Imperial College London

HIV Drug Therapy GLASGOW 2018

HOW SAFE IS PrEP?

An analysis of the safety of TDF/FTC as PrEP vs Control

Victoria Pilkington, Andrew Hill, Sophie Hughes, Nneka Nwokolo and Anton Pozniak

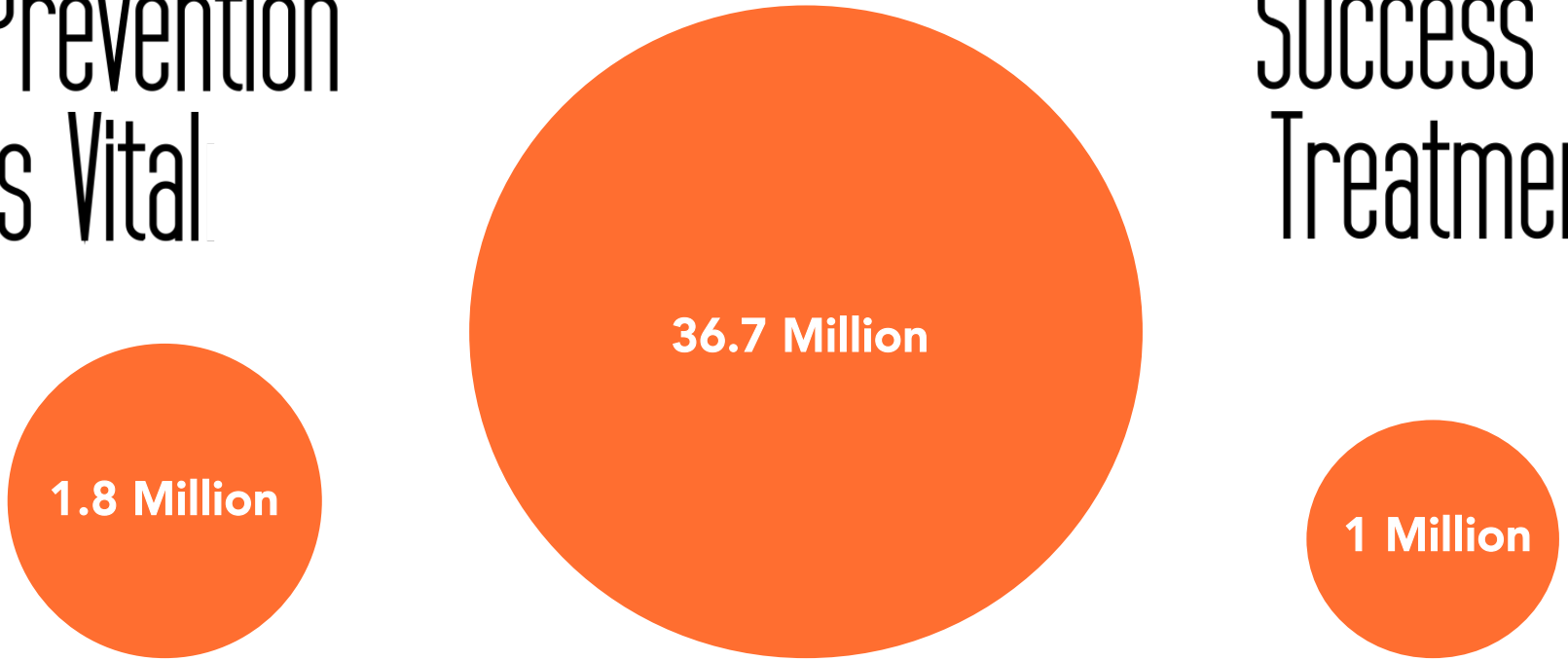
1.8 Million

New HIV infections worldwide every year

Pilkington et al. Glasgow HIV 2018. Poster 0143

Prevention is Vital

Success in Treatment

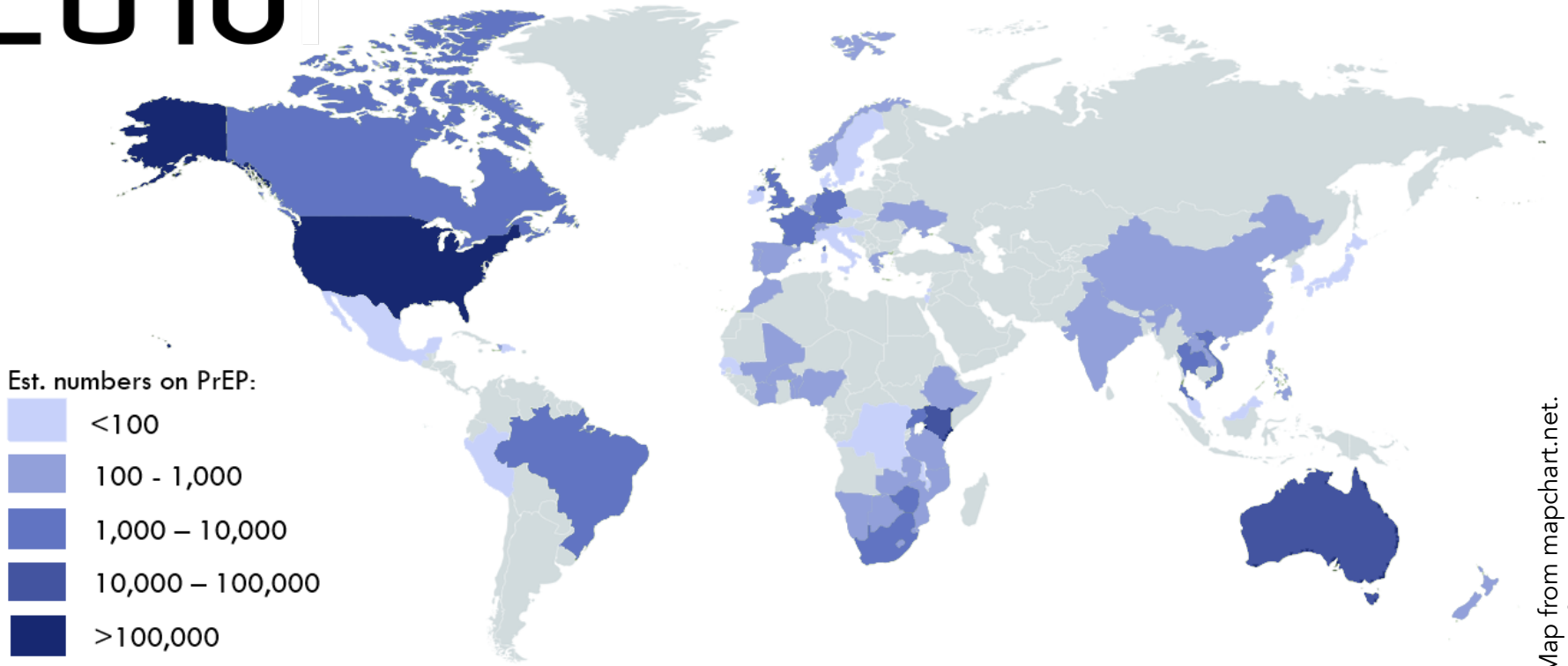


NEW INFECTIONS **LIVING WITH HIV** **DEATHS**

https://www.avert.org/global-hiv-and-aids-statistics
Data from UNAIDS Data report 2017.

2018

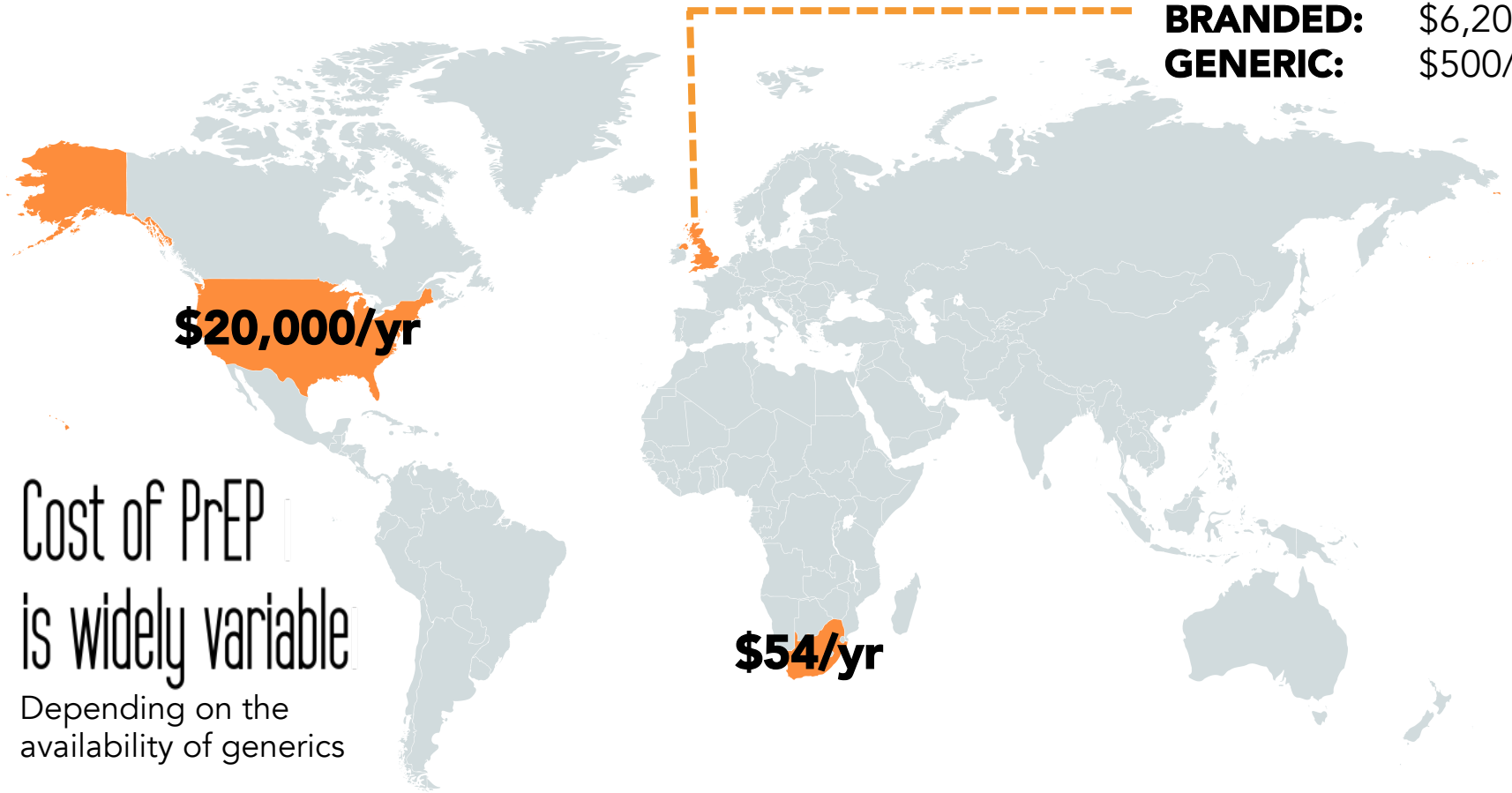
Over 300,000 take PrEP worldwide



Map from mapchart.net.
Data from AVAC.org 2018.

PrEP

Costs



Cost of PrEP is widely variable

Depending on the availability of generics

https://clintonhealthaccess.org/content/uploads/2016/11/2016-CHAI-ARV-Reference-Price-List_FINAL.pdf

https://medicineslawandpolicy.org/2018/09/cjeu-ruling-on-truvada-recalls-evergreening-goes-against-public-health-interests/

PrEP

Costs Uptake **Safety**

TDF use in treatment: Boosted

TDF/FTC + Booster Drugs

Bone: Risk Increase p=0.04
Renal: Risk increase p=0.002

Suggests there is **TOXICITY**

Unboosted

TDF/FTC

Bone: No significant risk
Renal: No significant risk

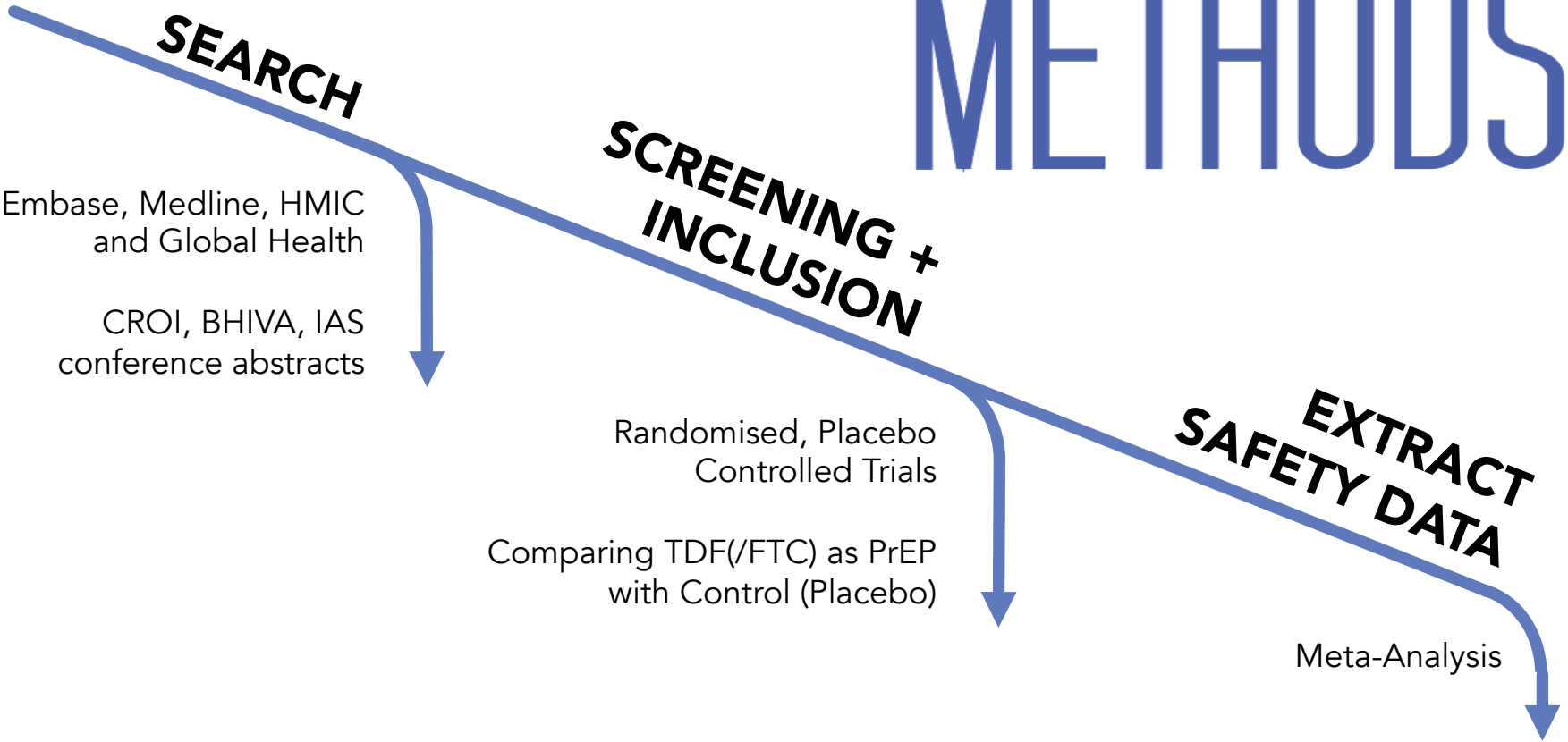
NO TOXICITY

Hill et al, JVE 2018

Primary research question:

Is TDF/FTC **safe** when used as PrEP?

METHODS

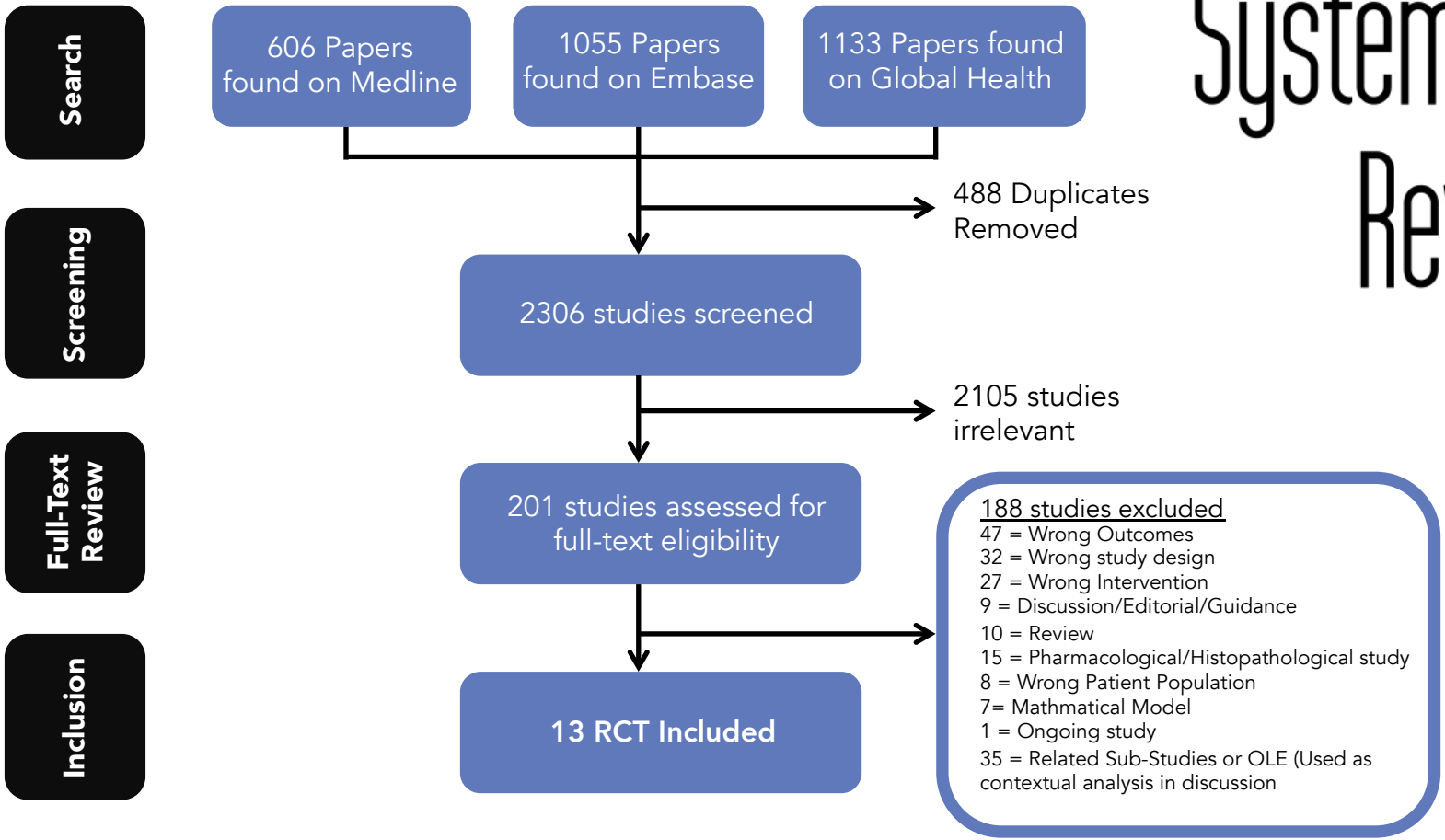

SEARCH
Embase, Medline, HMIC and Global Health
CROI, BHIVA, IAS conference abstracts
SCREENING + INCLUSION
Randomised, Placebo Controlled Trials
Comparing TDF(/FTC) as PrEP with Control (Placebo)
EXTRACT SAFETY DATA
Meta-Analysis

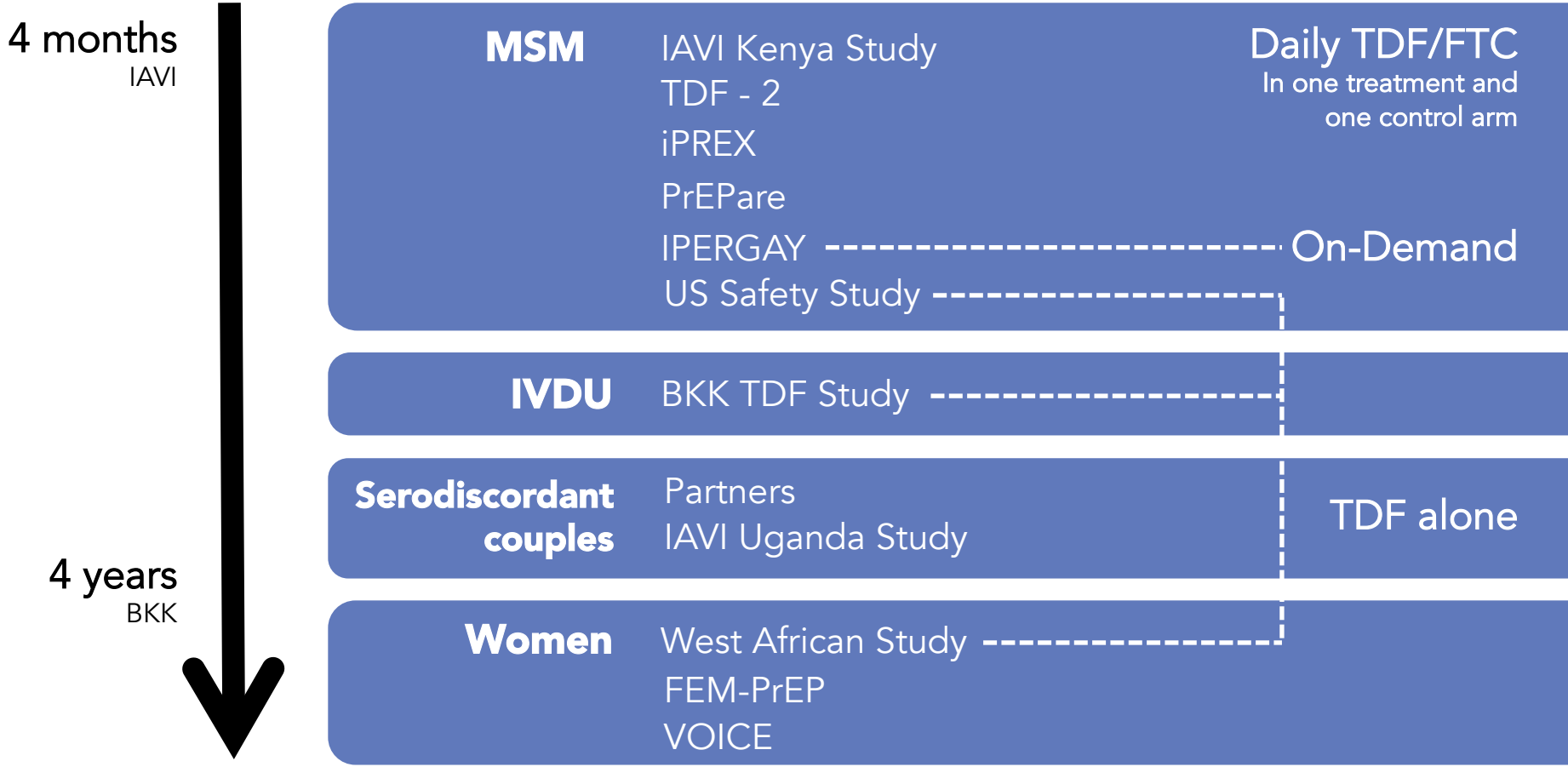
SAFETY ENDPOINTS

- Clinical - Grade 3 & 4 Adverse events
- Clinical - Protocol defined Serious Adverse Events
- Lab - Serum creatinine elevations (Grade 3+) — Renal Damage
- Bone Fractures — Loss BMD

RESULTS

Systematic Review

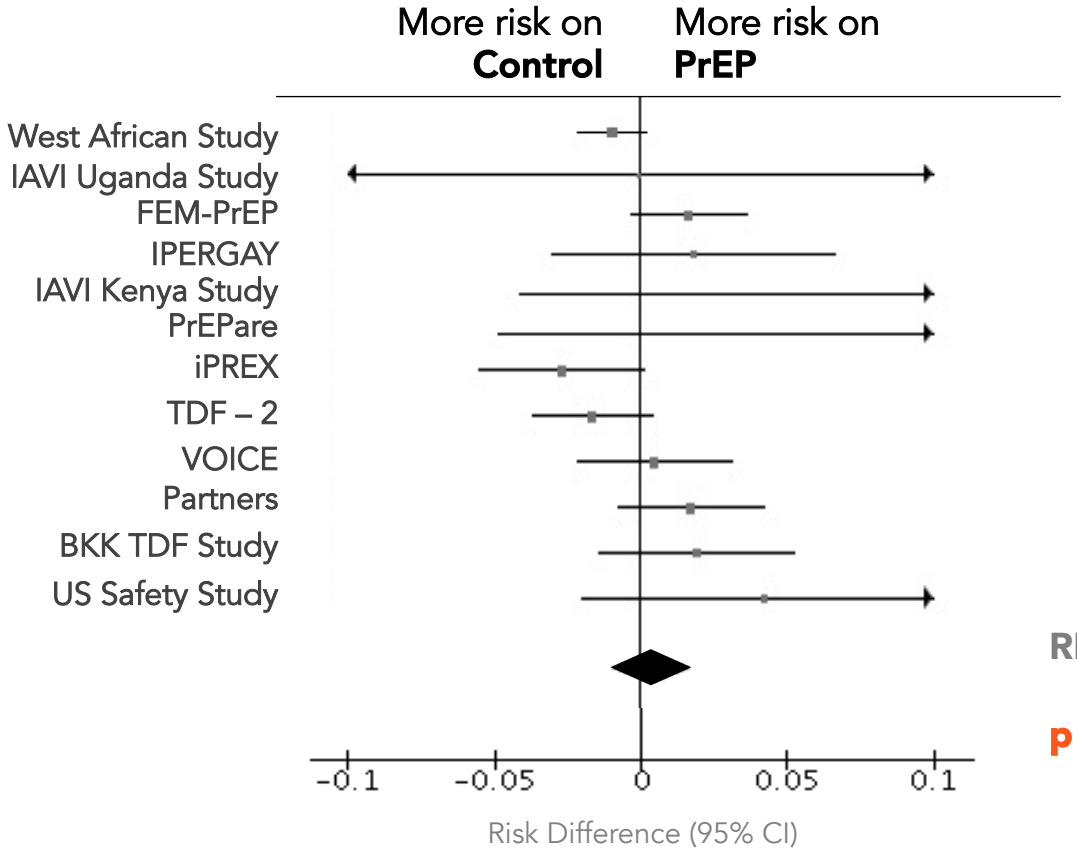



4 months
IAVI
4 years
BKK
MSM
IAVI Kenya Study
TDF - 2
iPREX
PrEPare
IPERGAY
US Safety Study
Daily TDF/FTC
In one treatment and one control arm
On-Demand
IVDU
BKK TDF Study
Serodiscordant couples
Partners
IAVI Uganda Study
TDF alone
Women
West African Study
FEM-PrEP
VOICE
13 trials
15,678 participants
22,250 PYFU

Grade 3+4
Adverse Events

No significant increased in risk on PrEP

%Events /Total people	Control:	PrEP:
	16.8%	**17.4%**

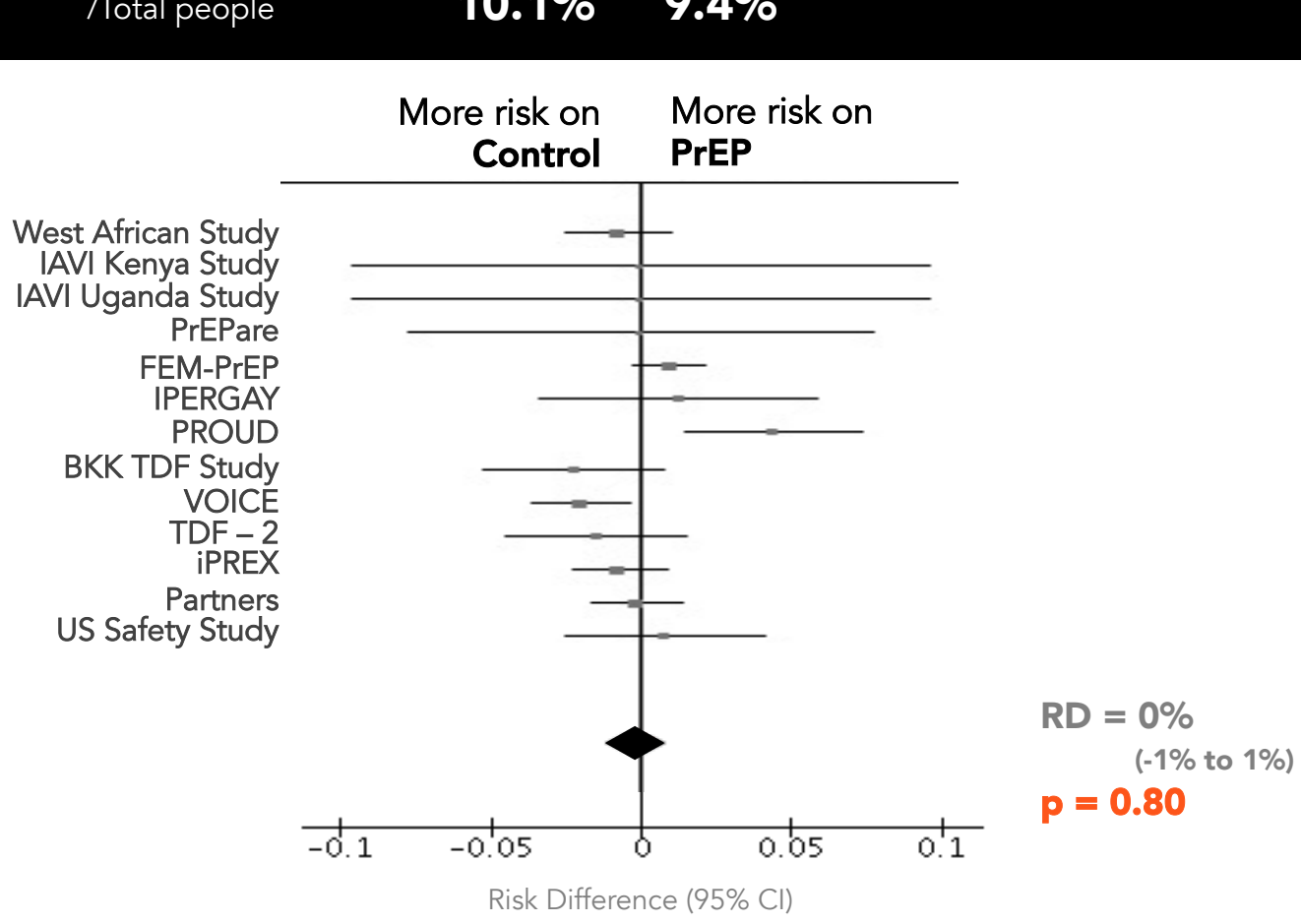


RD = 0%
(-1% to 2%)
p = 0.53

Pilkington et al. Glasgow HIV 2018. Poster 0143

Serious Adverse Events

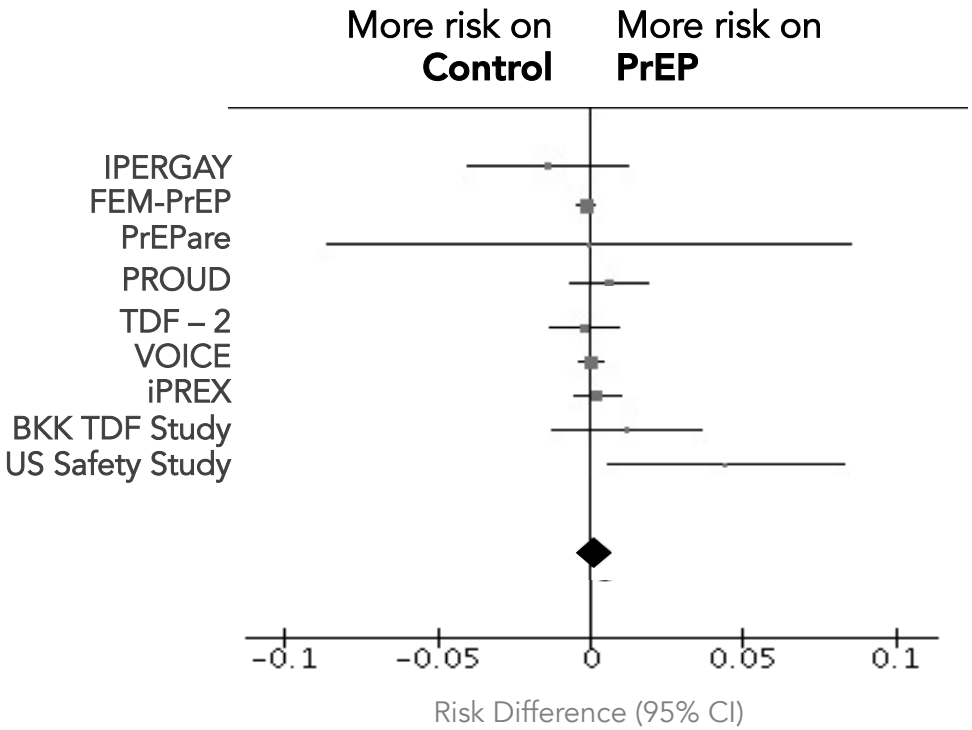
No significant increased in risk on PrEP



Pilkington et al. Glasgow HIV 2018. Poster 0143

Bone Fractures

%Events /Total people	Control:	PrEP:
	3.3%	**3.7%**



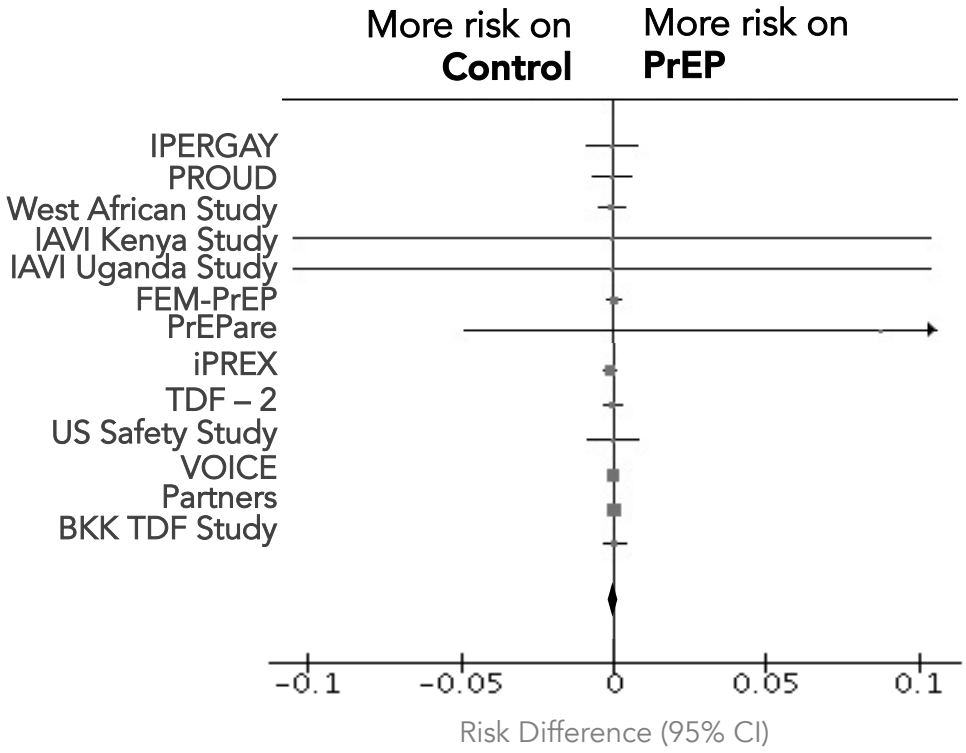
RD = 0%
(0% to 1%)
p = 0.50

No significant increased in risk on PrEP

Pilkington et al. Glasgow HIV 2018. Poster 0143

Creatinine Elevations
(Grade 3+)

%Events /Total people	Control:	PrEP:
	0.1%	**0.1%**



RD = 0%
(0% to 0%)
p = 0.68

No significant increased in risk on PrEP

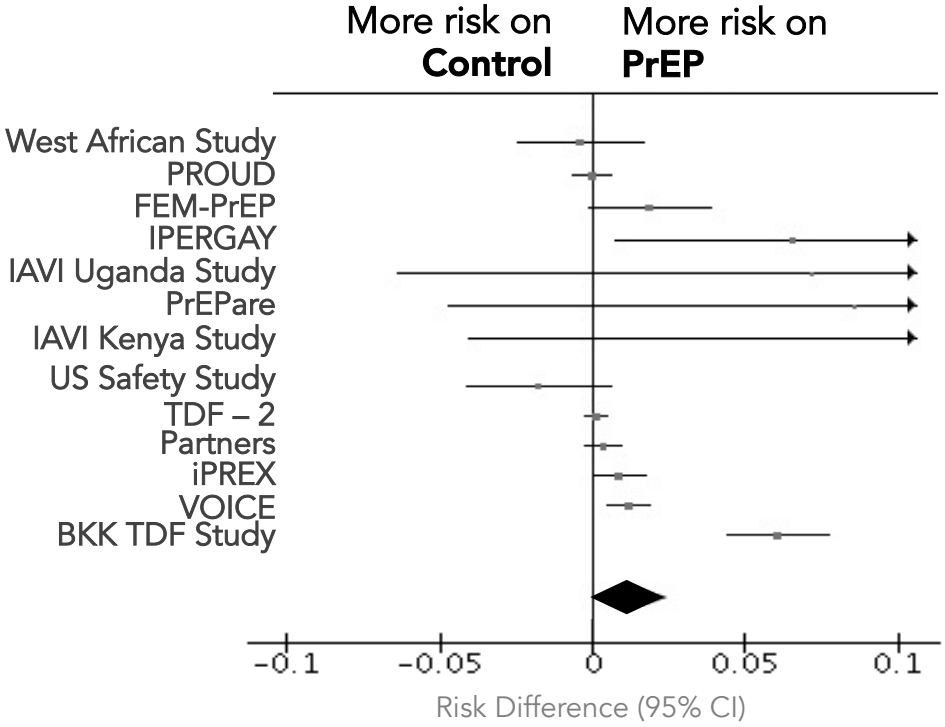
Pilkington et al. Glasgow HIV 2018. Poster 0143

Creatinine Elevations
(Grade 1-4)

%Events /Total people

Control: **2.3%**

PrEP: **4.3%**



RD = 2%
(0% to 3%)
p = 0.04

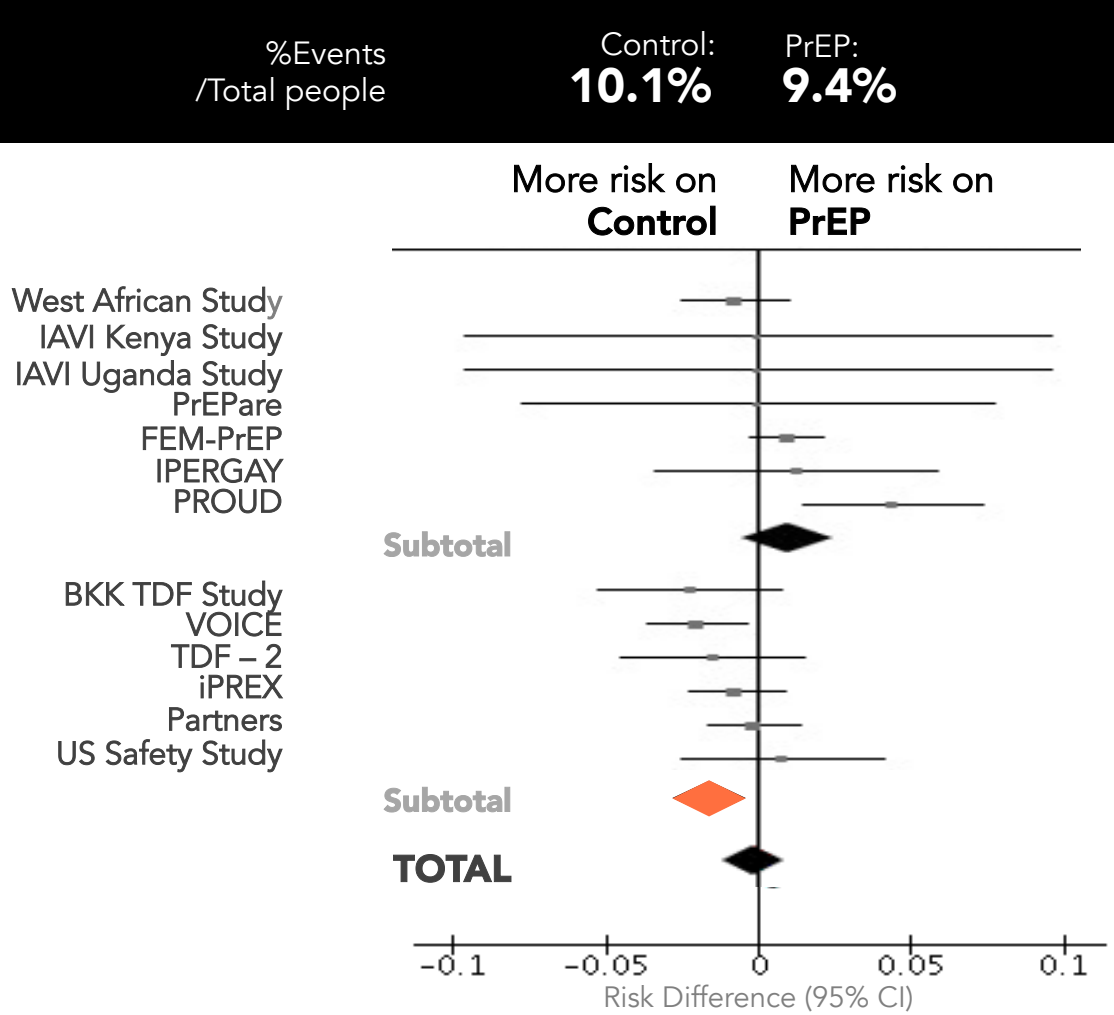
Borderline significant increased in risk on PrEP

Pilkington et al. Glasgow HIV 2018. Poster 0143

SENSITIVITY ANALYSES

		Effect on overall significance:
Regimen	Daily/intermittent or TDF/TDF+FTC	**None**
Reporting	Number of events vs number of people experiencing events	**None**
Sex	Studies in males, females and both	**None**
Follow-Up	Studies split by those </>1yr average follow-up time	**SAE**

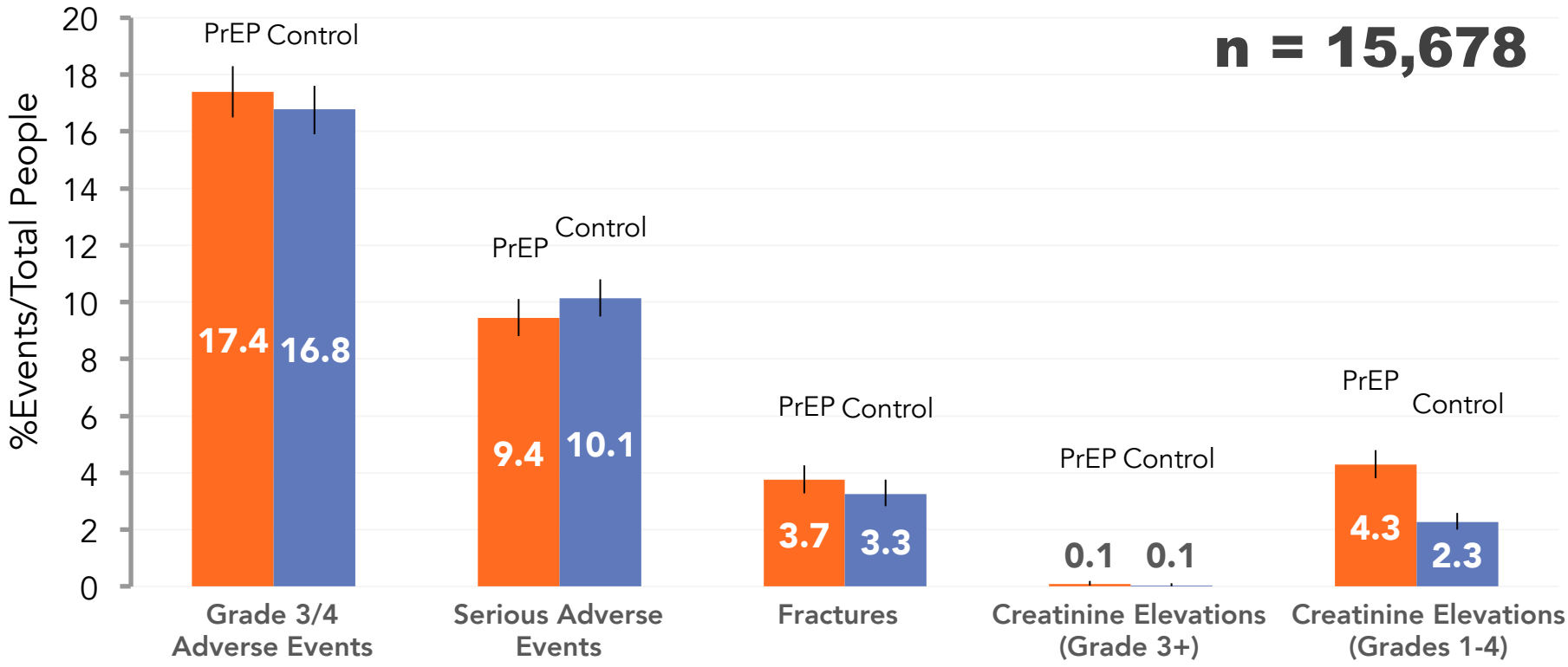
Serious Adverse Events



Statistically significant decrease in risk on PrEP in longer-term follow-up studies

Pilkington et al. Glasgow HIV 2018. Poster 0143

Significant Increase in Risk on PrEP?	None	None	None	None	p=0.04



Pilkington et al. Glasgow HIV 2018. Poster 0143

STRENGTHS

Low risk bias

~22,250 total PYFU

LIMITATIONS

Low baseline risk

Low adherence

Not all groups/world regions represented

APPLICABILITY

CLINICAL Prescribing, uptake and adherence

POLICY Funding and advocacy for widespread rollout of PrEP

This review found **no evidence** of any increased risk of **severe adverse events** on TDF/FTC as PrEP

TDF vs TAF

If TDF is safe –
is expenditure on TAF justified?

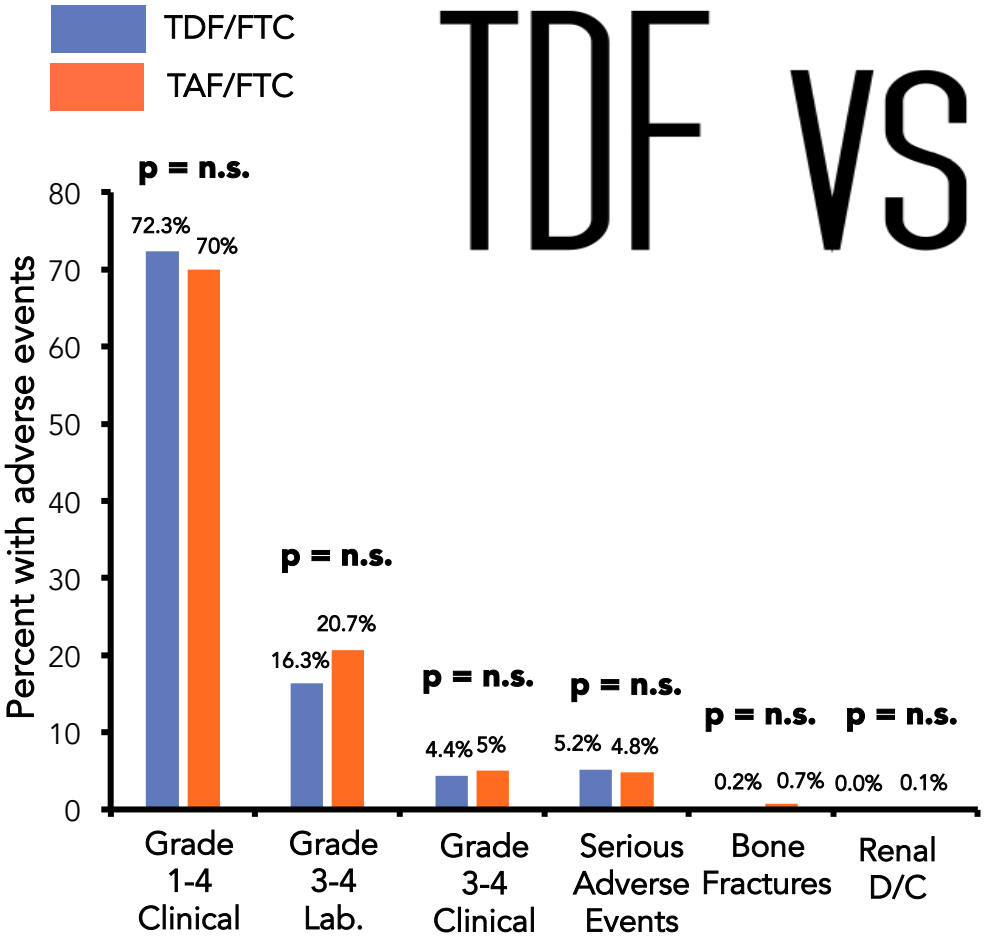
Newer drug

Better safety profile?

More expensive

Hill et al, J Virus Erad 2018, 4:72-78

TDF vs TAF



Unboosted TDF/FTC vs TAF/FTC (n=3181)

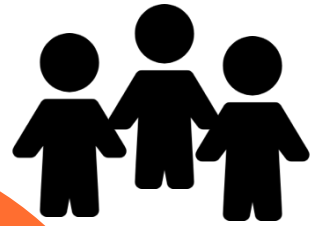
Grade 3+4	No risk difference
Serious Adverse Events	No risk difference
Bone Fractures	No risk difference
Renal D/C	No risk difference

Hill et al, J Virus Erad 2018, 4:72-78

Pilkington et al. Glasgow HIV 2018. Poster 0143

CONCLUSIONS

PrEP has great potential



1.8 Million Infections

Tens of Millions at risk

FEWER NEW INFECTIONS

FEWER LIVING WITH HIV

Pilkington et al, BHIVA 2018, Edinburgh, Poster 94

PrEP has great potential

PrEP is becoming more affordable

PrEP has great potential

PrEP is becoming more affordable

TDF/FTC as PrEP is safe

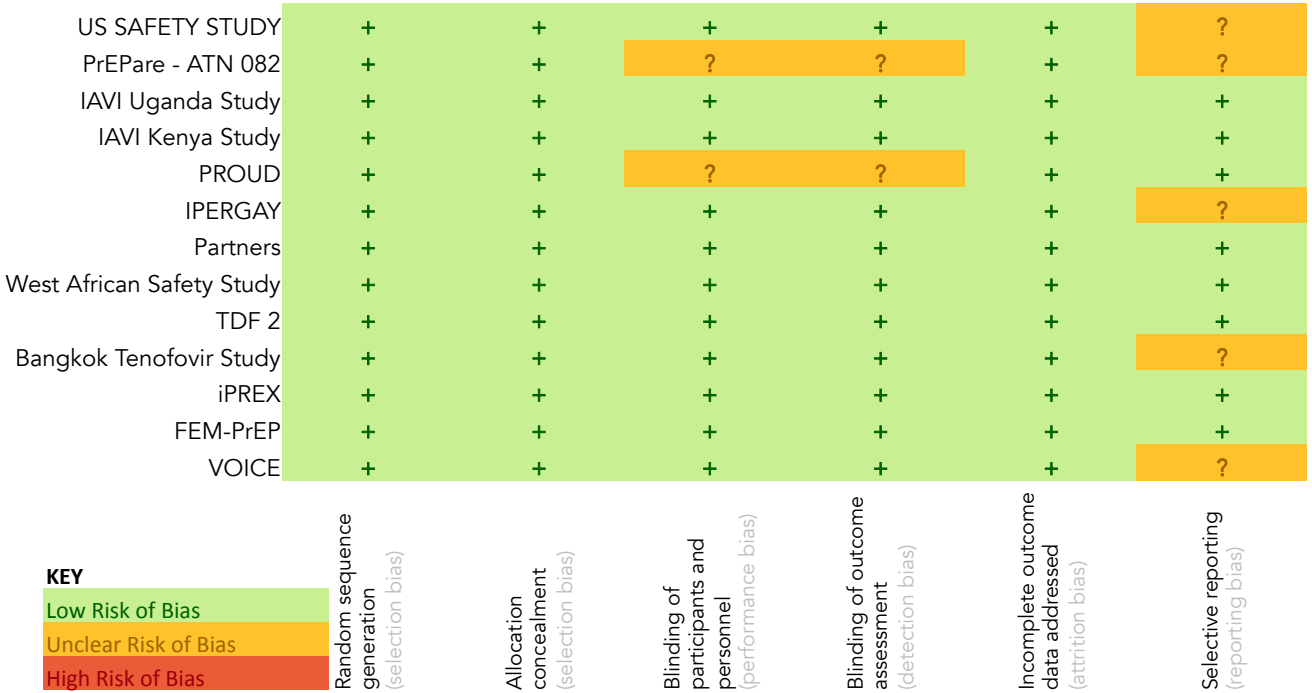
Pilkington et al. Glasgow HIV 2018. Poster 0143

THANK YOU

SUMMARY TABLE

	PrEP Events/ People	Control Events/ People	Risk Difference (95% CI)	Significance
Grade 3/4 AE	1306/ 7504	1259/ 7502	0% (-1% to 2%)	**p = 0.53**
Serious Adverse Events	740/ 7843	795/ 7835	0% (-1% to 1%)	**p = 0.80**
Bone Fractures	217/ 5789	189/ 5795	0% (0% to 1%)	**p = 0.50**
Grade 3+ Creatinine Elevations	8/ 7843	4/ 7835	0% (0% to 0%)	**p = 0.68**
All Creatinine Elevations	336/ 7843	178/ 7835	2% (0% to 3%)	**p = 0.04**

RISK OF BIAS


US SAFETY STUDY
PrEPare - ATN 082
IAVI Uganda Study
IAVI Kenya Study
PROUD
IPERGAY
Partners
West African Safety Study
TDF 2
Bangkok Tenofovir Study
iPREX
FEM-PrEP
VOICE
KEY
Low Risk of Bias
Unclear Risk of Bias
High Risk of Bias
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data addressed (attrition bias)
Selective reporting (reporting bias)

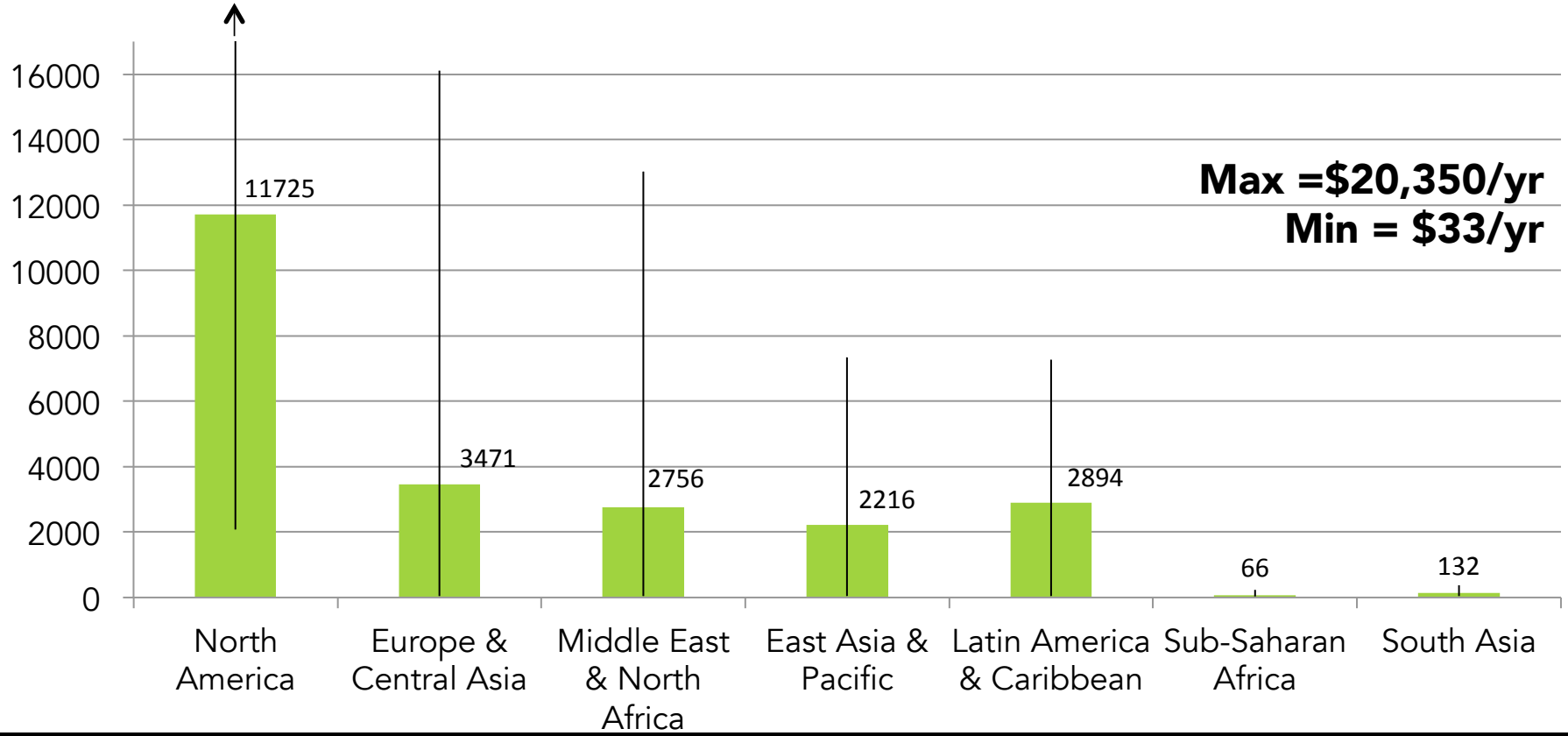
SEARCH TERMS

INTERVENTION	DISEASE	OUTCOME
Pre-exposure prophylaxis/ Chemoprophylaxis/ Pre-Exposure Prophylaxis.mp PrEP.mp	HIV/ Human immunodeficiency virus/ Human Immunodeficiency Virus.mp. HIV.mp.	drug efficacy/ safety/ adverse drug reaction/ adverse outcome/ adverse event/ Treatment Outcome/ safety/ efficacy.mp. Safety.mp. adverse.mp. adverse event*.mp. adverse outcome*.mp.

CRITERIA

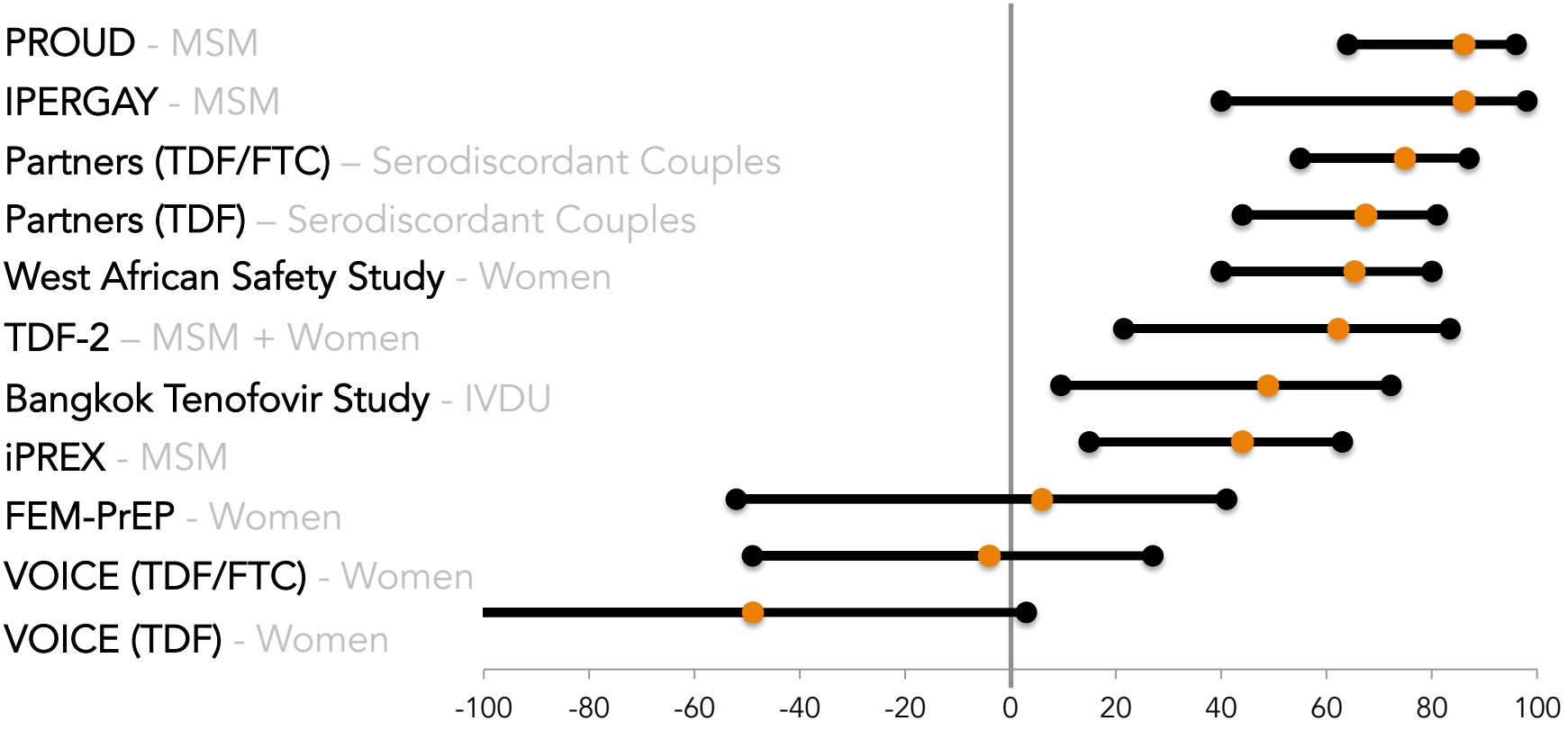
PREP TRIALS	
INCLUSION	**EXCLUSION**
• Controlled randomised controlled trials, with a placebo or comparison arm. • Published in a peer reviewed journal • Clinical trials which asses safety of the treatment drug and report absolute numbers of adverse events occurring in both arms.	• Non Human Trials • Earlier than phase III. • Trials of non-oral PrEP (eg. Microbicide) • Substudies looking at the wrong outcome eg. Measures of adherence and dosing, and measure of qualitative wellbeing or commitement etc

Average Price of PrEP by World Region



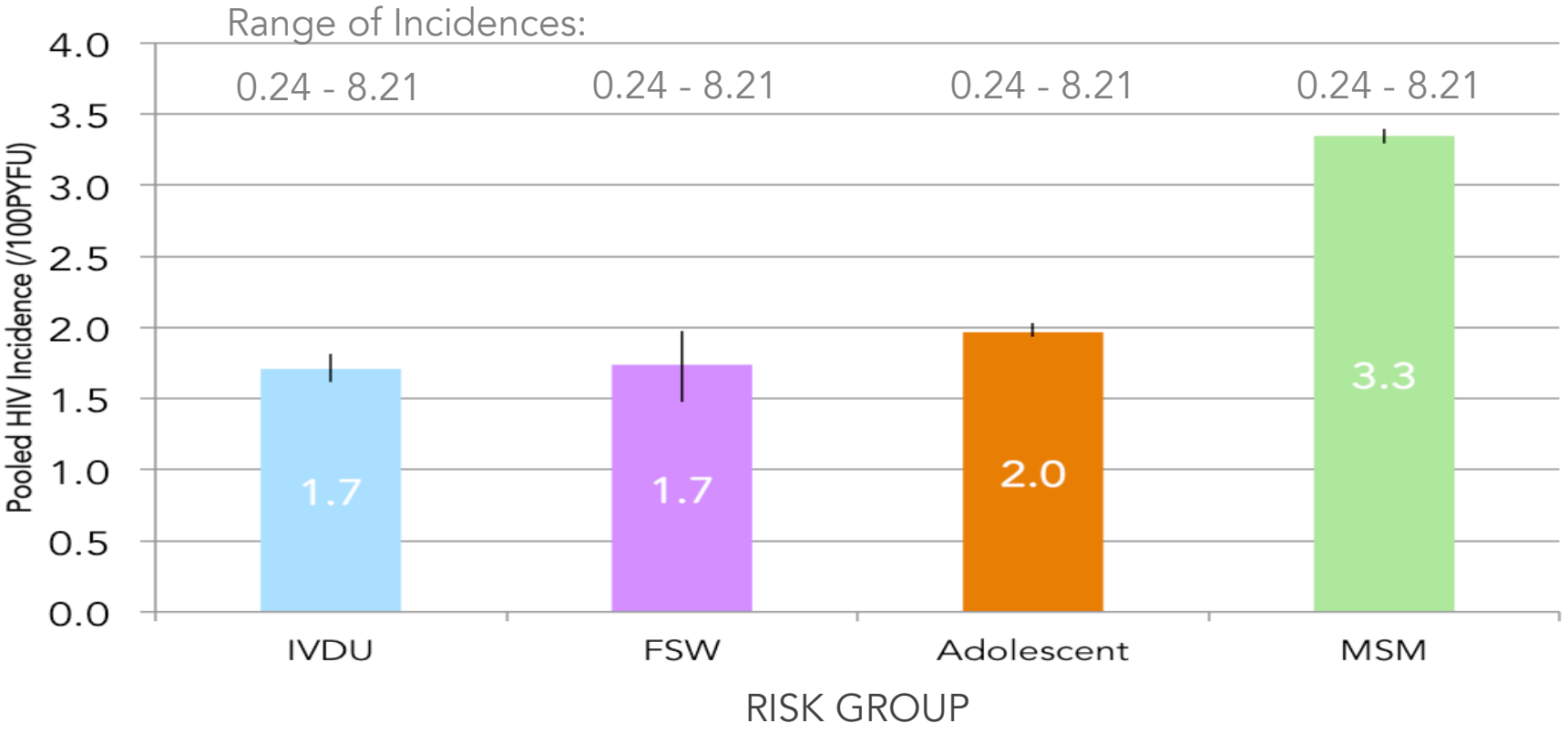
Pilkington et al. Glasgow HIV 2018. Poster 0143

Summary of Efficacies of Oral PrEP Trials



Pilkington et al. Glasgow HIV 2018. Poster 0143

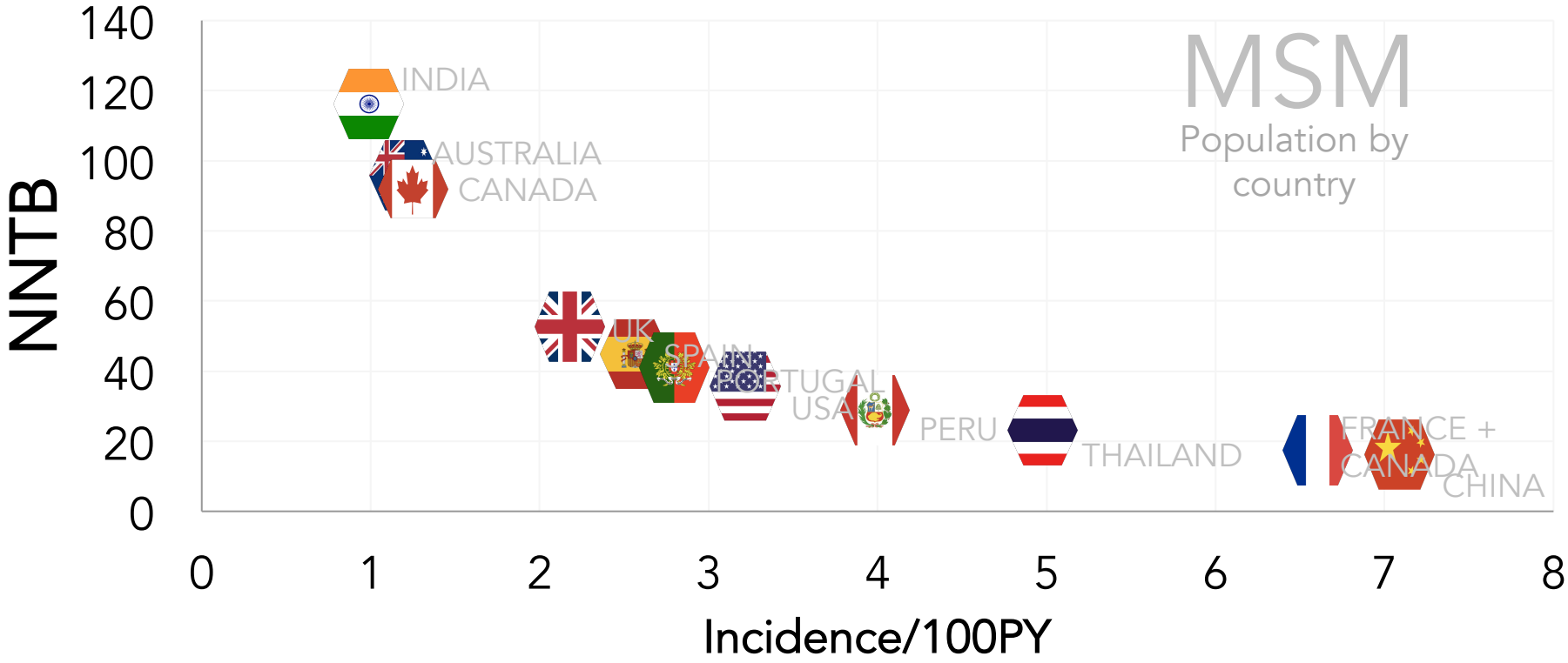
Pooled incidence by Risk Group



Pilkington et al. Glasgow HIV 2018. Poster 0143

NNTB falls as incidence increases

Countries with higher HIV incidence can treat fewer to prevent new infections



Pilkington et al. Glasgow HIV 2018. Poster 0143

SOUTH AFRICA

HIV Incidence	270,000
Number on PrEP	9,500
RATIO	**28:1**

AUSTRALIA

HIV Incidence	1,100
Number on PrEP	14,600
RATIO	**1:13**

Data from AVAC.org 2018
Data from UNAIDS Data report 2017.