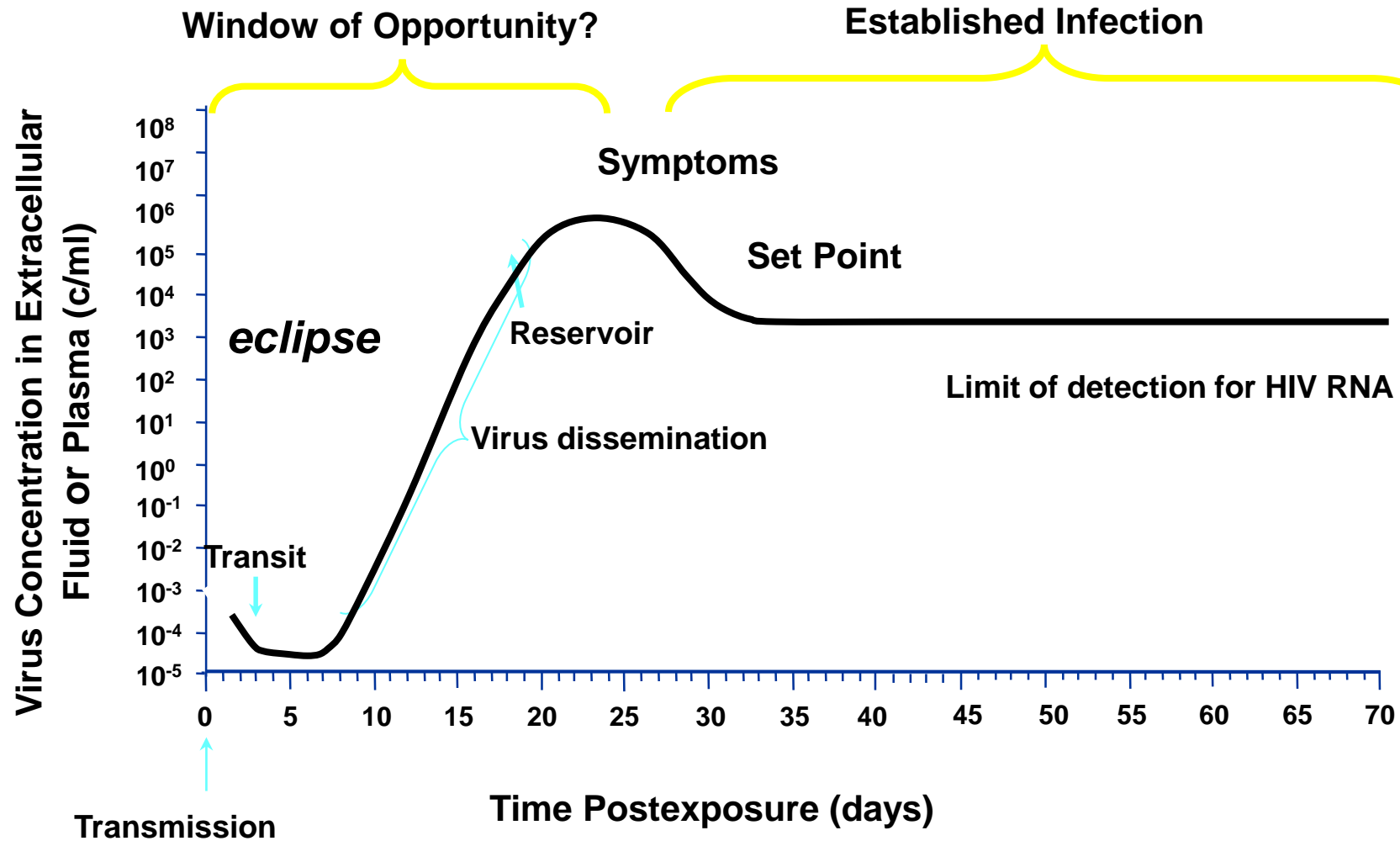
**Migration
to lymphoid organs**

**CD4
DC-SIGN
CCR5
T-cell**

**Transmitted HIV:
99% R5, 82% 1 variant**



HIV-1 Acquisition and Acute Infection





Shifting paradigms in HIV Prevention

Clinical trial evidence for preventing sexual HIV transmission –2011

Study

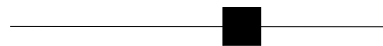
Effect size (CI)

Medical male circumcision
(Orange Farm, Rakai, Kisumu)



54% (38; 66)

HIV Vaccine
(Thailand)



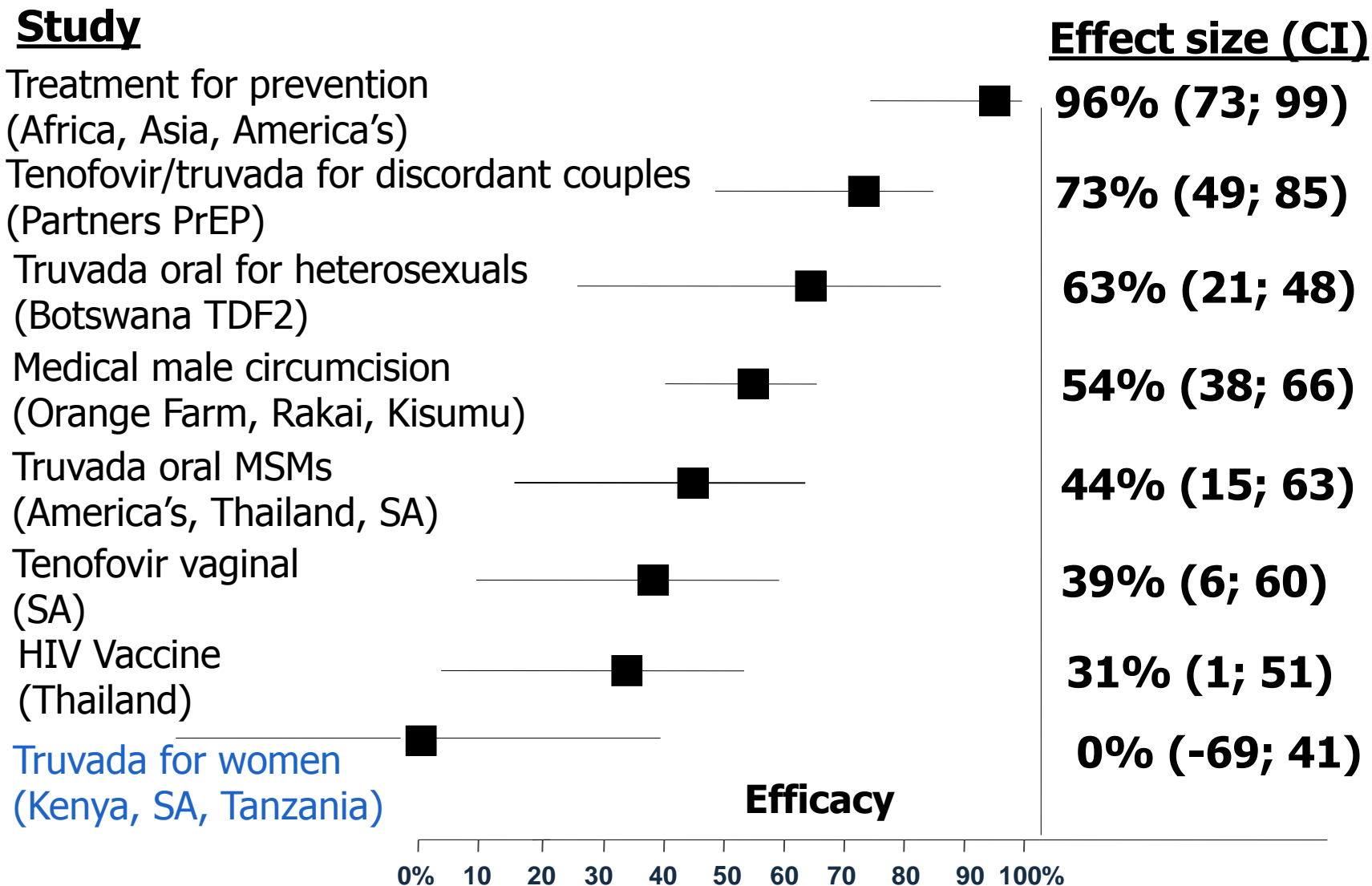
31% (1; 51)

Efficacy

0% 10 20 30 40 50 60 70 80 90 100%

Modified from Slim Karim 6th Transmission Workshop, 2011

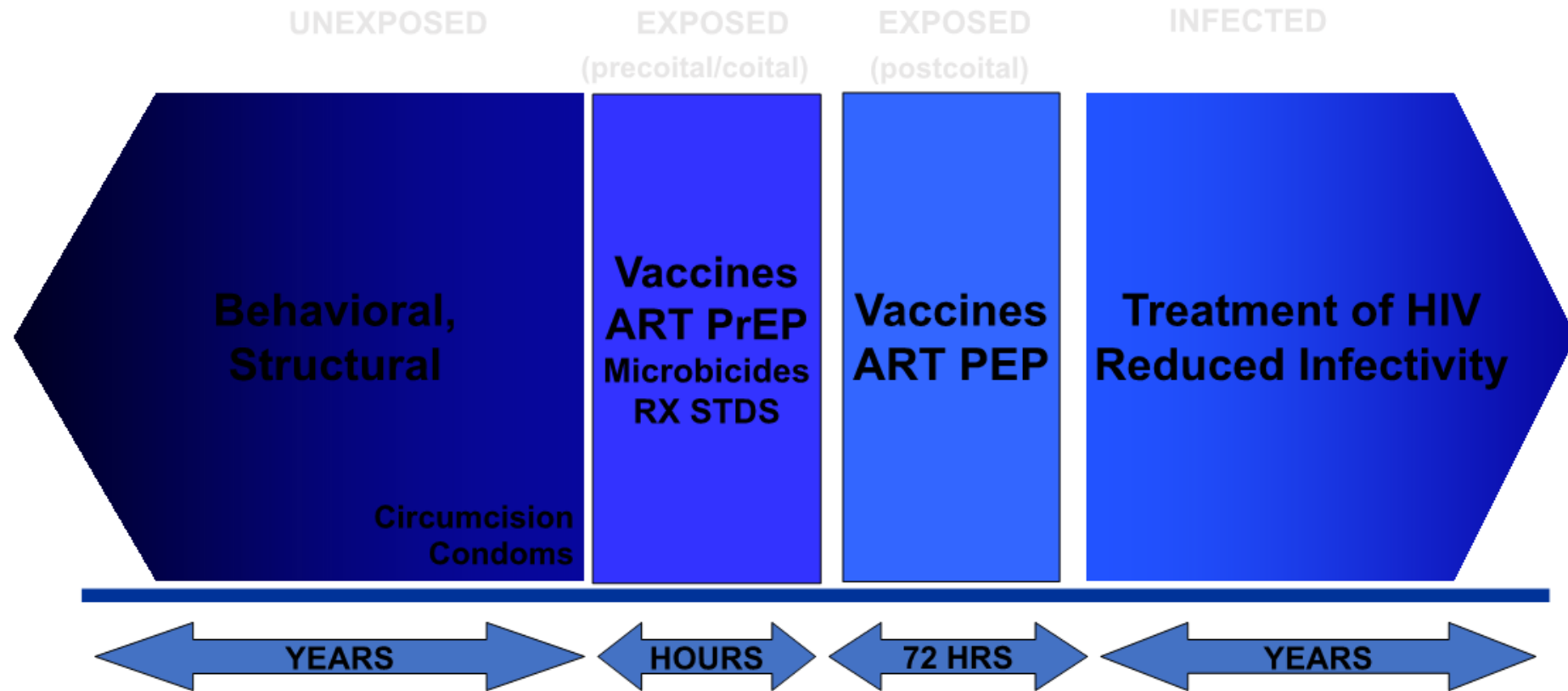
Clinical trial evidence for preventing sexual HIV transmission –2011



Modified from Slim Karim 6th Transmission Workshop, 2011

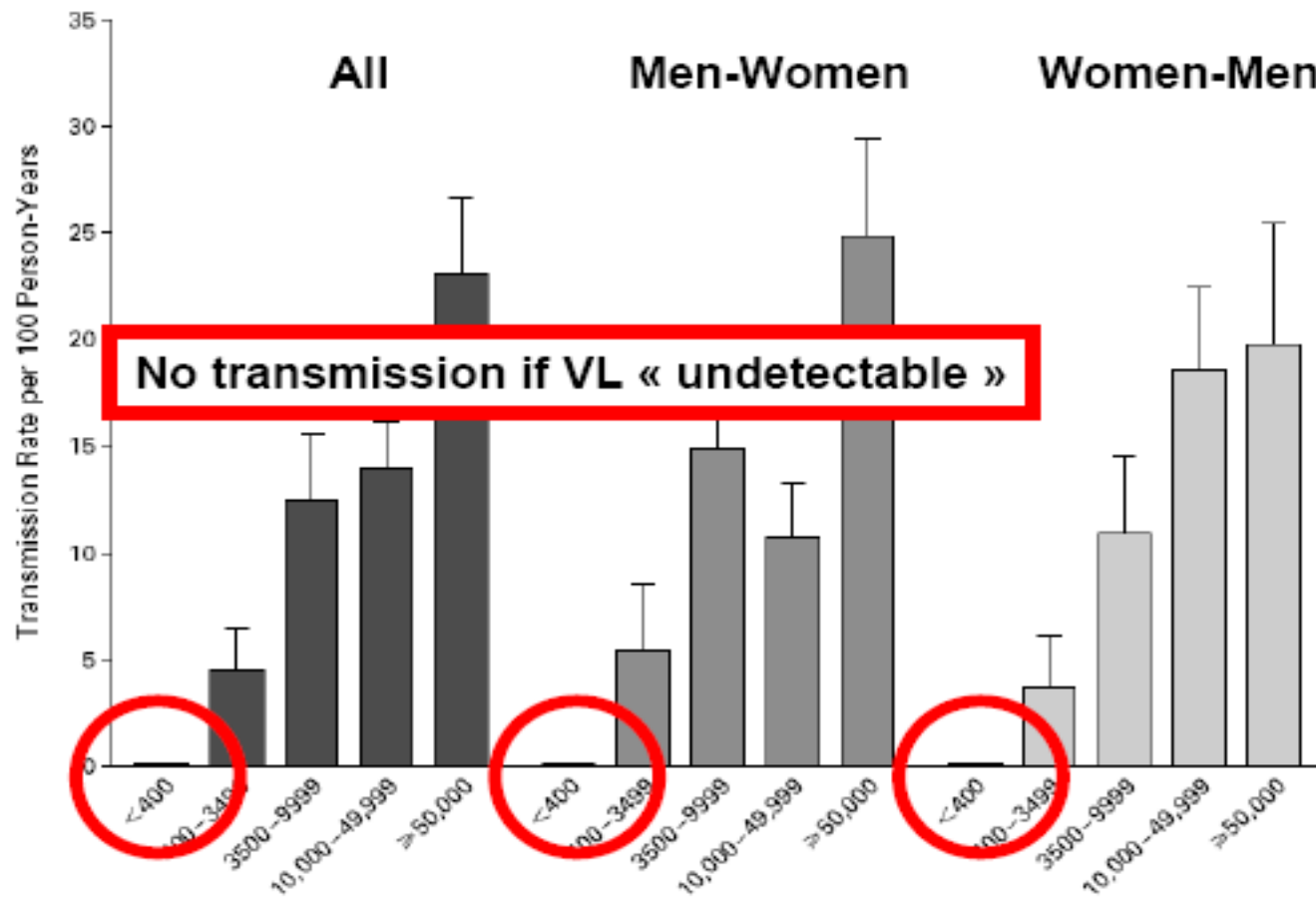
Four HIV-1 Prevention Opportunities

Cohen et al. JCI 2008; Cohen. IAS Journal online 2008





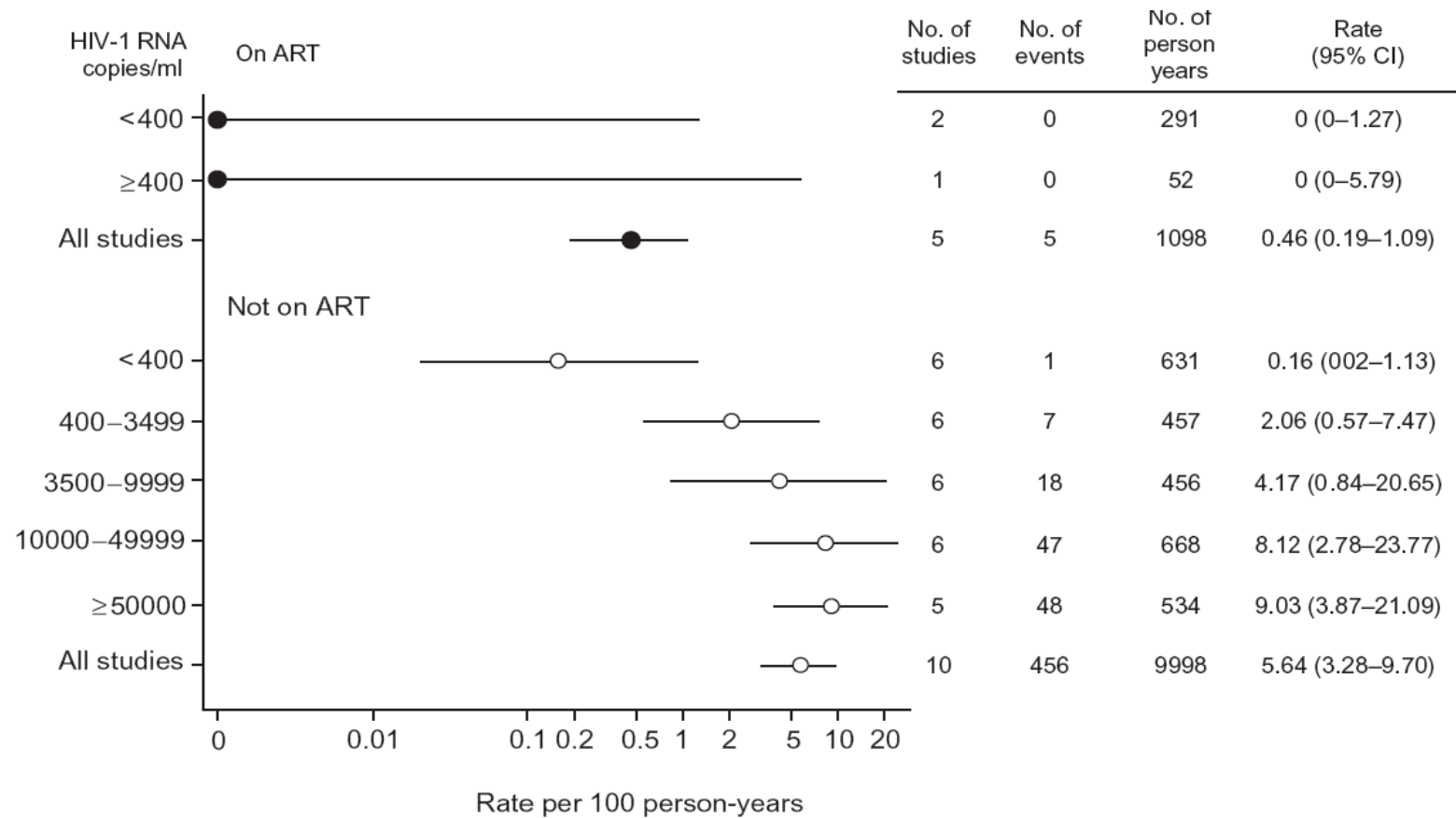
Treatment as Prevention



« Rakai » Study: Transmission risk as a function of viral load

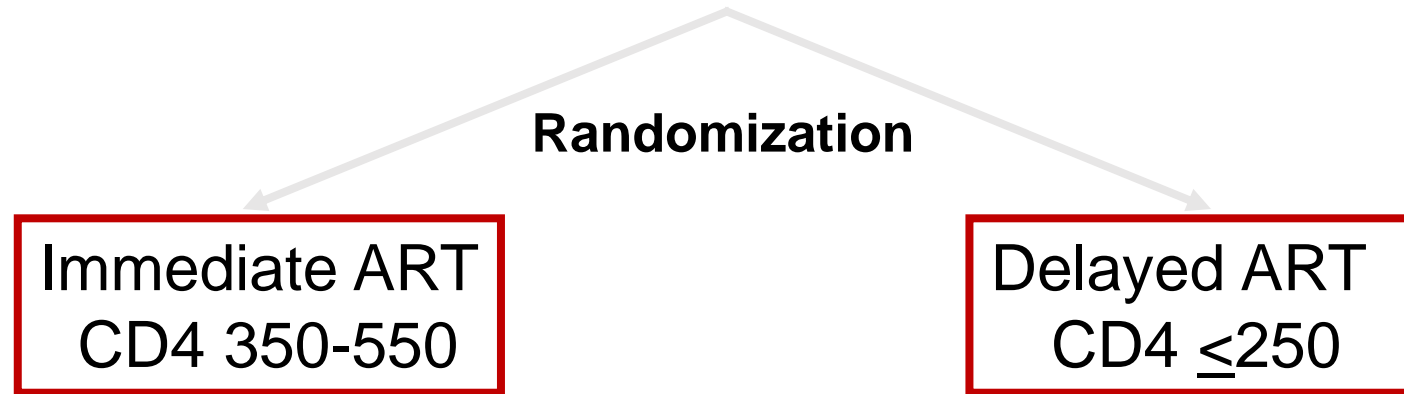
Quinn et al. *N Engl J Med* 2000;342:921-9

Meta-analysis: ART and viral load and transmission



HPTN 052 Study Design

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³

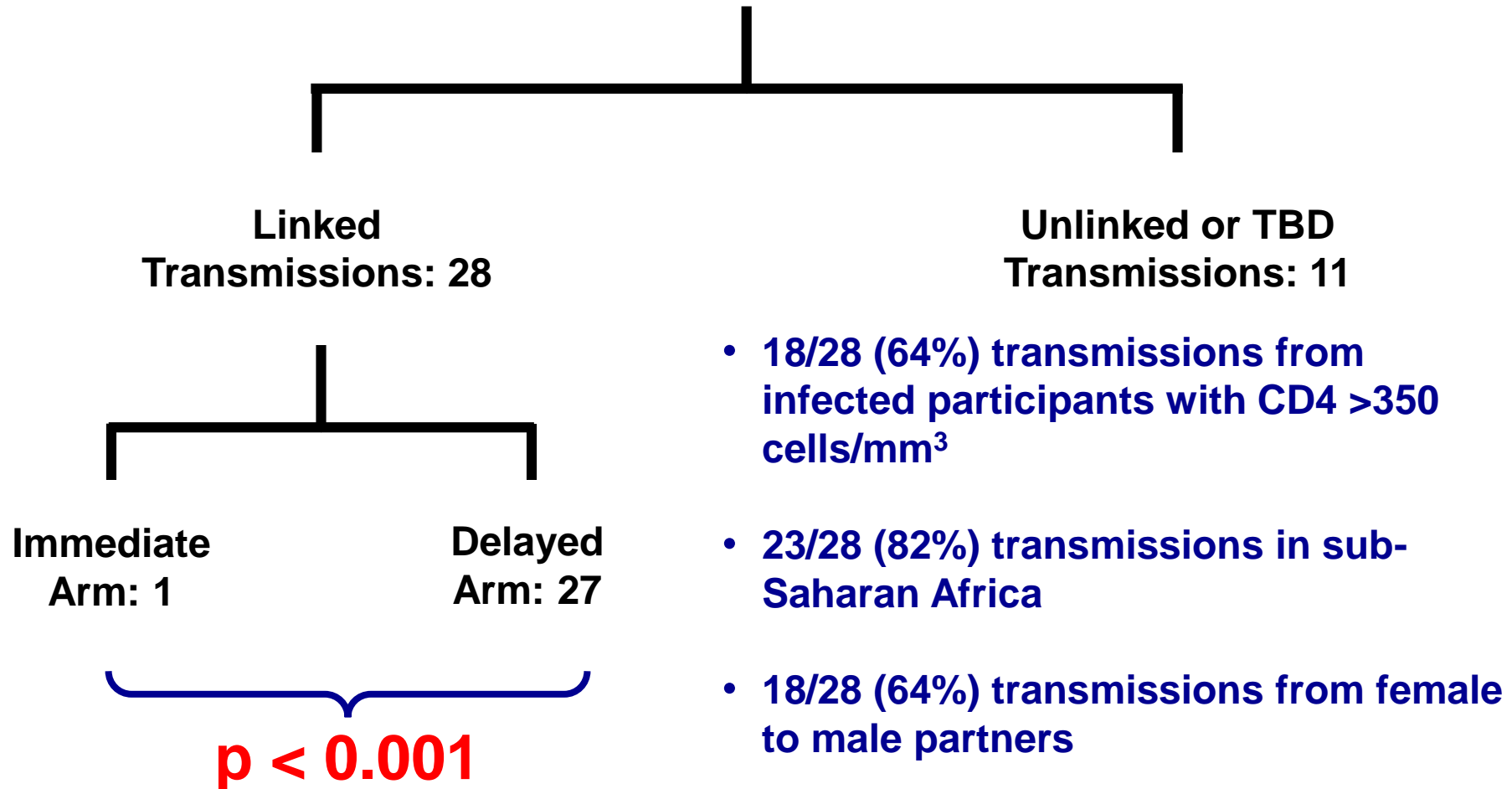


Primary Transmission Endpoint
Virologically-linked transmission events

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

HPTN 052: HIV-1 Transmission

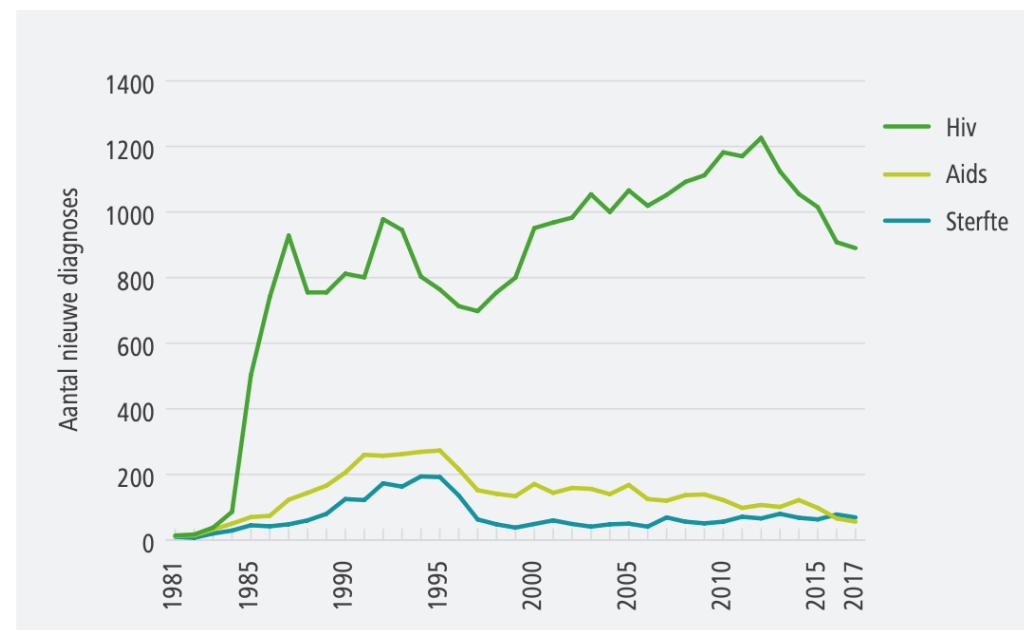
Total HIV-1 Transmission Events: 39



In Belgium

- ▶ In this legislature, reimbursement for all people living with HIV regardless of CD4 count
- ▶ Prescribed in HIV reference centres

Figuur 1 | Jaarlijks aantal nieuwe hiv- en aids-diagnoses en gerapporteerde sterfte, België 1982-2017



Implications for GP

- ▶ Test for HIV – include sexual health into consultation whenever possible
- ▶ Condom use
- ▶ Pregnancy



**Hoge
Gezondheidsraad**

**HERZIENING VAN ADVIES 8902 VAN DE HGR
BETREFFENDE HET CONDOOMGEBRUIK
TER VOORKOMING VAN HIV BESMETTING
BIJ SERODISCORDANTE PARTNERS WAARBIJ
DE BESMETTE PERSOON EEN ANTIRETROVIRALE
BEHANDELING VOLGT**

**FEBRUARI 2019
HGR NR. 9517**

3. ADVIES VAN DE HGR

Als antwoord op de adviesaanvraag over de update van het vorige advies van de HGR (8902 van 2013) in verband met het condoomgebruik bij serodiscordante koppels en rekening houdend met de evolutie van de epidemiologische en wetenschappelijke kennis sindsdien, raadt de HGR de autoriteiten bevoegd voor de informatiecampagnes de volgende aanpak aan:

in geval van een relatie tussen twee HIV-serodiscordante partners van wie de seropositive partner:

- een cART-therapie volgt die heeft geleid tot een ondetecteerbare virale lading (virale lading \leq **50 virale kopieën/mL**);
- **nauwgezet en volledig zijn behandeling en de medische follow-up naleeft** (evaluatie van therapietrouw);

is het niet meer nodig om een condoom te gebruiken (bijvoorbeeld indien het koppel een kinderwens heeft¹, hun levenskwaliteit willen verhogen, hun seksleven en welzijn willen verbeteren enz.).

Aangezien het serologische statuut van de andere partner (gekend als niet-drager van HIV) voor andere seksueel overdraagbare aandoeningen (SOA's) niet gekend is, **raadt de HGR nog altijd aan om een condoom te gebruiken in het kader van de preventie van de overdracht van SOA's**, zoals ook wordt aangeraden door andere Belgische en internationale medische instanties.

Bovendien is er sinds enkele jaren een merkbare stijging van de prevalentie van SOA's, zowel in België als internationaal.

Opsporing (van HBV, HCV, syfilis en bepaalde andere SOA's) bij de twee partners moet dus altijd worden aanbevolen aan de hand van het risicoprofiel dat de arts heeft opgesteld en volgens de bestaande richtlijnen.

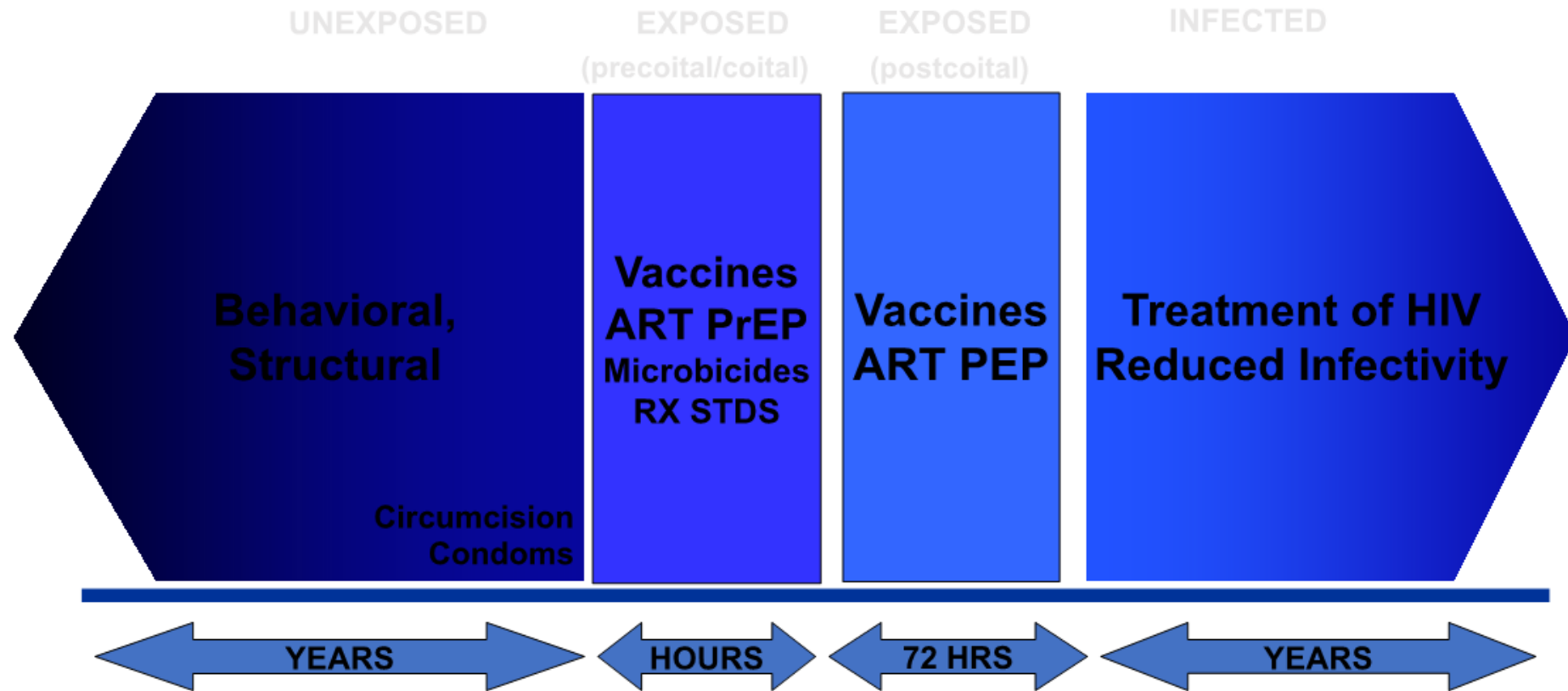
Daar waar andere SOA's doorgaans de transmissie van HIV vergemakkelijken, wijst de recente literatuur erop dat bij een ondetecteerbare virale lading HIV niet wordt overgedragen zelfs in aanwezigheid van andere SOA's (Bavito *et al.*, 2018; Rodger *et al.*, 2016).



Post-exposure Prophylaxis

Four HIV-1 Prevention Opportunities

Cohen et al. JCI 2008; Cohen. IAS Journal online 2008



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

- ▶ Based on animal models & cohort studies – **72 h window and 28 treatment period**
- ▶ **Decisions should be taken on a case by case basis**, taking into account the kind of risk the patient has encountered and factors increasing the risk of transmission.
 - ▶ NONOPEP is recommended when there is a significant risk of HIV transmission (risk > 1/1000).
 - ▶ NONOPEP may be considered if the transmission risk is between 1/1000 and 1/10,000.
 - ▶ NONOPEP is not recommended if the transmission risk is < 1/10.000.
- ▶ **Establish the HIV status of the source.**
- ▶ **NONOPEP is not recommended**
 - ▶ Sustained (>6 months) plasma viral load (pVL)<200 copies/ml.
 - ▶ In case of fellatio with ejaculation as the risk of transmission is estimated to be < 1/10.000 (except if suspicion of primary infection and oropharyngeal trauma).
- ▶ Mostly used in **MSM with breach of barrier method (condom) or sexual violence**

GP implication

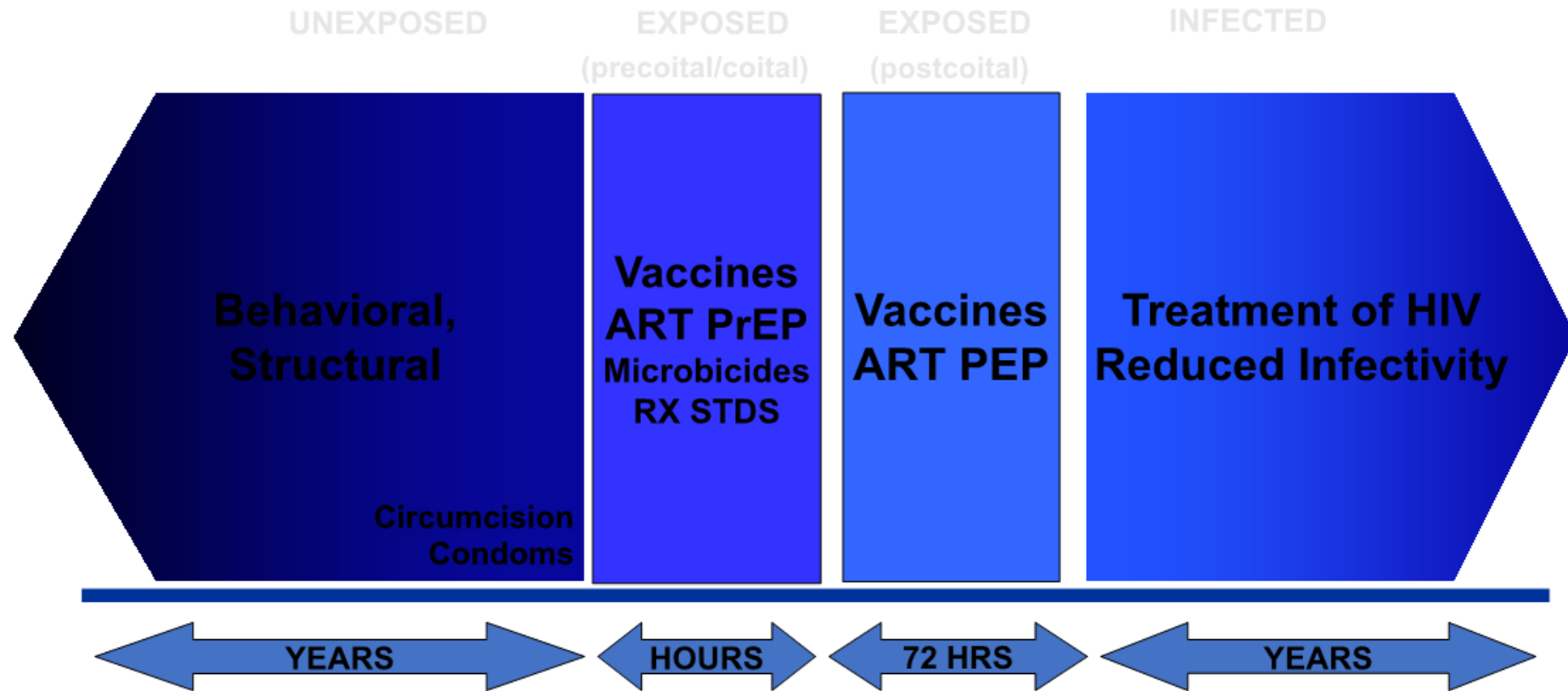
- ▶ Refer patient within 72 hour window period to ER department to assess the risk and start PEP if applicable



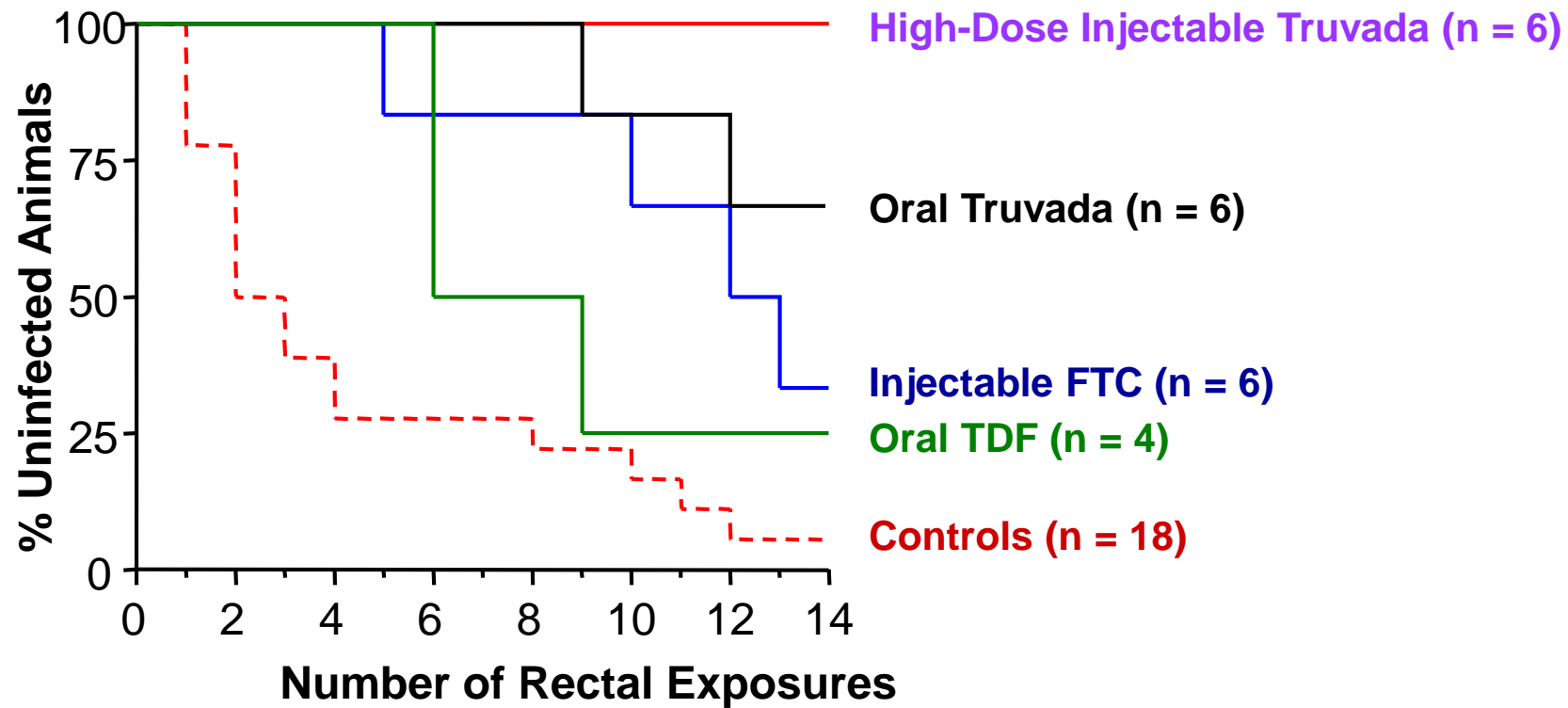
Pre-exposure Prophylaxis

Four HIV-1 Prevention Opportunities

Cohen et al. JCI 2008; Cohen. IAS Journal online 2008



PrEP in Macaques



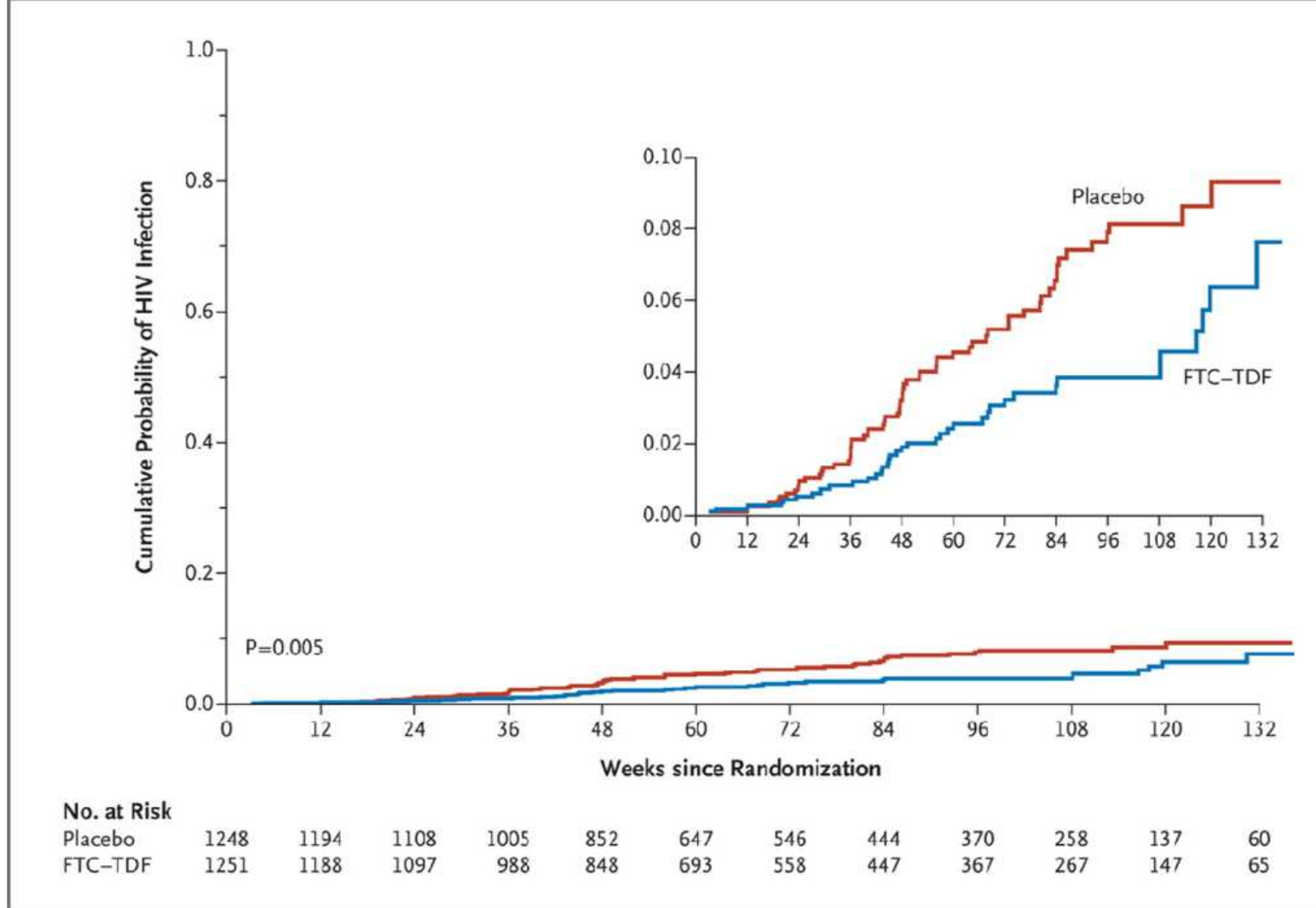
iPrEX Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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 Caceres, M.Sc., Matthew Cohen, M.D., M.P.H.



- 44% reduction in HIV (95% CI: 15-63%) (p=0.005)
- 58%reduction (95% CI: 32-74%)(p=0.01) if reported URAI in 6m preceding enrolment

FEM-PREP – closed on 18 April 2011

Equal numbers of HIV seroconversions (28 each gp)

- Women from Kenya, South Africa and Tanzania, many of whom were commercial sex workers
- Daily truvada (tenofovir + emtricitabine)
- 28 seroconversions in each group (estimated 95% CI for HR: 0.59-1.69)
- Higher pregnancy rate in the women taking truvada
- Self-reported adherence ~ 95% overall

Partners PrEP Study



4758 HIV serodiscordant couples
(HIV+ partner not yet medically eligible for ART)



Randomize HIV- partners
(normal liver, renal, hematologic function)

TDF once daily

FTC/TDF once daily

Placebo once daily

All receiving comprehensive

HIV prevention services



Follow couples for up to 36 months

1° endpoint: HIV infection in HIV- partner
Co- 1° endpoint: Safety

Primary efficacy results

- Primary analysis: modified intention-to-treat (mITT)
 - excluding infections present at randomization (3 TDF, 3 FTC/TDF, 6 placebo)

	TDF	FTC/TDF	Placebo
Number of HIV infections	18	13	47
HIV incidence , per 100 person-years	0.74	0.53	1.92
HIV protection efficacy, vs placebo	62%	73%	
95% CI	(34-78%)	(49-85%)	
p-value	0.0003	<0.0001	
Z-score, vs. $H_0=0.7$	-2.17	-2.99	



***Effect of TDF and FTC/TDF
statistically similar (p=0.18)***

Subgroup analysis - gender

- Both TDF and FTC/TDF significantly reduced HIV risk in both men and women

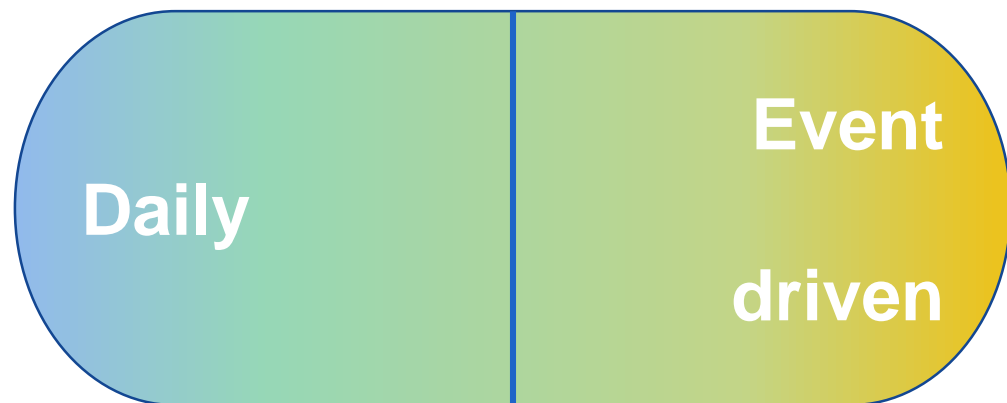
Women: 42 total infections: 8 TDF, 9 FTC/TDF, 25 placebo

Men: 36 infections: 10 TDF, 4 FTC/TDF, 22 placebo

	Efficacy	95% CI	P-value	Interaction p-value
TDF				
Women	68%	29-85%	p=0.01	p=0.54
Men	55%	4-79%	p=0.04	
FTC/TDF				
Women	62%	19-82%	p=0.01	p=0.24
Men	83%	49-94%	p=0.001	



Daily and event driven PrEP



2 days/pills before and 2 days after (Men)
7 days before and 7 days after (Women)

Be-PrEP-ared:

- ▶ Initial choices: 76% daily, 24% event-driven
- ▶ 44 /200 participants changed their regimen at least once
- ▶ Adaptation of use to their own needs
- ▶ Key issue is how to start/stop safely
- ▶ Simplify guidelines ?

MSM coming forward for PrEP are at high risk for HIV

Final results (N=200)



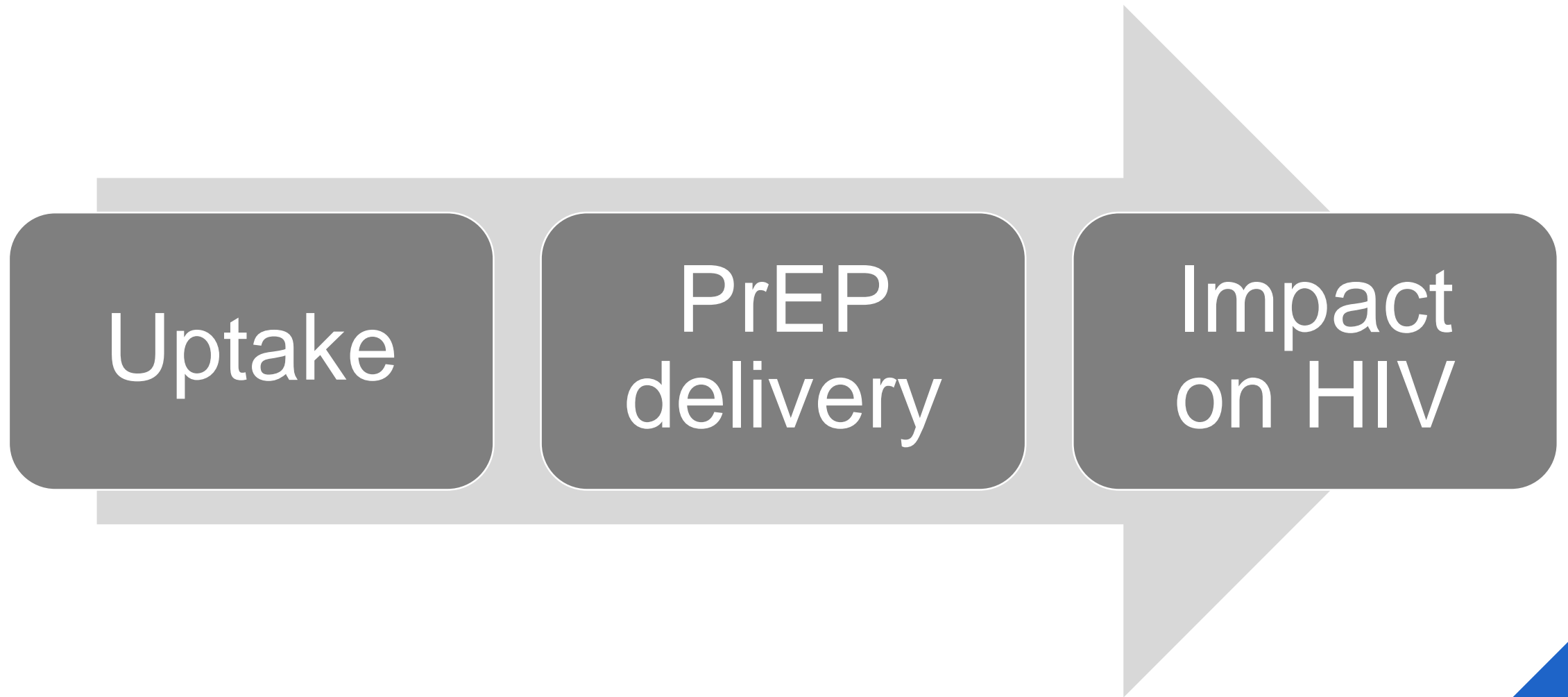
Be-PrEP-ared

- ▶ 8 HIV seroconversions before enrolment

During follow-up:

- ▶ No new HIV infection
- ▶ 94% of all high risk sex contacts covered by PrEP
- ▶ Condom use decreased from 50% to 30% (receptive anal intercourse with anonymous partners)
- ▶ 64% contracted at least 1 bacterial STI (gonorrhoea, chlamydia, syphilis or mycoplasma) and 11 acquired Hepatitis C

The road from efficacy to impact of PrEP

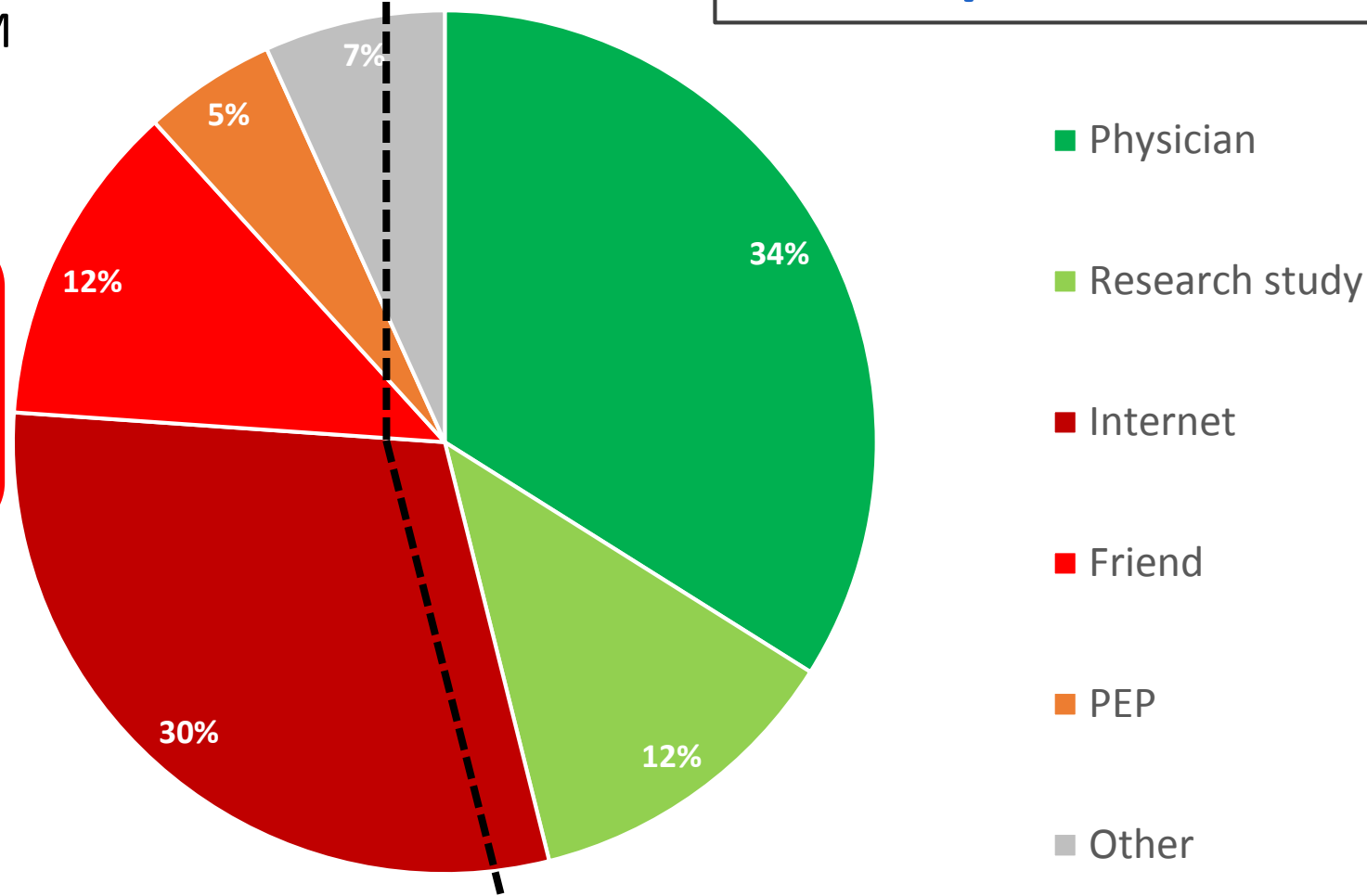


Where do MSM obtain PrEP ?

N=887 (unknown excluded)
Total survey = 12 053 MSM

Results from the 2017 ECDC/Hornet survey on PrEP in Europe and central Asia

**54%
informally
using PrEP**



A Bourne, B Alba, A Garner G Spiteri, A Pharris, T Noori. The use, and likelihood of using, HIV pre-exposure prophylaxis among men who have sex with men in Europe and Central Asia: findings from a 2017 large geosocial networking application survey. STI 2018. In press.

PrEP delivery model in Belgium

ARC is needed for:

- ▶ Screening
- ▶ Counselling
- ▶ Prescriptions
- ▶ 3-monthly follow-up

*On-line survey among 1444 HIV- MSM
(11/2016-3/2017):*

- 28% prefer to go for PrEP in ARC
- 56% prefer to go for PrEP to family physician



Table 1. Number and characteristics of pre-exposure prophylaxis (PrEP) users in seven Aids Reference Centres (ARCs) in Belgium (up to 28 February 2018)

ITM, Institute of Tropical Medicine; CHU, Centre Hospitalier Universitaire (university hospital); UZ, Universitair Ziekenhuis (university hospital); SAM, sub-Saharan African migrants; MSM, men who have sex with men

	No. PrEP users							Total
	Antwerp ITM	Brussels CHU St Pierre	Brussels Hospital Erasme	Brussels UZ	Charleroi CHU	Gent UZ	Liège CHU	
No. started PrEP (at end Feb. 2018)	345	187	152	66	31	157	112	1050
Started before 1 June 2017	0	3	31	0	0	0	10	44
Started after 1 June 2017	345	184	121	66	31	157	102	1006
Risk category								
MSM	345	186	152	66	31	146	105	1031
SAM	0	0	0	0	0	0	2	2
MSM+SAM	0	6	0	0	0	0	1	7
Other	0	1	0	0	0	0	4	5
Unknown	0	0	0	0	0	11	0	0
Regimen chosen at start						A		
Daily	221	103	86	32	22	95	25	584
Event driven	124	82	66	34	9	52	68	435

^A*n* = 147 for UZ Ghent (for 10 people, the starting regimen was not known).

PrEP delivery model in France



Appointment by phone
HIV + STI test 1 wk before visit
Peer counseling by community

Roll-out of PrEP

- ▶ Specialized HIV clinics (hospitals): 1/2016
- ▶ STI clinics (CEGIDD): 6/2016
- ▶ GP can renew prescriptions: 2/2017

Funding support in 2018

PrEP delivery in The Netherlands

- ▶ Public Health Service Amsterdam: AMPrEP (2015) and DISCOVER
- ▶ Informal PrEP delivery by community initiative (2016)

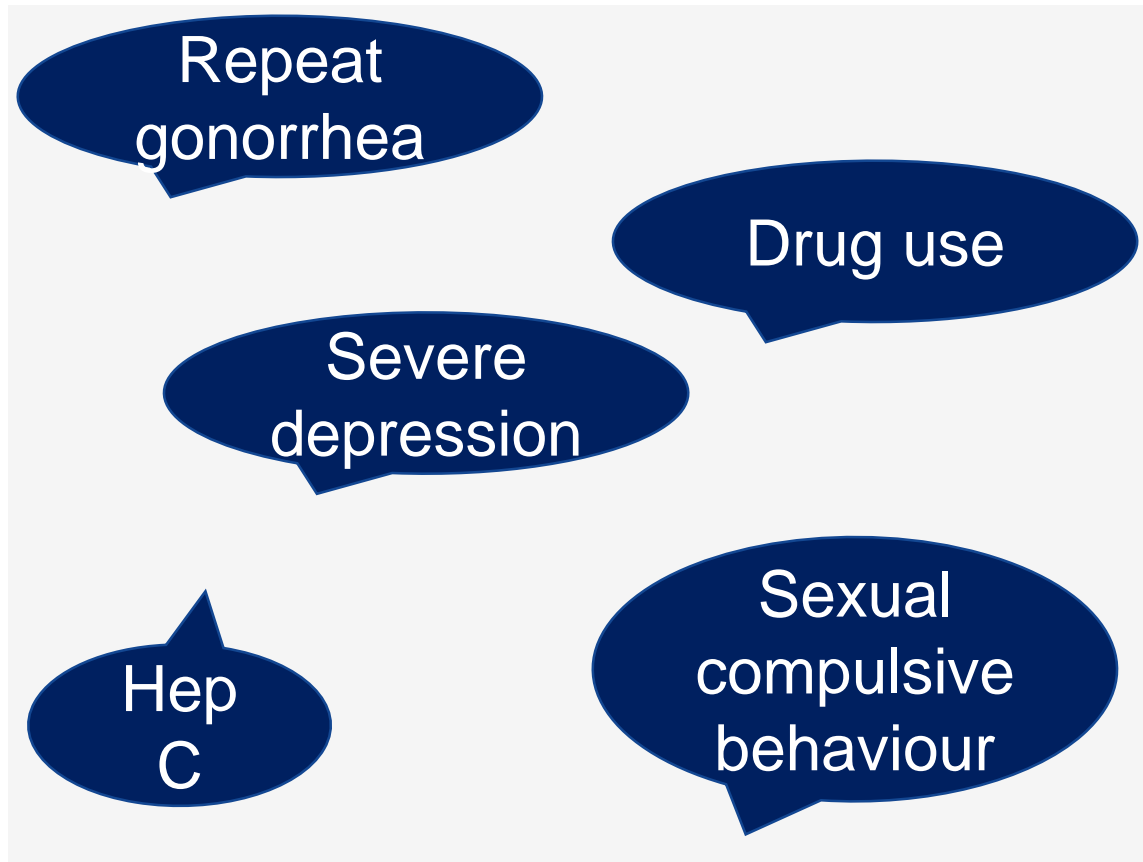
2017: generic PrEP available

- ▶ STI-clinics
- ▶ Some dedicated GP's
- ▶ Specialized HIV centres (PEP-PrEP)

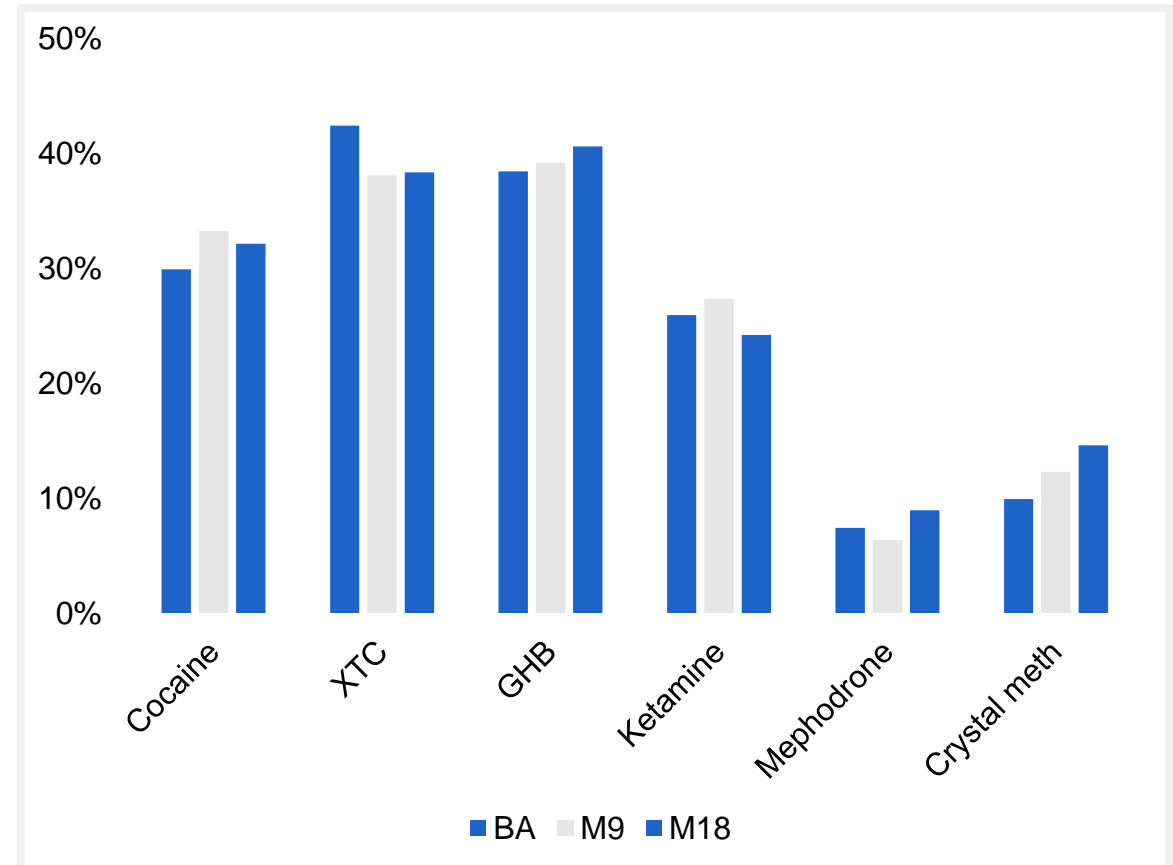


Some PrEP users have more needs than just HIV prevention

Syndemics in PrEP users



Drug use last 3 M (Be-PrEP-ared)



Box 1. Criteria for reimbursement of pre-exposure prophylaxis (PrEP) in Belgium^A

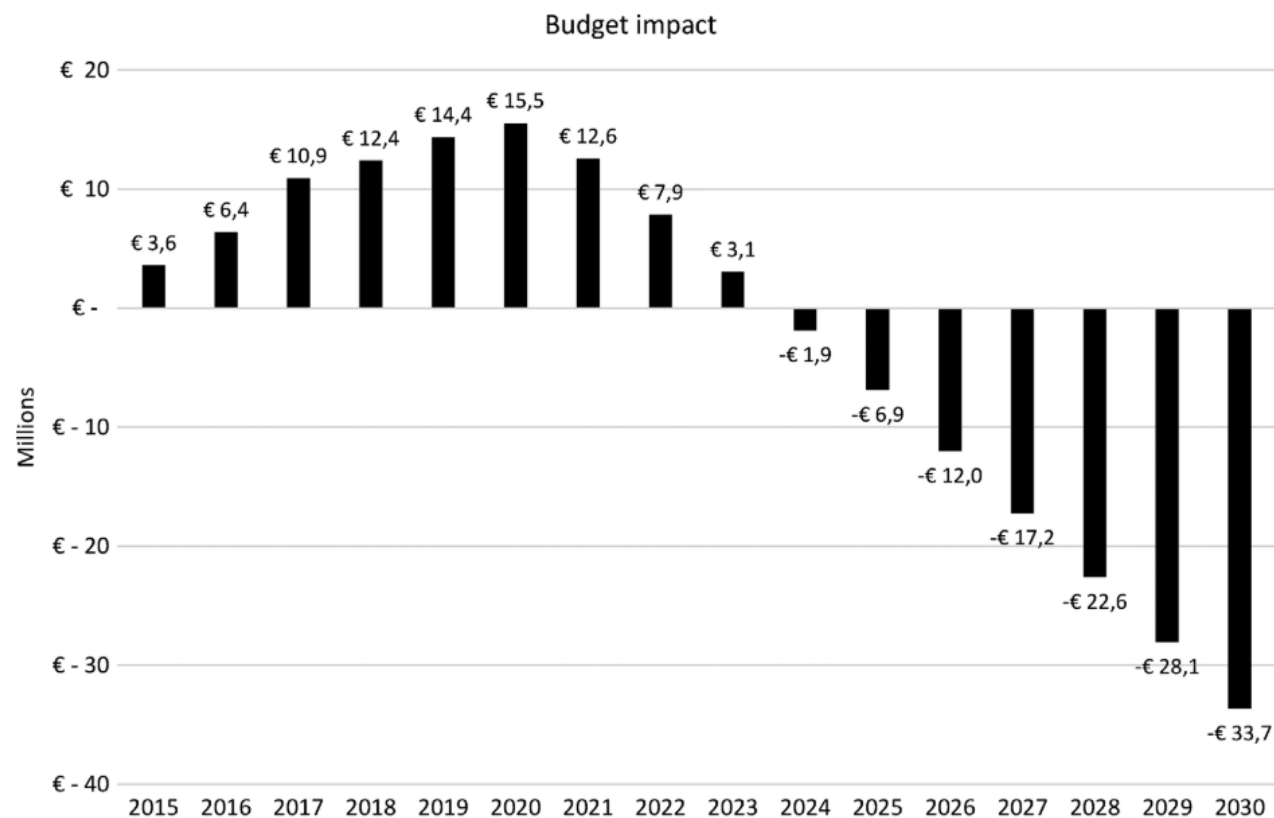
Criteria allowing re-imburement in Belgium:

- For men who have sex with men
 - Having had unprotected anal intercourse with at least two partners in the past 6 months
 - Having had multiple sexually transmissible infections in the past year
 - Having taken post-exposure prophylaxis in the past year
 - Using psychoactive substances during sexual activities
- Other people at high risk of HIV
 - People who inject drugs and share needles
 - Sex workers who are exposed to unprotected sex
 - Partners of HIV-positive people without viral suppression

^AFrom Rijksinstituut voor ziekte – en invaliditeitsverzekering (<http://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/wijzigingen/Paginas/geneesmiddelen-PrEp-HIV.aspx#.WqErna0zU3E>, accessed 5 September 2018).

1 Vuylsteke B, Reyniers T, Lucet C, *et al.* High uptake of pre-exposure prophylaxis (PrEP) during early roll-out in Belgium: results from surveillance reports. *Sex Health* 2018. DOI:10.1071/SH18071.

Savings achieved through combined HIV prevention



Figuur 1 | Jaarlijks aantal nieuwe hiv- en aids-diagnoses en gerapporteerde sterfte, België 1982-2017

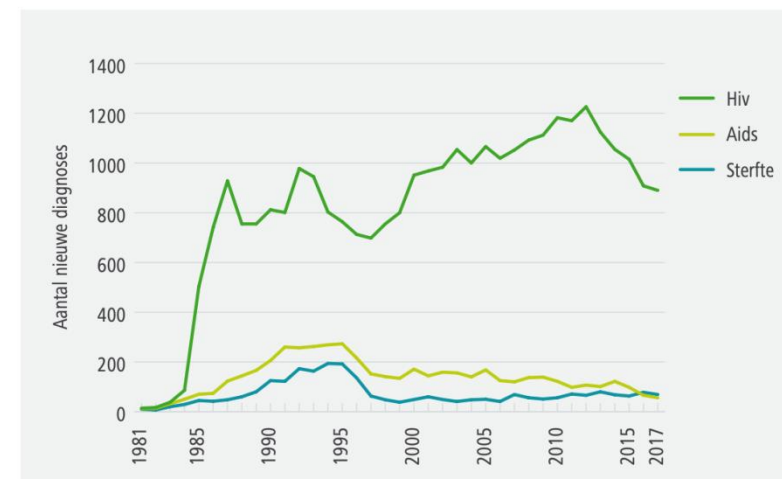
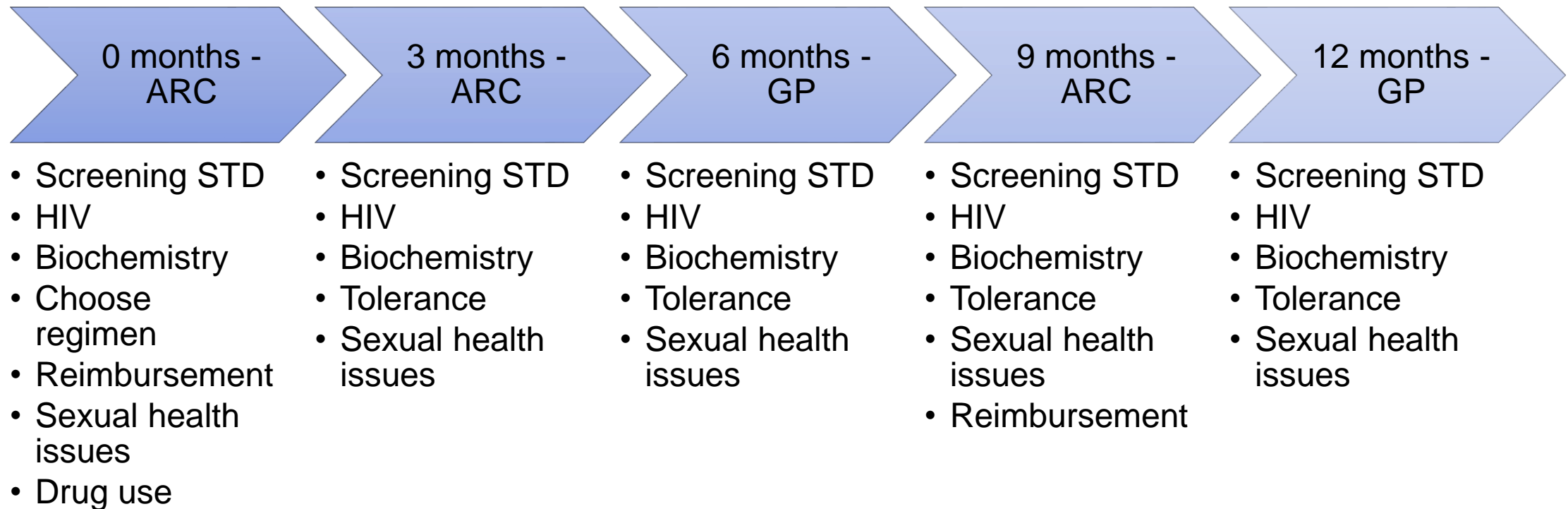


Figure 3. (Top) Yearly estimates for number of new HIV diagnoses for the outreach+TasP+PrEP (new world) vs. no additional prevention (old world) analysis scenario. (Bottom) Yearly estimates of budget impact (outreach+TasP+PrEP additional expenditure/ savings versus no additional prevention).

1 Vermeersch S, Callens S, De Wit S, *et al.* Health and budget impact of combined HIV prevention – first results of the BELHIVPREV model. *Acta Clin Belg* 2017; **3286**: 1–14.

Implications for GP



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Volg ons op

