CURE

Cura- porquê?

Do we need a cure for HIV?

We don't!

- We have excellent treatment
- Focus our funding and science towards prevention, PrEP, Vaccine and long-acting ART
- Access to ART has already reached over 21 million…we are over half way there globally!
- For people well and happy to take ART we don't need to do anything

WE DO?!

- ART needs to be provided lifelong for all PLWH globally
- ***Global instability*** of funding, health care systems, resources, politics, UNAIDS estimate **$26.2 billion annual bill by 2020**
- ART drug resistance threatening the effectiveness of current ART regimens
- ART toxicity eg dolutegravir teratogenicity

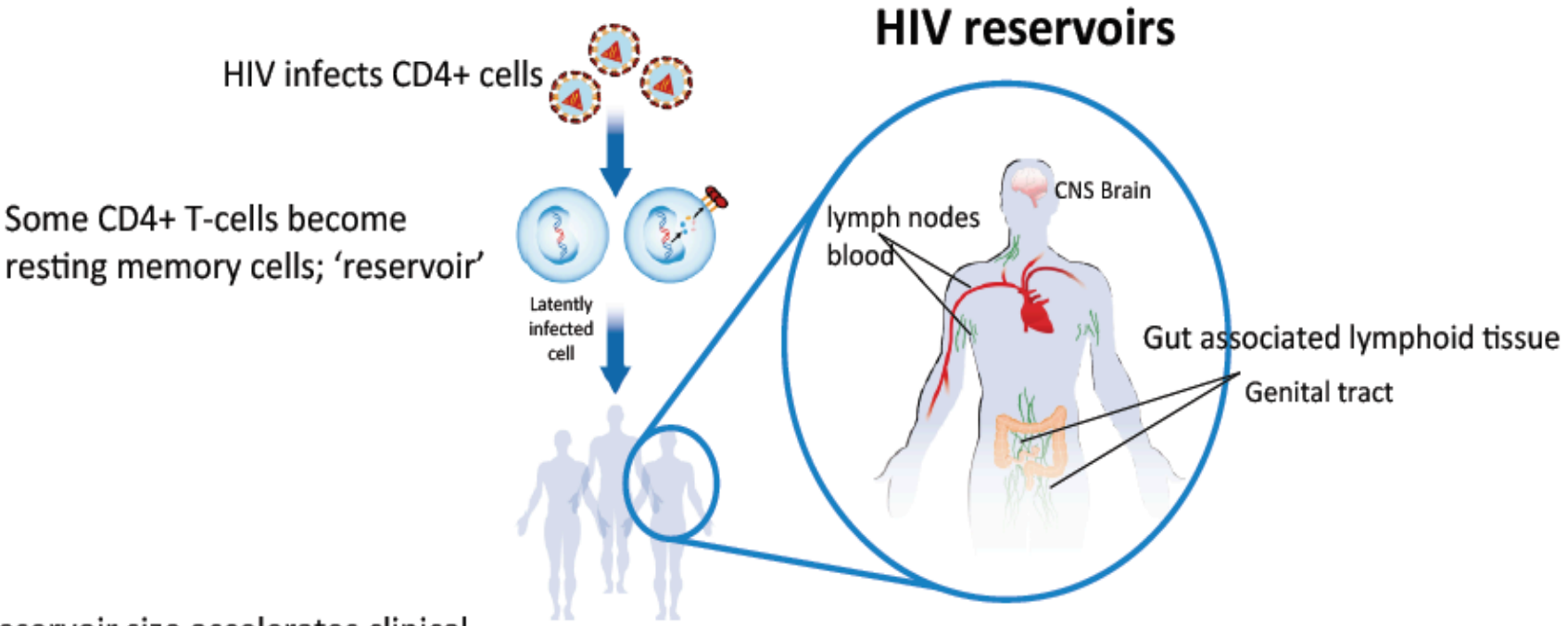
Two types of HIV "Cure"

Sterilising cure → Replication-competent virus eliminated? → Extremely difficult to achieve

Functional cure →
- Host control of viral replication without continued treatment
- Immune function restored and stabilised
- HIV-induced inflammation reduced
- Risk of transmission to others reduced (if low viral load)

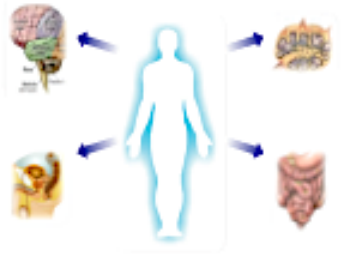
→ More plausible?

Why can't ART cure HIV?



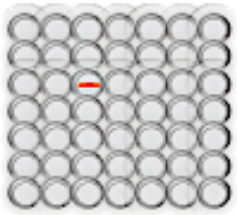
Larger reservoir size accelerates clinical progression
& predicts time to viral rebound

Strategies to cure HIV



HIV persistence in tissues

Eradication strategy should reach tissues



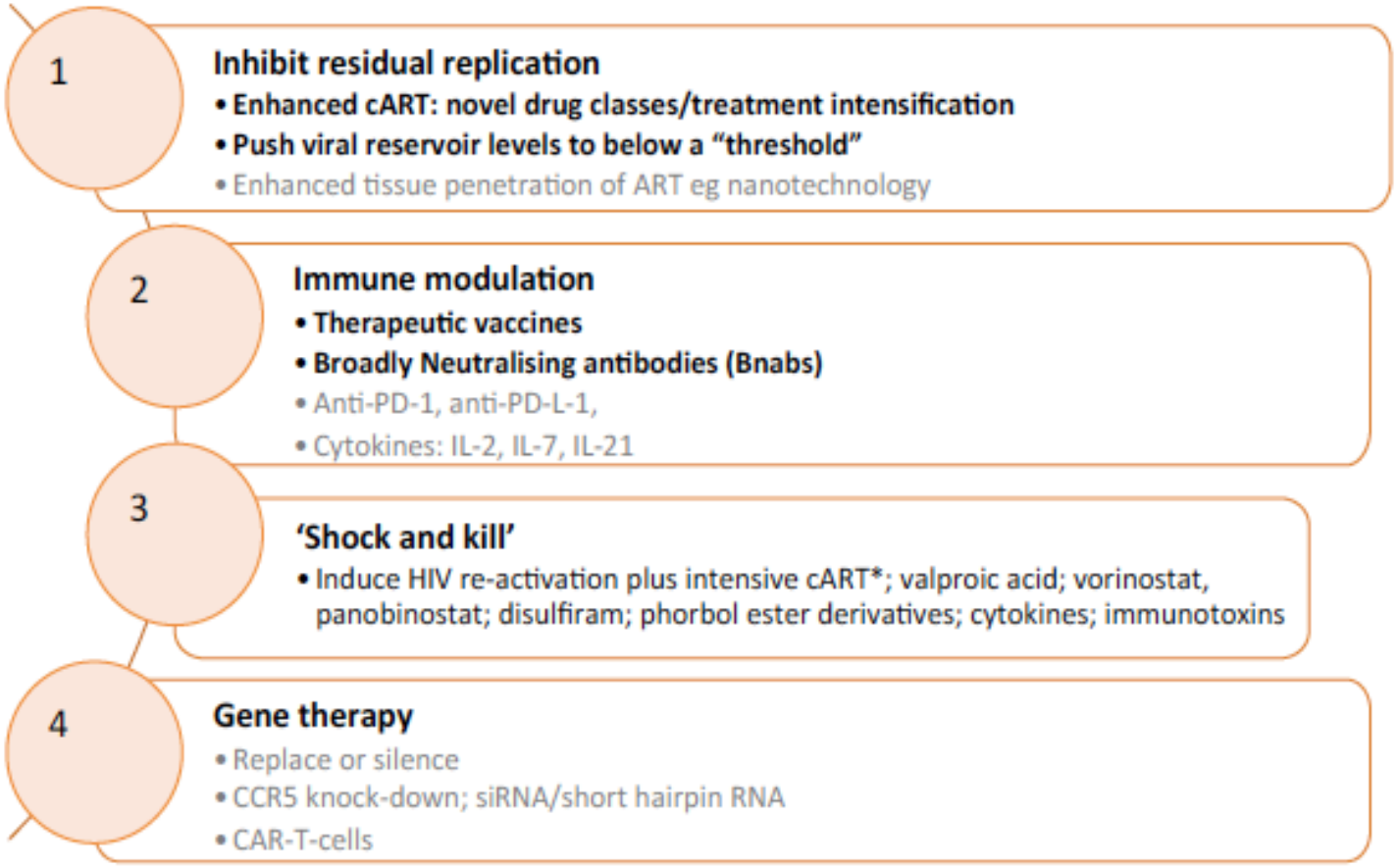
Latently infected cells are rare and undistinguishable from uninfected cells

Eradication strategy should specifically target these cells

Latently infected cells are diverse

Eradication strategy should target all infected cells

Different approaches to cure HIV



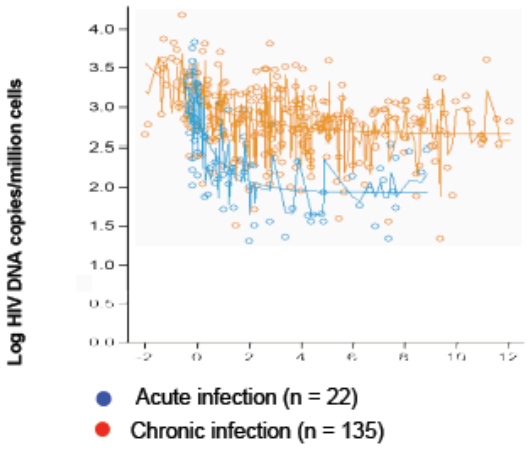
Different approaches to cure HIV

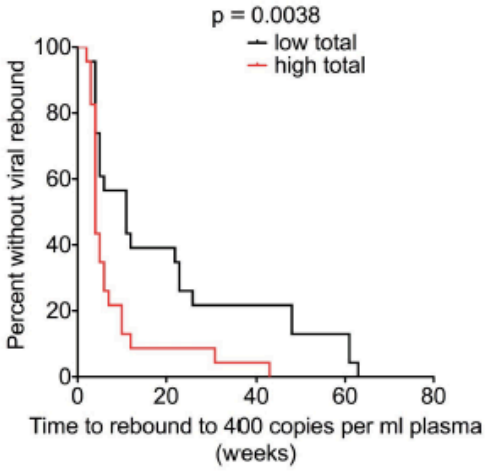
1. Push viral reservoirs below a “threshold”

novel drug classes/treatment intensification (no effect)
Start ART very early after acute infection

Different approaches to cure HIV

What is the threshold below which ART could be safely stopped?





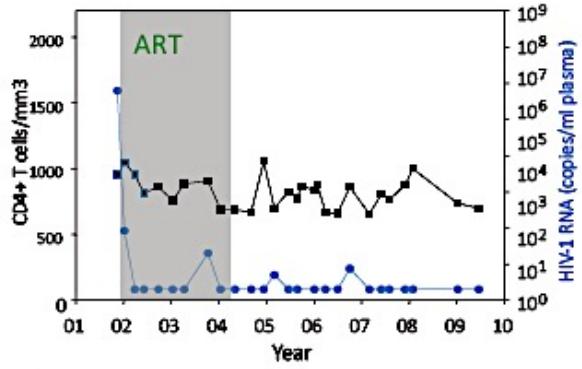
Hocqueloux L, et al. J Antimicrob Chemother 2013;68(5):1169-78.

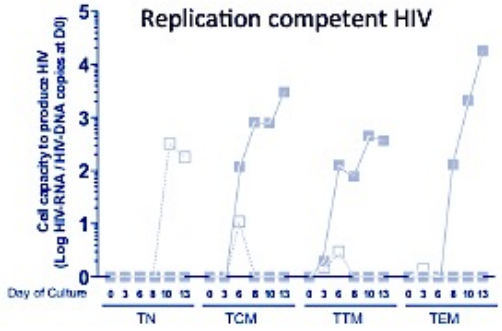
Williams et al eLife 2014 3 e03821

Different approaches to cure HIV

Visconti Long-term HIV control off ART started in Primary infection

- 14 post-treatment controllers from the ANRS/Visconti study
- ART started within 10 weeks after primary infection, for a median time of 36.5 months
- Virological control following ART cessation for an average time 89 months





› **Post treatment controllers naturally "control" a reservoir of small magnitude**

A. Saez-Cirion et al. PLoS Path 2013

Different approaches to cure HIV

Summary

- Although the earlier ART is commenced the lower the size of the reservoir, for the majority of individuals interruption of ART leads to rapid viral rebound
- VERY early ART before antibody development maybe too early to allow time for HIV-specific immunity to develop
- There maybe a threshold of HIV reservoir below which post-treatment viral control will occur but this is uncertain and may differ for each individual.
- The risks of viral rebound for the individual are minimal, but the risks of inadvertent onward transmission maybe significant.

Different approaches to cure HIV

2. Immune modulation

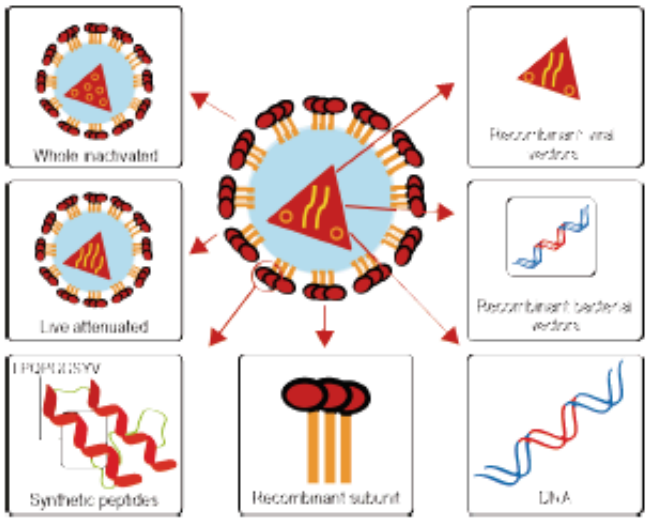
- Therapeutic vaccines
- Broadly Neutralising antibodies (bNabs)
- Anti-PD-1, anti-PD-L-1,
- Cytokines: IL-2, IL-7, IL-21

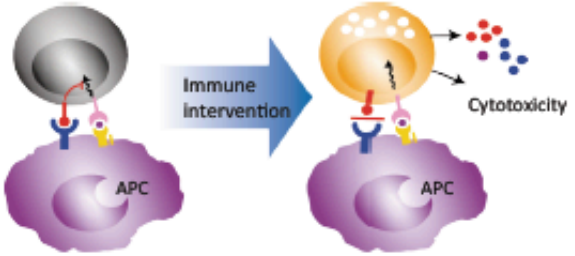
Different approaches to cure HIV

Principle of immune potentiation

Restore immune function with therapeutic vaccines in HIV infection[1]

Generate de novo or boost pre-existing HIV-specific T-cell responses[2]





Exhausted T cell

Reinvigorated T cell

APC, antigen-presenting cell.

1. Adapted from Gorry PR, et al. Retrovirology 2007;4:66. 2. Adapted from Freeman G, et al. J Exp Med 2006;203:2223–7.

Different approaches to cure HIV

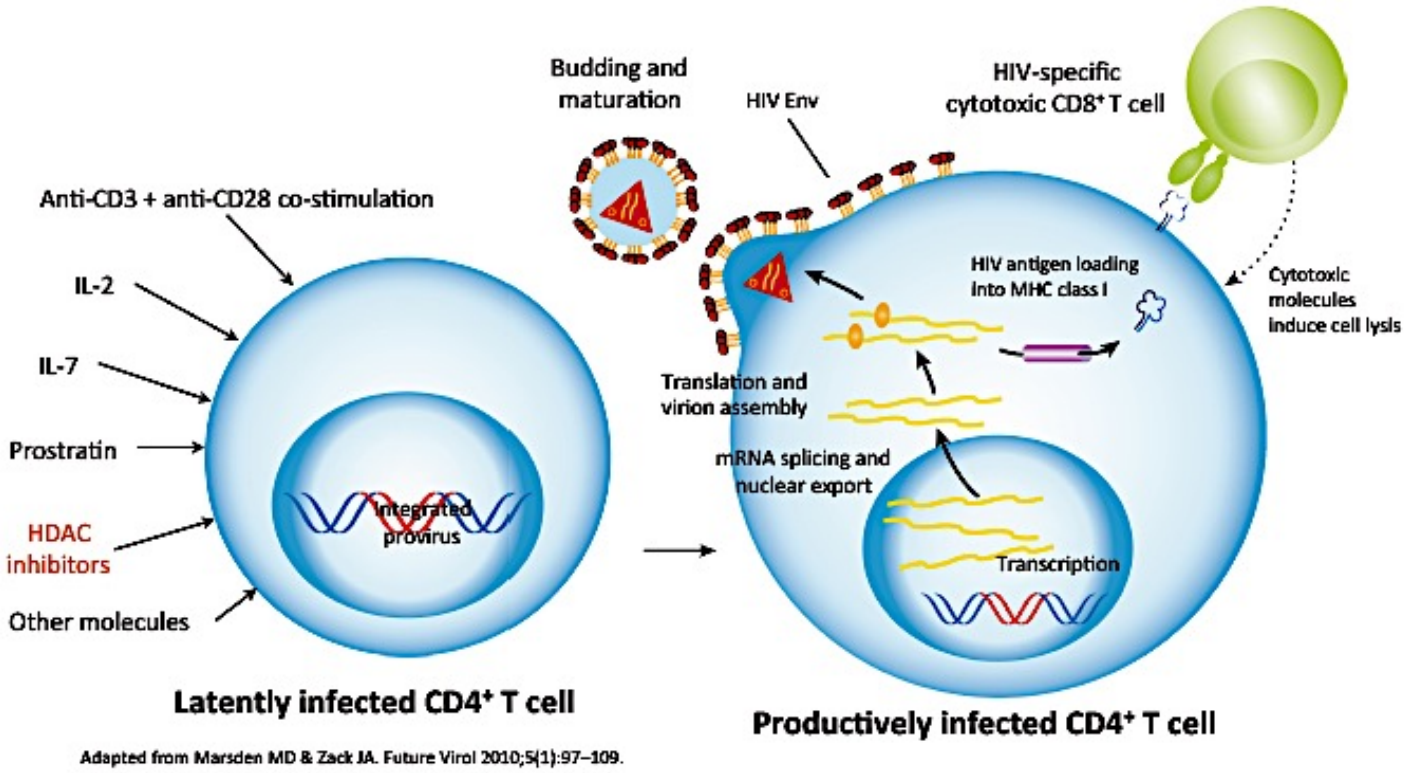
Therapeutic T-cell HIV-1 vaccines and HIV reservoir

ERAMUNE 02	ART intensification (raltegravir or maraviroc) ± immunomodulation (DNA + HIV-rAd5 vaccine) did not significantly reduce the HIV DNA reservoir in blood or rectal tissue
RISVAC 03	MVA-B vaccination increased Gag- and Env-gp120-specific T-cell responses but had only marginal impact on VL rebound after cART interruption
ACTG A5197	rAd5 HIV-1 Gag vaccine showed positive correlation between Gag-specific cells and lower viral rebound during treatment interruption, although the effect decreased over time
NCT00659789	Vacc-4x, a p24Gag HIV-1 vaccine, lowered VL but did not affect the proportion of participants resuming cART before end of study or change in CD4 counts during treatment interruption
NCT00751595	HIV-1 Tat protein was safe, well tolerated and induced anti-Tat Abs in most patients. Vaccination promoted a durable and significant restoration of T, B, NK cells, and CD4+ and CD8+ central memory subsets. A significant reduction of blood proviral DNA was seen after Week 72
HVTN 090	rVSV vaccine recipients became seropositive for VSV after two vaccinations. Gag-specific T-cell responses were detected in 63% of participants by interferon-γ enzyme-linked immunospot at the highest dose postboost

No impact on HIV reservoir

Different approaches to cure HIV

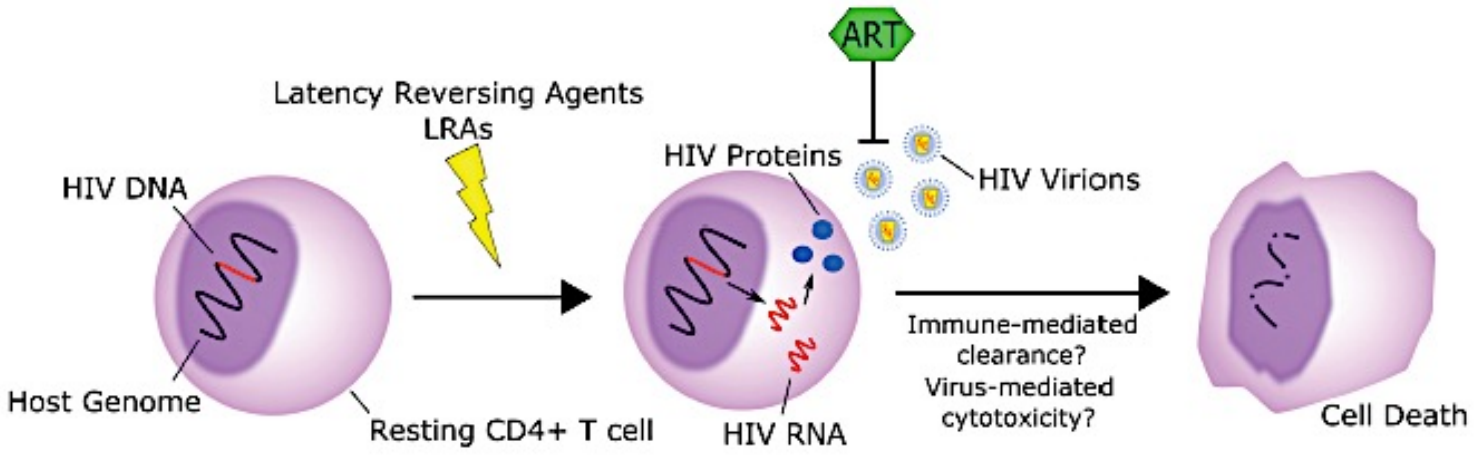
Activating latent virus maybe a necessary step in many HIV cure strategies



Adapted from Marsden MD & Zack JA. Future Virol 2010;5(1):97–109.

Different approaches to cure HIV

HIV Kick and Kill approach



Different approaches to cure HIV

Clinical studies testing Kick and Kill

Study	Primary endpoint	Design	Intervention	Result
BCN02	Viral rebound after TI	Acute infection Observational	ChAd/MVA vaccine Romidepsin	5/13 undetectable after TI <24 weeks
Reduc *J Infect. 2017 Dec; 75(6): 555-571*	QVOR, total HIV DNA, integrated HIV DNA	Chronic infection Observational N = 20	Vacc4x + Romidepsin	Total HIV-1 DNA declined screening to 6 weeks after romidepsin treatment (mean reduction 39·7%, 95% CI −59·7 to −11·5; p=0·012).
RIVER	Total HIV DNA week 16&18	RCT Acute infection N = 60	ChAD/MVA vaccine Vorinostat	No impact on total HIV RNA qVOA
VORVAX	QVOR	Single group N = 12	Vorinostat AGS004 vaccine	2020

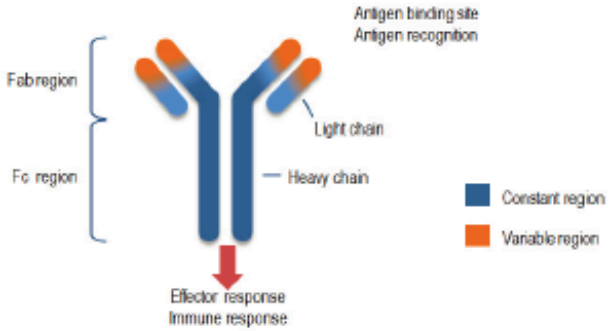
Different approaches to cure HIV

Summary of Kick and Kill studies using LRA and T-cell vaccines

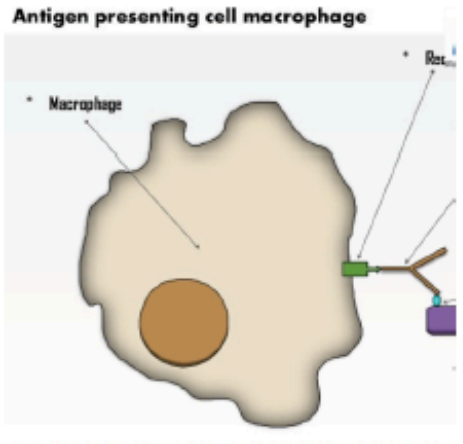
- One RCT (RIVER) shown no effect of HDACi (Vorinostat) + T-cell vaccine vs ART alone
- Latency reversal using HDACi maybe inadequate or T-cell vaccine epitopes may not recognize the correct viral sequences
- There are other ways to induce the kick and kill

Different approaches to cure HIV

Broadly Neutralising antibodies (Bnabs)



- The antigen binding region is HIV envelope specific bNabs behave as antiviral agents
- The Fc region has other functions; ADCC and facilitates binding to APC to enhance T-cell function
- "Vaccinal" effect
- Next generation bNAbs have extended half-lives (up to 3-6 months)



Different approaches to cure HIV

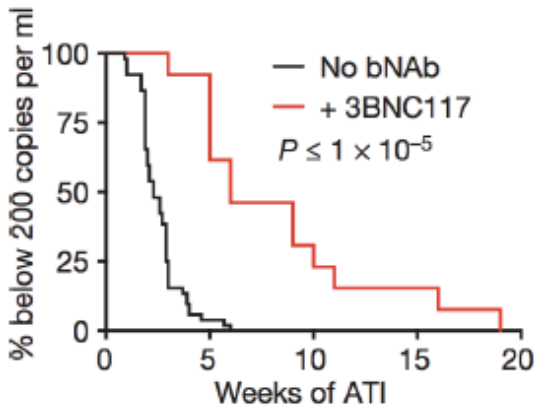
LETTER

doi:10.1038/nature18929

HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid[1,2]*, Joshua A. Horwitz[1]*, Yotam Bar-On[1], Edward F. Kreider[3], Ching-Lan Lu[1], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[1], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[5], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[6], Boris Juelg[7], Tibor Keler[8], Thomas Hawthorne[8], Barry Zingman[9], Roy M. Gulick[5], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[10], Pamela J. Bjorkman[6], Florian Klein[1,11,12], Sarah J. Schlesinger[1], Bruce D. Walker[7,13], Beatrice H. Hahn[3], Michel C. Nussenzweig[1,14] & Marina Caskey[1]

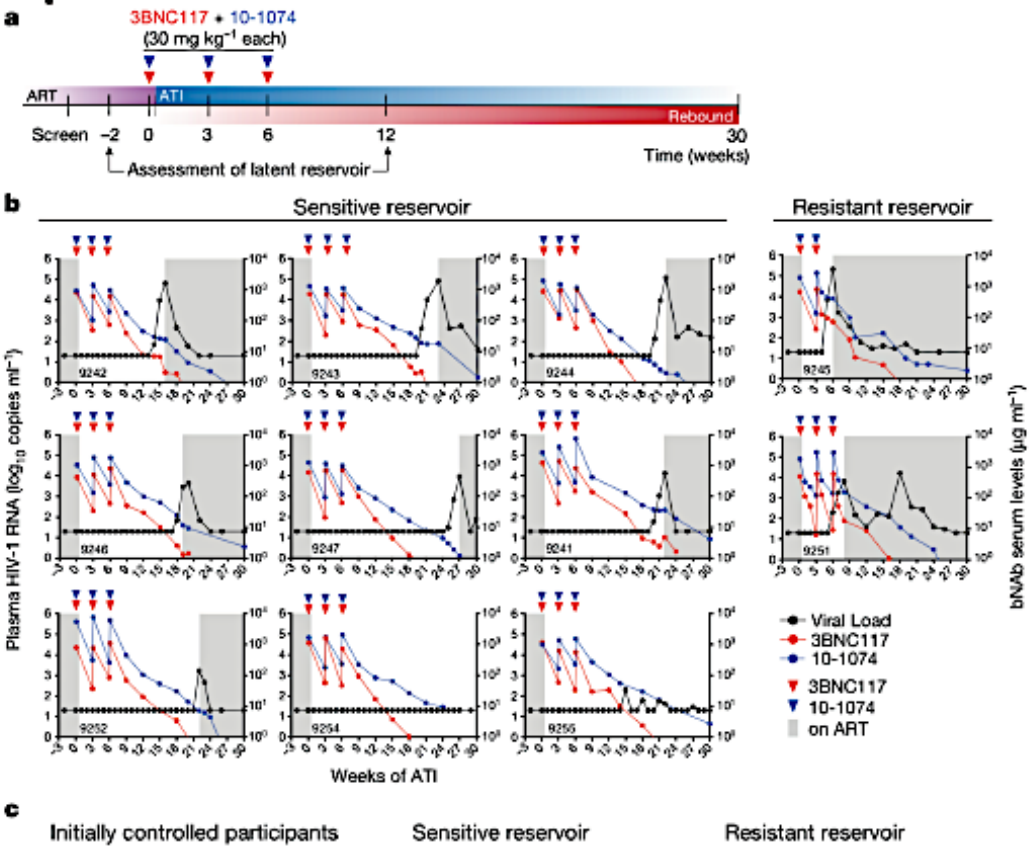
July 2016



- N=13 with chronic HIV infection suppressed for >12 months
- Infusions of 3BNC117. TI 2 days later
- **Up to 19 week delay in rebound** vs historical controls (2.6 weeks)
- Rebound occurred with escape variants or once antibody levels had dropped

Different approaches to cure HIV

- **Double bNab (3BNC117+10-1074) maintain viral suppression n = 9 individuals up to 30 weeks post ATI**



Mendoza et al Nature 2018 561 479

Different approaches to cure HIV

HIV ongoing cure studies

Network	Institution	Name of trial	Description	Products
NA	Rockefeller, Aarhus, Cologne	MCA-0896	3BNC117 & romidepsin in HIV+ adults on ART	3BNC117
NA	HIVACAR	2017-000566-30	10-1074 & romidepsin & iHIVARNA & MVA.HTI in HIV+ adults ART+ / ATI	10-1074
NA	Aarhus	2015-002234-53	3BNC117 & romidepsin in chronically infected, viremic HIV+ adults	3BNC117
NA	UPenn	ES 38445	3BNC117 & 10-1074 & type I IFN during ATI	3BNC117 & 10-1074
IMPAACT	NA	P1115	VRC01 in 48h HIV+ or at-risk +/-ART infants (+/- RAL) + ATI	VRC01
NA	Case W	TBD	VRC07-523LS & IL-2 in ART+ HIV+ adults	VRC07-523LS
NA	Harvard	TBD	VRC01-LS & 10-1074 in long-term suppressed children	VRC01-LS & 10-1074
NA	UNC	IGHID 11802	VRC07-523LS & Vorinostat in ART+ HIV+ adults	VRC07-523LS
NA	UCSF	TBD	VRC07-523LS & 10-1074 & HIV vaccine & booster & TLR9ag	VRC07-523LS & 10-1074
ACTG	NA	TBD	VRC07-523LS & 10e8VLS & PGT121LS & TLR9ag	VRC07-523LS & 10E8VLS & PGT121LS
NA	UKZN	TBD	VRC07-523LS & PGT121LS & TLR9ag in FRESH cohort	VRC07-523LS & PGT121LS
NA	Aarhus, UCSF, Melbourne	TBD	3BNC117 & 10-1074 + TLR9ag in HIV+ adults on ART and during ATI	3BNC117 & 10-1074
NA	Frontier	TBD	3BNC117 & albuvirtide in HIV+ adults on ART and during ATI	3BNC117

Completed | Enrolling | In development | In proposal phase

Different approaches to cure HIV

Human bNab studies

- The new innovation for prevention as well as remission
- long-acting function currently under investigation
- Combination approaches of 3 bNabs plus LRA + T-cell vaccination
- Safe, well tolerated and works with ART
- Now ongoing n = 14 proof of concept studies on combination bNabs in humans for cure

Cura

Conclusion

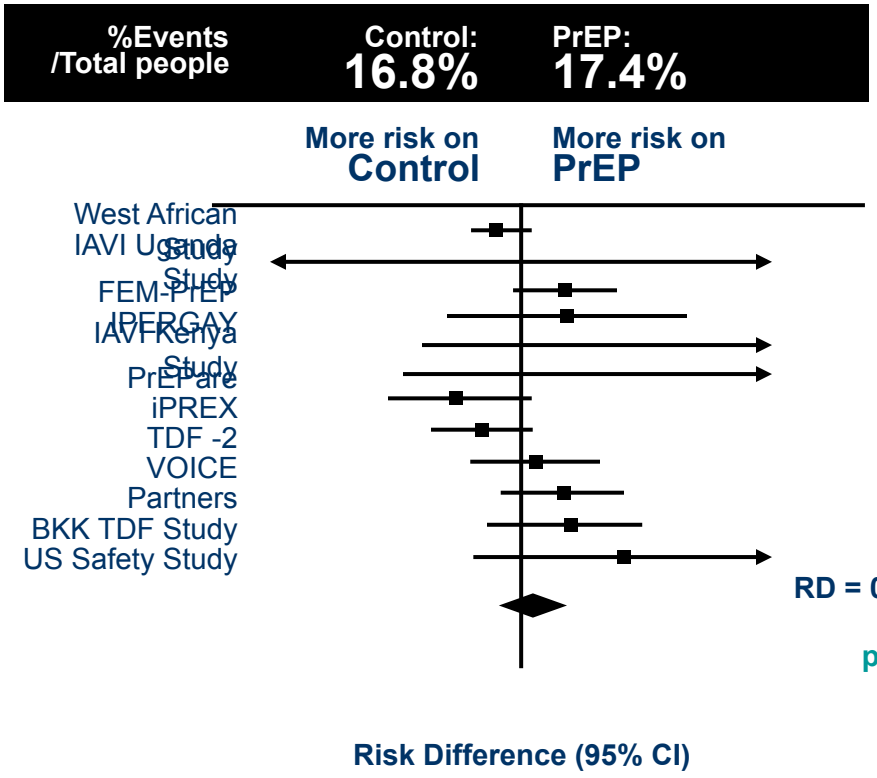
- Multiple approaches towards HIV remission in addition to early or long-term ART to limit the size of the measured HIV reservoir look encouraging
- Will probably need a combination approach
- Important to balance risk vs benefits of each strategy
- May end up with induction then remission and maintenance therapy following a cancer treatment model and removing the need for daily ART
- When will there be a cure?
  - Post-treatment viral control maybe 5-10 years combination + ART
  - Sterilising Cure a Long time….

PREP

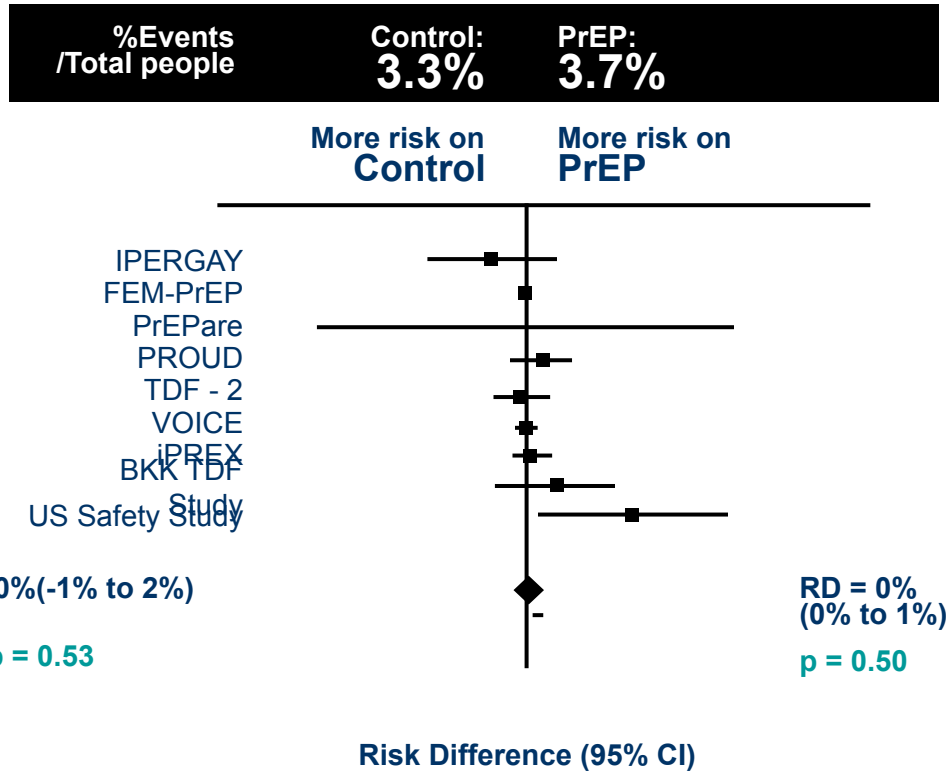
Meta-Analysis of PrEP Safety

- Review of 2306 studies screened, 201 assessed for inclusion
- 13 RCT included, 15,678 participants, 22,250 pt/years

Serious Adverse Events



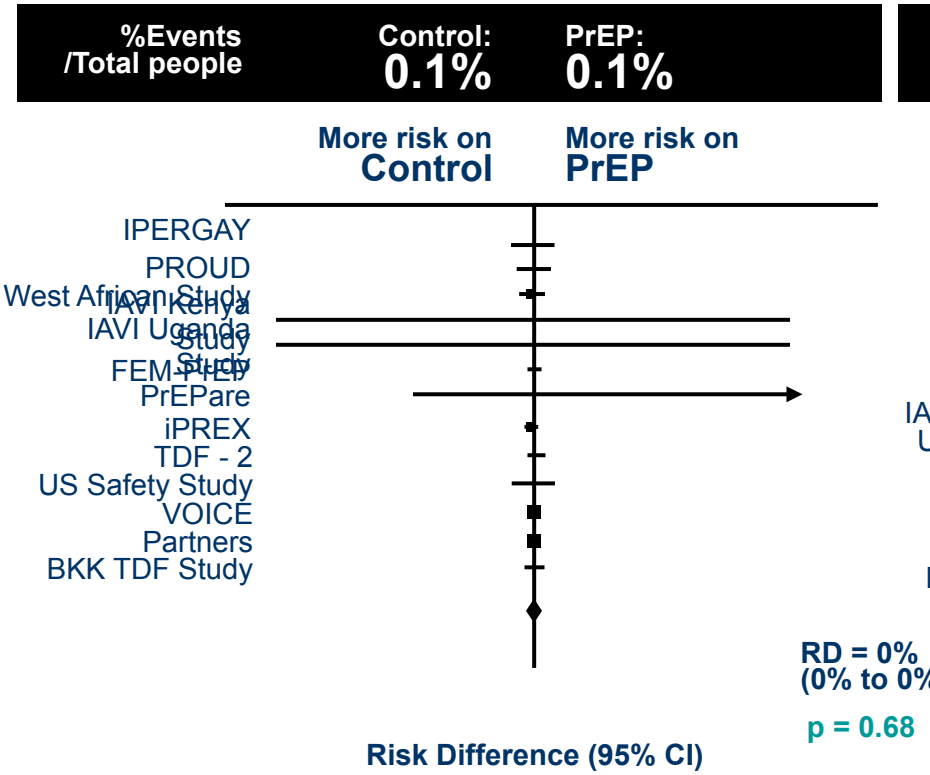
Bone Fractures



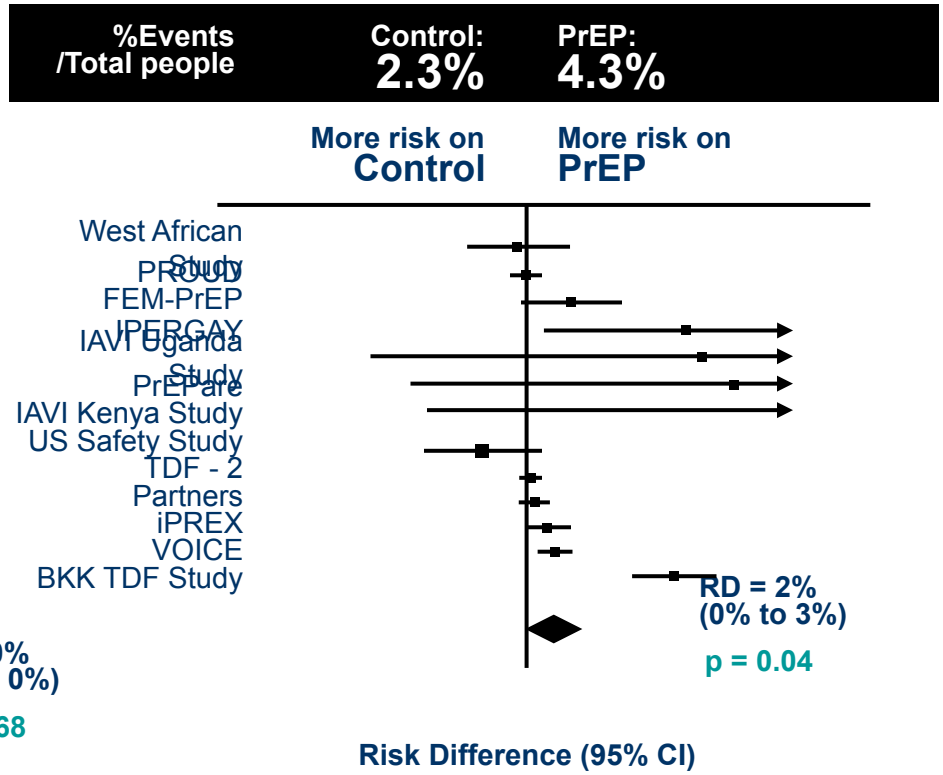
Pilkington et al Glasgow HIV 2018. Poster 0143.

Meta-Analysis of PrEP Safety (cont'd)

Grade 3+ Creatinine

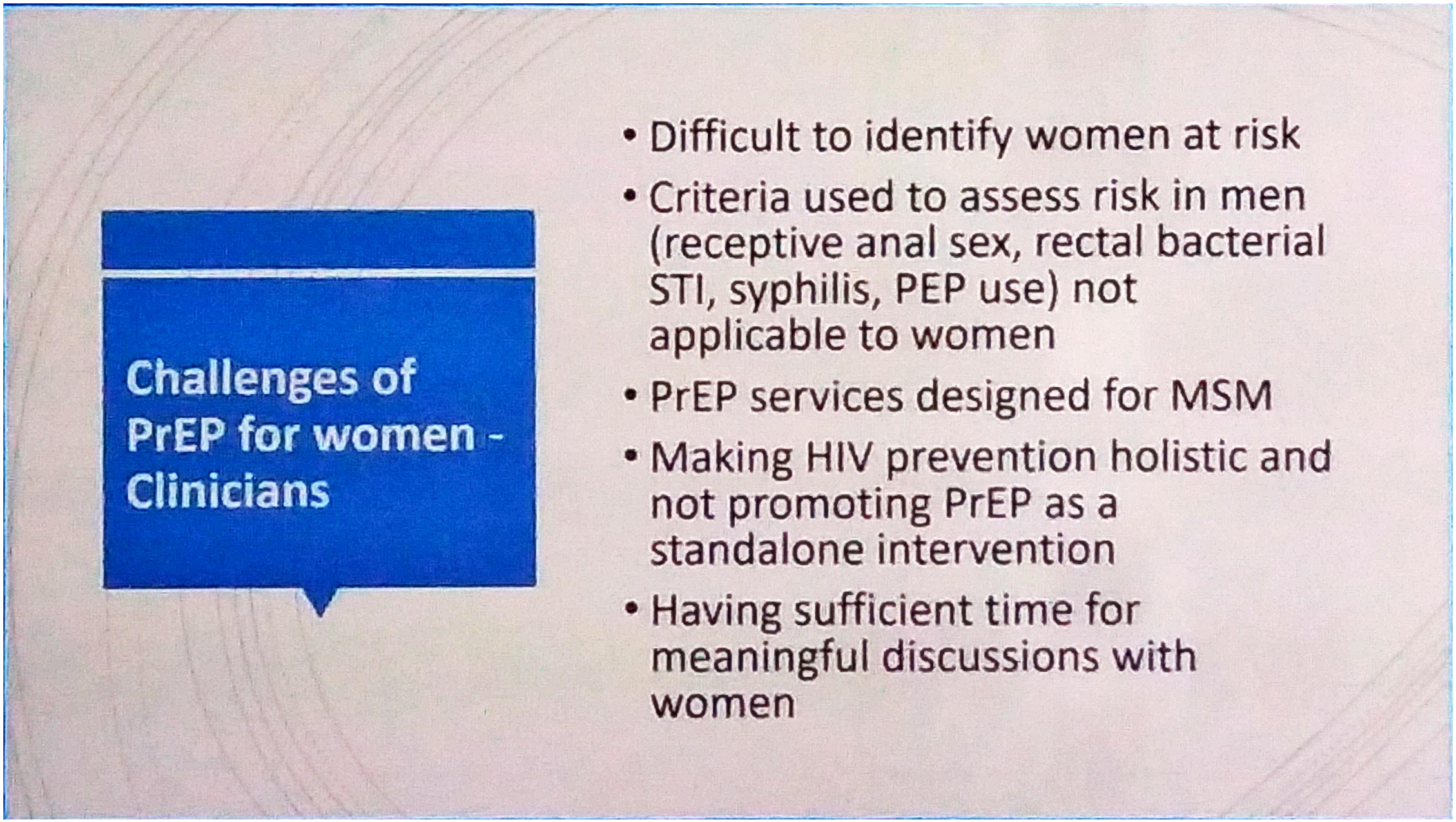


Grade 1-4 Creatinine



Pilkington et al Glasgow HIV 2018. Poster 0143.

PrEP
for women in Europe



PrEP
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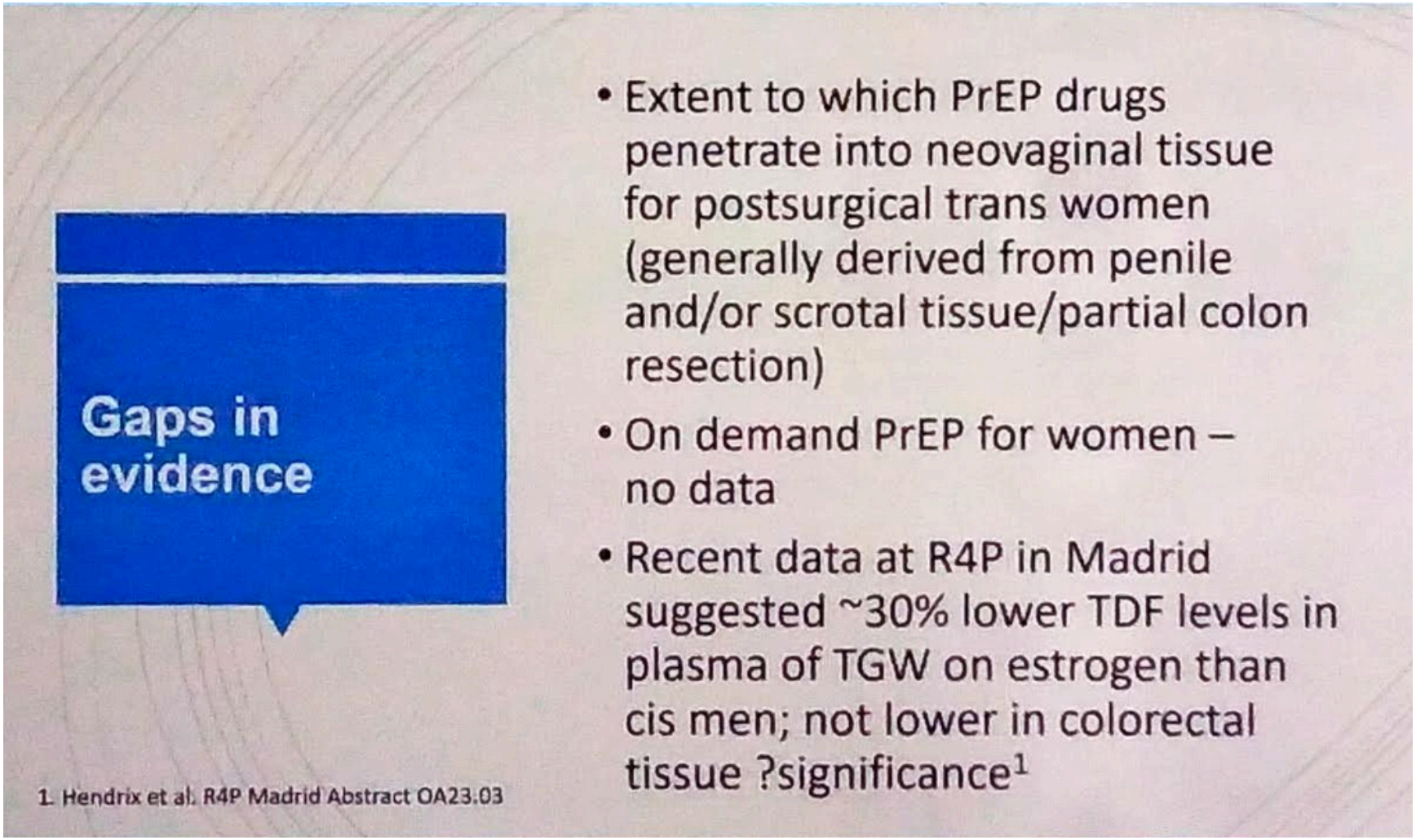
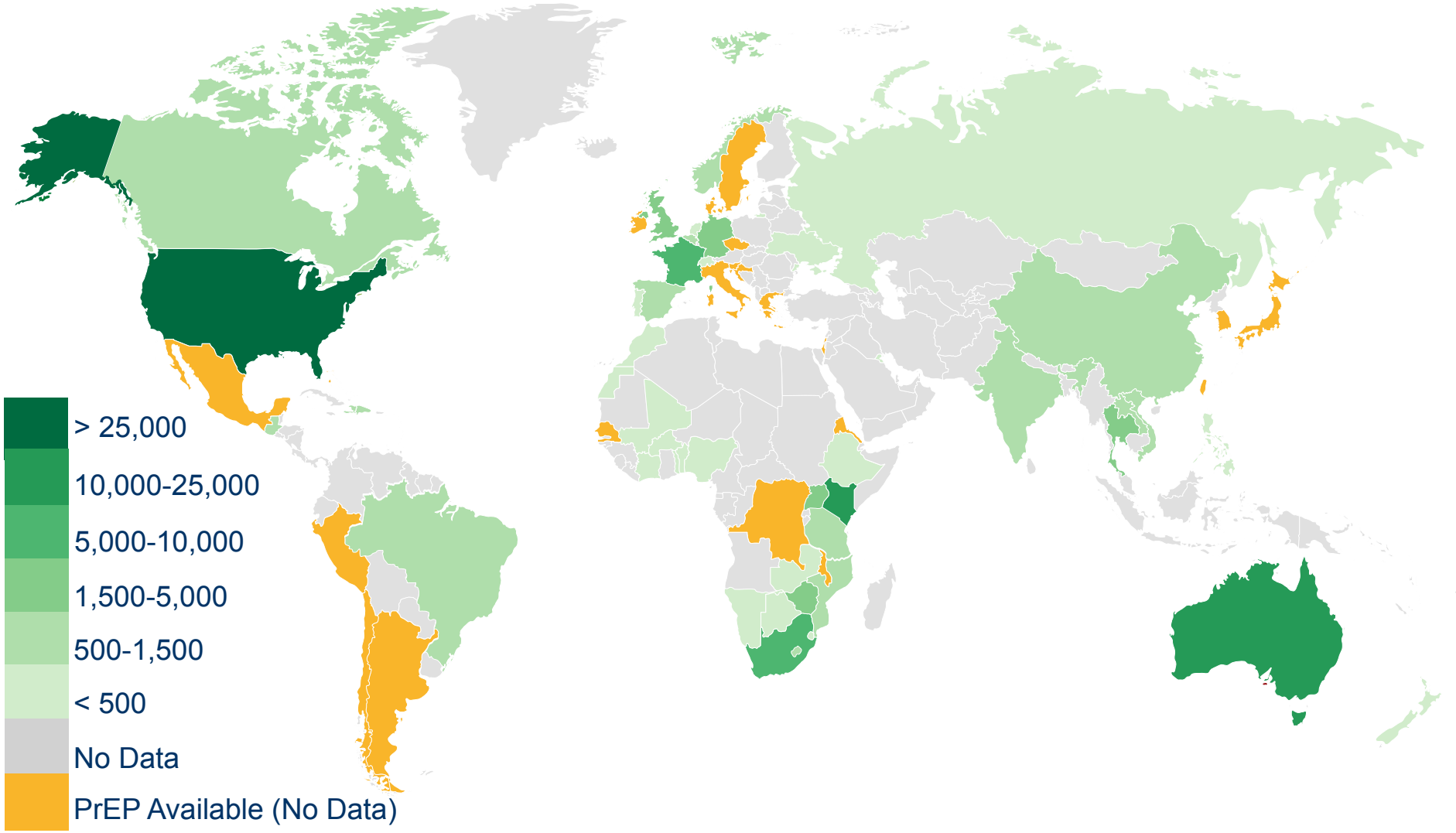


Nor should PrEP programmes be designed solely for MSM

- We must always remember that PrEP is only one component of combination HIV prevention
- People may use one or more modalities at the same or different times and pick them up and put them down depending on circumstances

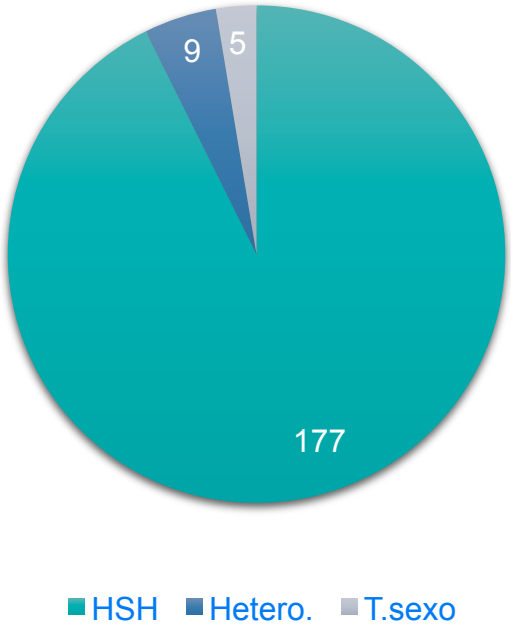
PrEP Initiations by Country (April 2018)



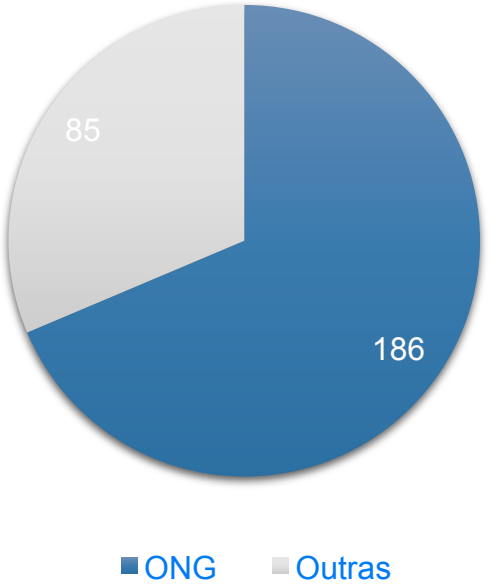
Source: AVAC Global PrEP Initiation Tracker 2018

PrEP em Portugal (setembro 2018)

n = 228 pessoas (com uma prescrição)



n = 271 pessoas (referenciadas)



PrEP em Portugal (setembro 2018)

- PrEP *net (setembro 2018)*

22 hospitais diferentes
(22/29)