Preferred Product Characteristics

World Health Organization

Monoclonal Antibodies for HIV Prevention

15 April 2021

Erin Sparrow, Vaccine Product and Delivery Research, Department of Immunization, Vaccines and Biologicals

Objectives and expected outcomes of the meeting

Objectives:

- Present the rationale and context for developing WHO PPC guidance for HIV monoclonal antibodies with a focus on meeting the needs of LMICs including in the context of other prevention products on the market or on the horizon.
- Evaluate the draft PPC document tables and discuss key characteristics & related issues
- Gather input on key issues/research priorities to include in an article in a peer reviewed journal, to complement and contextualise the PPC guidance.

Expected outcomes:

- Recommendations for finalization of the HIV mAb PPC document as a draft for public consultation.
- Identification of critical product attributes/characteristics that require further consideration for research and/or evidence to support policy and implementation discussions.

Agenda for the PDVAC meeting

Time (Geneva)	Topic	Duration	Detail	Moderators, speakers
15.00 – 15.05	Introduction	5’	• Welcome remarks, roll call, agenda and objectives	Martin Friede (WHO) Birgitte Giersing (WHO) David Kaslow (PATH)
15.05 – 15.20	The context for development of PPCs for HIV monoclonal antibodies	15’	• Public health need (epidemiology and different target populations) • Current WHO recommendations/schedule for PrEP and PMTCT and issues with current products (access, adherence, side-effects, resistance) • UNAIDS and WHO updated Guidance on Ethical considerations in HIV prevention trials, overview & implications	Michelle Rodolph (WHO)
15.20 – 16.00	Update on development of HIV prevention products	15’ 10’ 5’ 10’	• Long acting ARVs (e.g CAB-LA and others in the pipeline) • The dapivirine (DVP) vaginal ring • Results of the AMP trials of VRC01 (HIV mAb) • Other mAbs in the pipeline • Brief overview of vaccines in the pipeline • Questions	Sinead Delany-Moretlwe (Wits) Barney Graham (NIH) Jerome Kim (IVI)
16.00 – 16.20	The rationale for development of PPCs for HIV monoclonal antibodies	10’ 10’	• Value proposition: Potential contribution of mAbs to HIV prevention options • Discussion	Susan Buchbinder (SFDH)

16.20 – 17.00	Facilitated discussion on PPCs for HIV mAbs
	Note: *if time runs over some discussion can move to the closed session*
		40’	• HIV mAbs PPC overview and discussion with a focus on:
			  • Target populations
			  • Efficacy
			  • Dose regimen
			  • Route of Administration
				Erin Sparrow (WHO)

Context for development of PPCs for HIV monoclonal antibodies

Michelle Rodolph

WHO HIV, Hepatitis and STIs Department
Geneva, Switzerland

World Health Organization

15 April 2021

Outline

- Public health need
  - Epidemiology
  - Targeted populations

- Current WHO recommendations on PrEP
  - oral PrEP
  - DPV vaginal ring

- Guidance on Ethical considerations in HIV prevention trials (UNAIDS and WHO, 2021)

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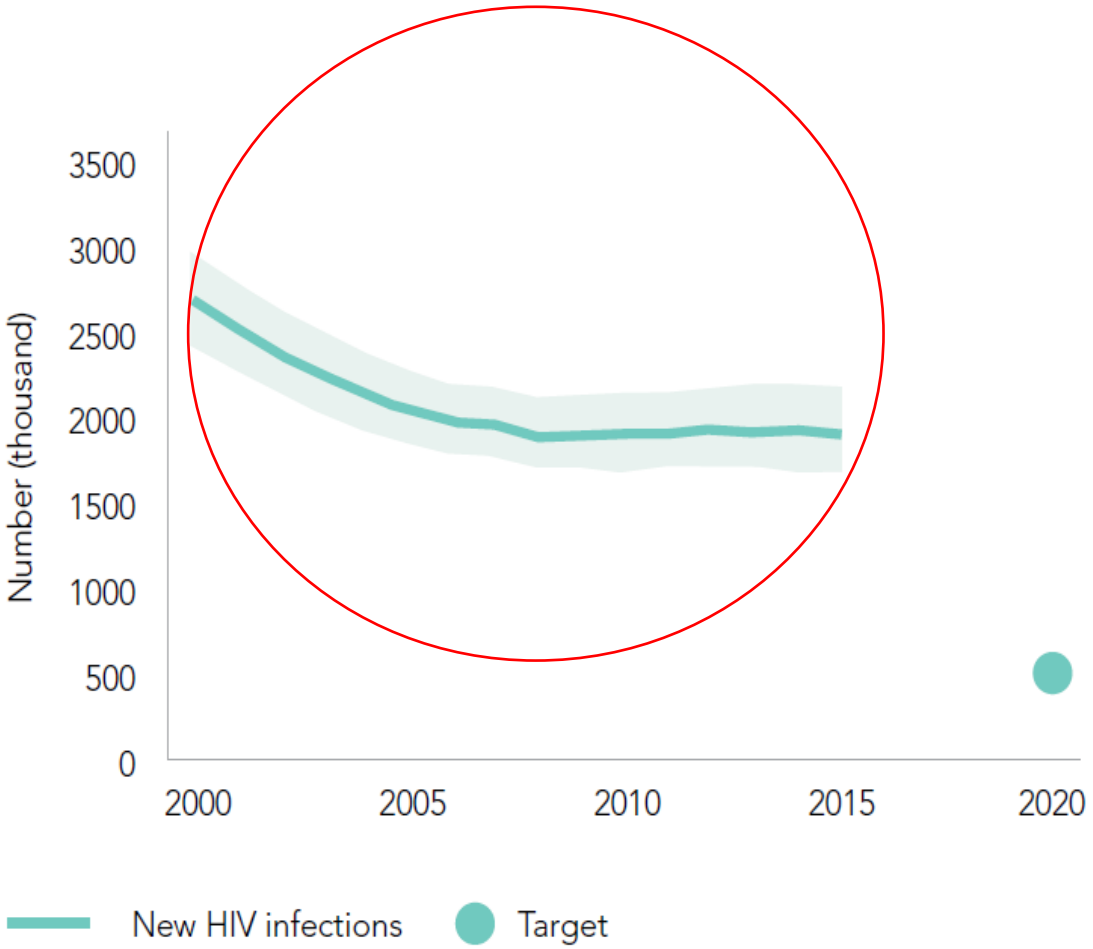
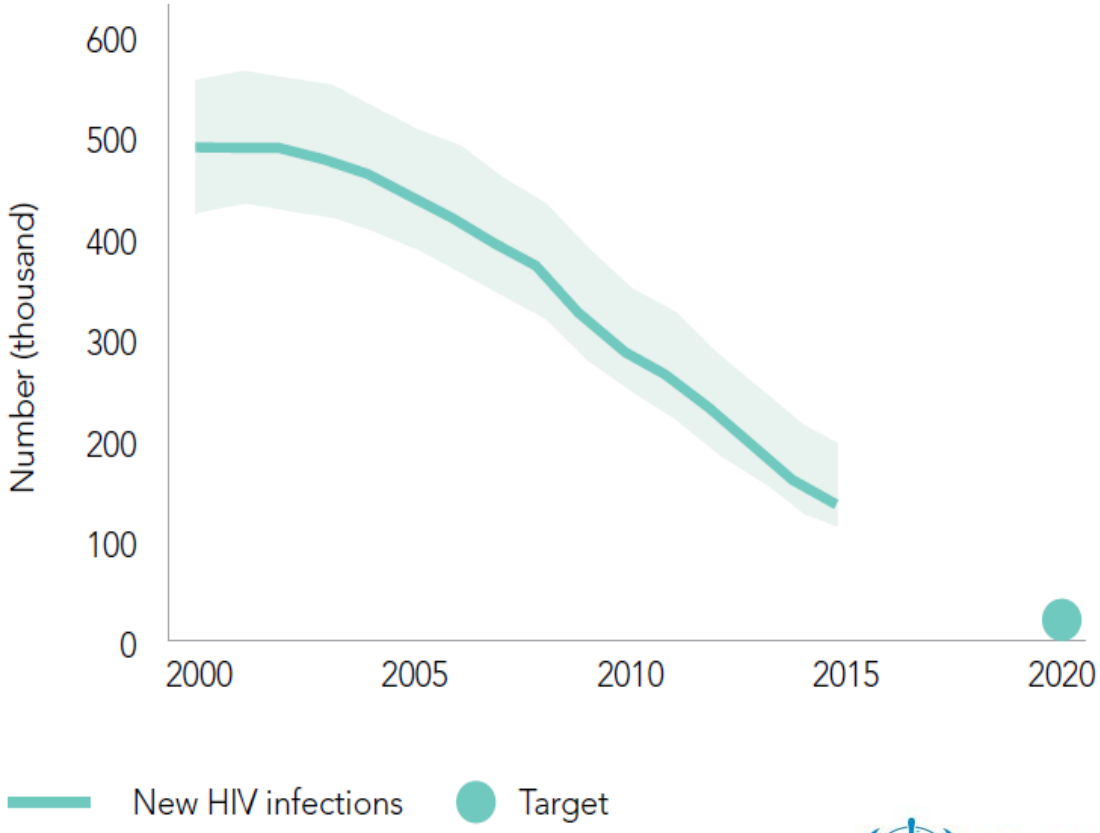
New HIV infections among adults >15, global, 2000–2015



New HIV infections among children, global, 2000–2015



Source: UNAIDS/WHO 2018 estimates.

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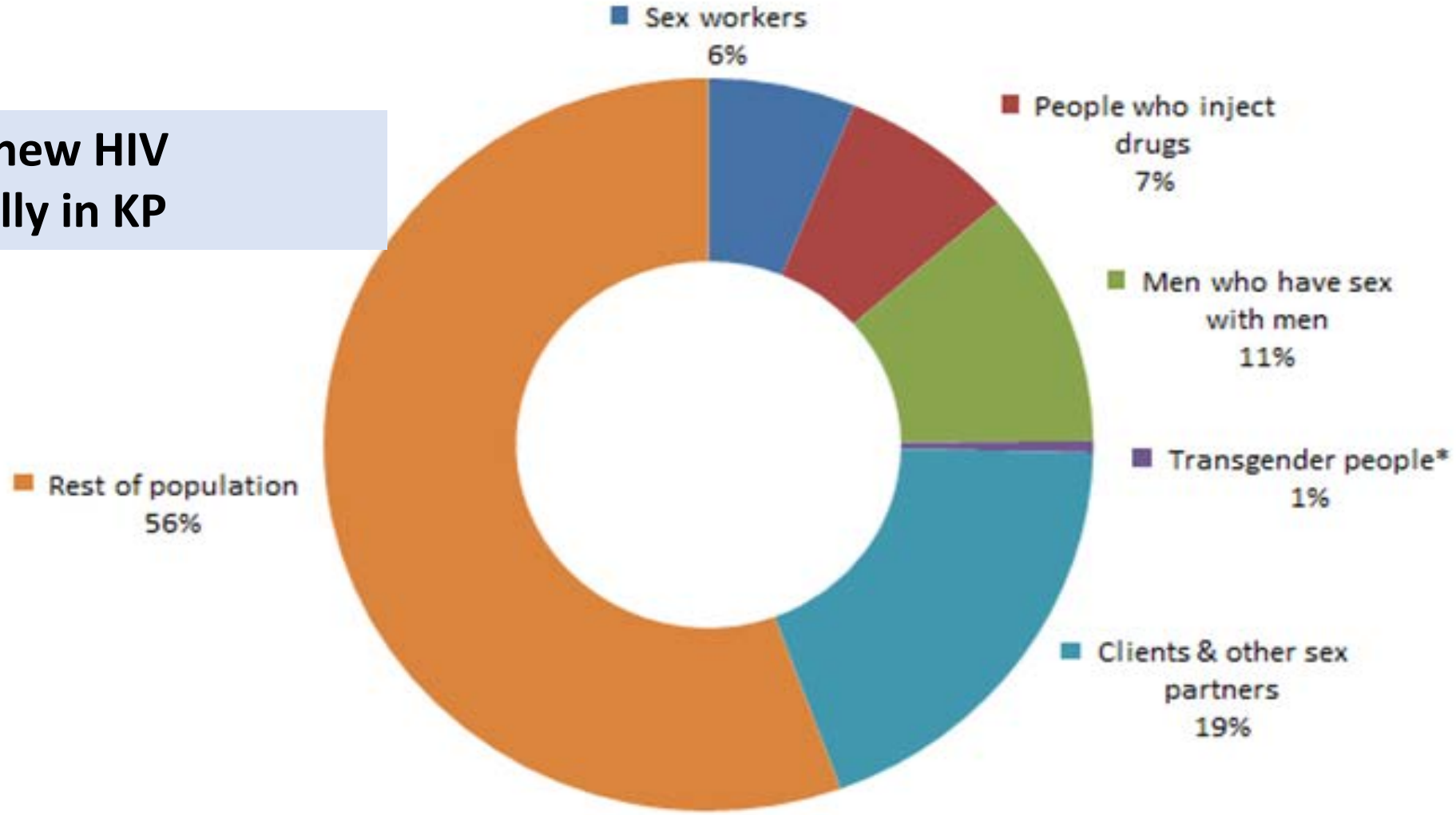
Prevention focus must be for KP

Global picture: new infections, by population group, 2016

At least 44% of new HIV infections globally in KP



* Reflects two regions only: Asia-Pacific and Latin America-Caribbean

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Target setting for population groups ("know your epidemic")

Everywhere

- Sero-discordant couples (SDC) – as a bridge to viral suppression of HIV+ partner

Many settings – all regions

- MSM and transgender populations (note heterogeneity of situation and risk)

Some setting in sub Saharan Africa

- Sex workers

Some (very specific) settings in southern and East Africa

- AGYW ;+/- 'higher risk' men; people who identify their risk and request PrEP

Very specific situations (e.g. People who inject drugs (and people who use drugs – overlapping risks and vulnerabilities) – but harm reduction the priority for PWID)

World Health Organization

Treatment is easy – prevention more complex

WHAT? Multiple options

- Harm reduction: NSP and OST
- VMMC
- PrEP
- PEP
- STI management
- Condoms and lubricants
- HIV testing
- Partner/couples testing
- Behavioural interventions
- Treatment (as prevention)
- Mobile technologies

Multiple HIV prevention options

WHO? Many populations

- Adolescent girls 15-19 y
- Young women 20-24 y
- Older women >25 y
- Serodiscordant couples
- Men and adolescent boys
- Key populations
- (MSM, SW, transgender people PWID and people in prisons)
- Other pop groups

Significant heterogeneity, and intersections

HOW? Numerous issues

- National leadership
- Partnerships and engagement
  - Public sector
  - Private sector
  - Community
- Evidence based normative guidance→ implementation guidance
- Complementary approaches also addressing structural issues
- Strategic information for action

Implementation packages and platforms

Oral PrEP: 7 yrs - from 1st RCT → increasing implementation

Iprex (multi site) PrEP 44% ↓ HIV (MSM)

Fem-PrEP (SA, Kenya, Tanzania) PrEP no↓ HIV (♀)

Partners (Kenya & Uganda PrEP 73% ↓ HIV (SDC)

TDF2 (Bostwana) PrEP 62% ↓ HIV (M&W)

US FDA approval of TDF/FTC for PrEP

Voice PrEP & gel no↓ HIV (♀)

Proud (UK) PrEP 86 % ↓ HIV (MSM)

iPergay (France) PrEP 86 % ↓ HIV (MSM)

EMA approval of TDF/FTC for PrEP

SA National PrEP program

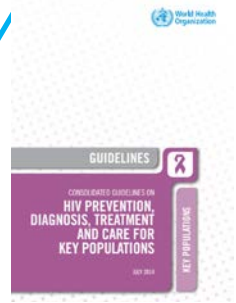
EML inclusion of TDF; TDF/FTC & TDF/3TC for PrEP

Numerous demo projects and OLE

2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018

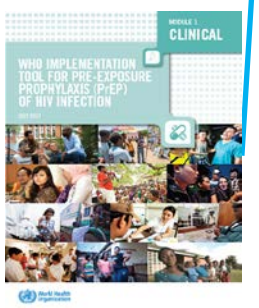
First WHO PrEP GL for demo projects MSM, TG & SDC

WHO PrEP KP rec for PrEP for KP (except PWID) (as part of KP GL)

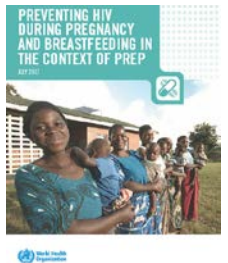


WHO enabling PrEP rec for all at 'substantial HIV risk' PWID) (as part of KP GL)

WHO PrEP implementation tool)



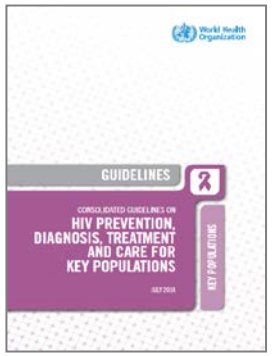
WHO update on PrEP use during pregnancy & BF)



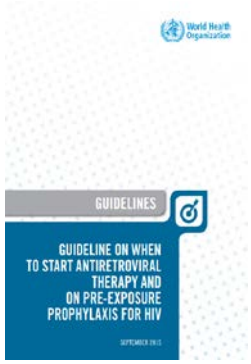
WHO PrEP issues for adolescents)

Evolution of WHO PrEP recommendations

2012 PrEP for SDC, MSM and TG (***conditional*** *recommendation in the context of demo projects)*



2014 PrEP for MSM (**strong** recommendation)
Other KP (***conditional*** *recommendation; no recommendation for PWID*)



2015 PrEP for people at substantial HIV risk (≈3 per 100 person years) *(**strong** recommendation*)

2016 PrEP drugs on EML *(TDF/FTC; TDF/3TC; TDF)*

How WHO makes it recommendations

- **Trial results** RCT > observational studies
- **Values and prefer**ence of users & providers
- **Costs**
- **Feasibility**
- **Benefits vs. harms**

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Pre-exposure prophylaxis

Key lessons to data with PrEP implementation

Key message

- ✓ **PrEP works**
  - Probably "easier" for MSM
  - Real world effectiveness better than trials
- ✓ **Not for EVERYONE**
  - Uptake and continuation is variable
- ✓ **Not for ALWAYS**
  - Seasons of HIV risk
- ✓ **Adherence** is critical for PrEP effectiveness
- ✓ **Other services beneficial, valued and necessary**
- ✓ **Many benefits beyond PrEP itself**

Implement strategically

- Start in the highest incidence areas
- Start with highest incidence groups
  - SDC
  - MSM and transgender women
  - Sex workers
  - People who inject (and use) drugs
  - Others…….
- Integration and linkages to existing services
- Maximise other inputs to increase impact
  - (STI, FP, hep B&C, other prevention, testing & ART linkage, GBV)
- Community awareness in critical

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Recommendation

The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk* of HIV infection as part of combination prevention approaches.

(conditional recommendation; moderate-certainty of evidence)

* Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP

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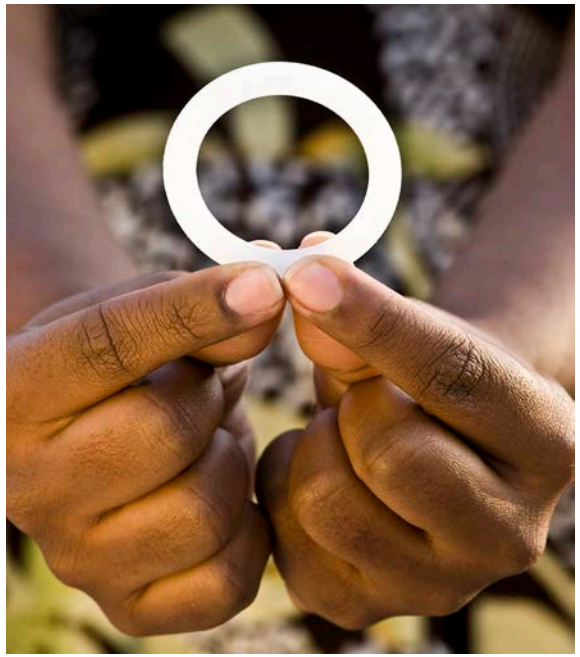
Implementation considerations / Research gaps

- Addressing the provision of the DPV-VR as part of **comprehensive services**;
- Ensuring women are offered full information in order to make an **informed choice** about the benefits and potential risks when considering to use the ring;
- **Adolescent girls and young women** may need more support during initiation and for continuation;
- Acceptability among women from **key population groups;**
- Additional **adherence support** and **demand creation;**
- **Training and support for providers** to understand and be able to offer this new product;
- Further information on **safety in pregnancy and breastfeeding** and **cost-effectiveness.**



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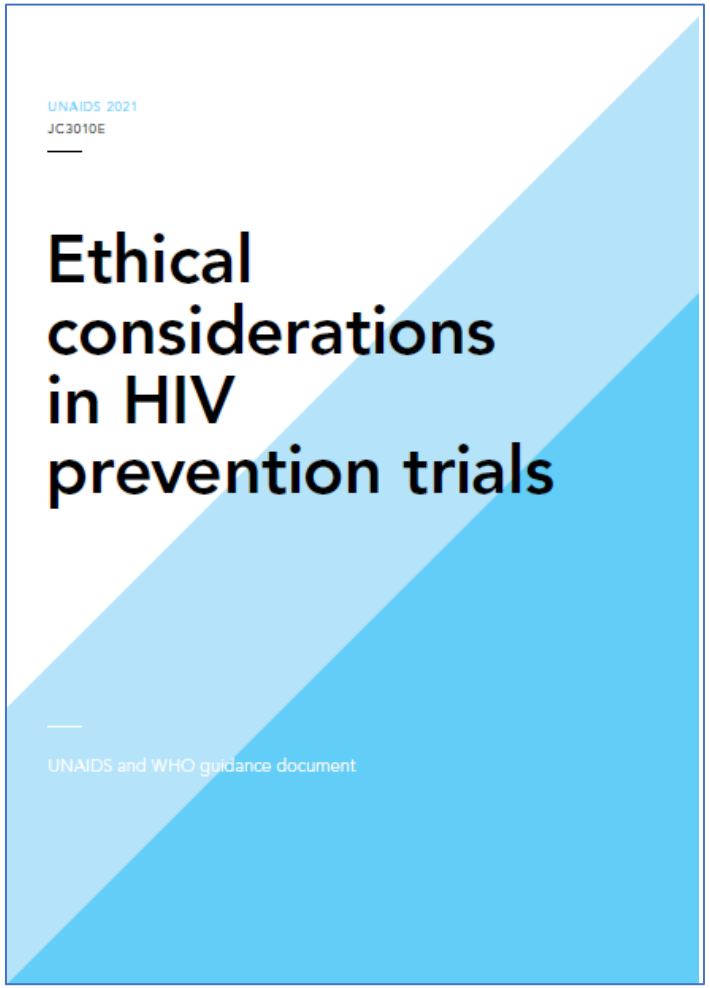
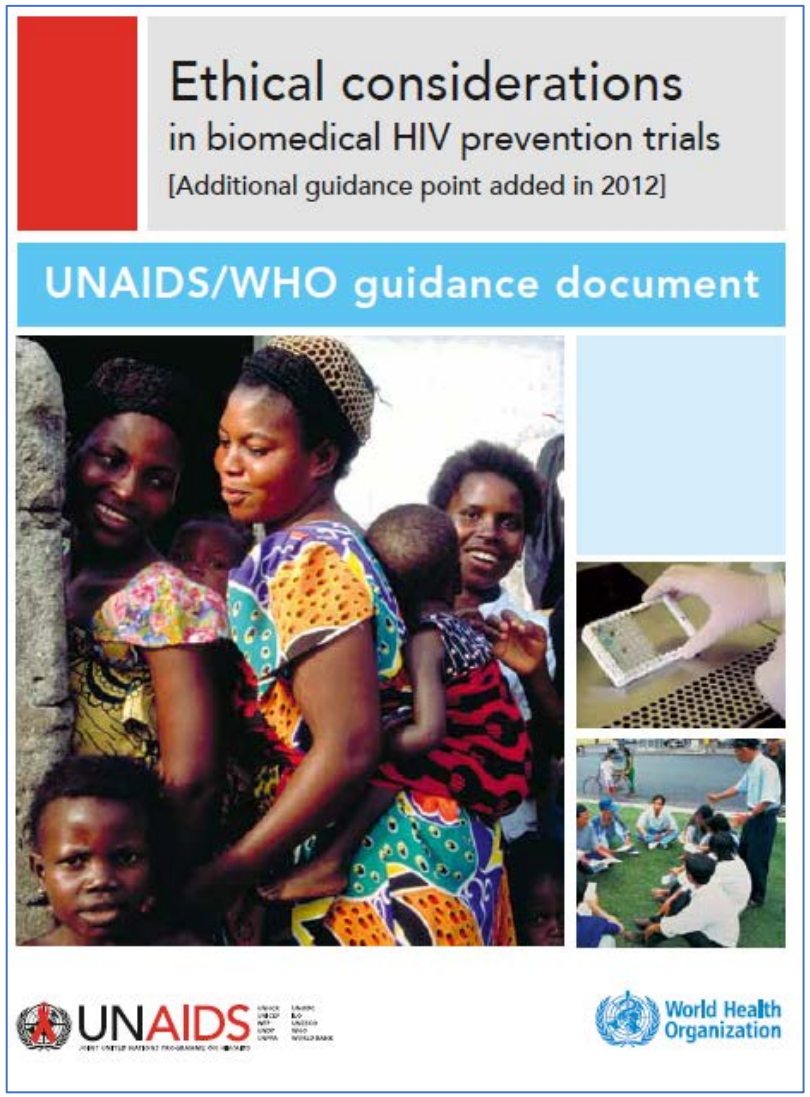
Ethical considerations in HIV prevention trials UNAIDS and WHO Guidance (2021)



Download the Guidance

UNAIDS/WHO Ethical considerations in HIV prevention trials

https://bit.ly/3a35KmO



HIV Prevention Trials

Asking people to consent to join an experiment in which HIV infection is the outcome

14 revised or new guidance points

- **Necessity for HIV Prevention Trials**
- **Community Partnership**
- **Scientific and Ethical Conduct and Review**
- **Scientific Validity**
- **Fair and Inclusive Selection of Study Populations**
- **Social or Political Contexts of Vulnerability**
- **Potential Harms**
- **Benefits**
- **Informed Consent**
- **Confidentiality and Privacy**
- **Standard of Prevention**
- **Care and Treatment**
- **Trial Monitoring**
- **Post-trial access**

Updated guidance….Key points

- Includes a number of **key revisions** to the 2012.
  - Involvement of **community members** is highlighted at all stages of research projects
  - **Equal partnership** among research teams, trial sponsors, key populations, potential participants and the communities that live in settings where trials are taking place.
- **Fairness** is emphasized.
  - Inclusive selection of study populations without arbitrary exclusion on the basis of characteristics such as age, pregnancy, gender identity or drug use
- Underlines **contexts of vulnerability**—
  - people and groups should not be labelled as vulnerable, but rather the emphasis should be on the social or political contexts in which people live that may render them vulnerable.
- That researchers and trial sponsors should, at a minimum, **ensure access to the package of HIV prevention methods** recommended by the World Health Organization for every participant throughout the trial and follow-up is set out in the updated guidance, along with the need for post-trial access by participants to products that are shown to be effective.

Summary

- Human subject research has a long history of entanglement, engagement and elucidation of ethical principles
- Despite some effective tools, 1,700,000 people were newly infected with HIV last year
- Biomedical science holds the promise of expanding the choice of prevention tools, many of which might provide long-term protection to those at risk of infection.
- The new UNAIDS and WHO document provides guidance for ethical review of research studies that preserves the primacy of the rights of individual research participants while promoting progress towards our common goal of ending the HIV epidemic

Acknowledgements

WHO
Rachel Baggaley, Robin Schaefer, Annette Verster, Andreas Reis and Ioannis Mameletzis, Erin Sparrow, Martin Friede

UNAIDS
Peter Godfrey-Faussett, Rosalind Coleman

World Health Organization

Long-acting antiretroviral PrEP – the current landscape

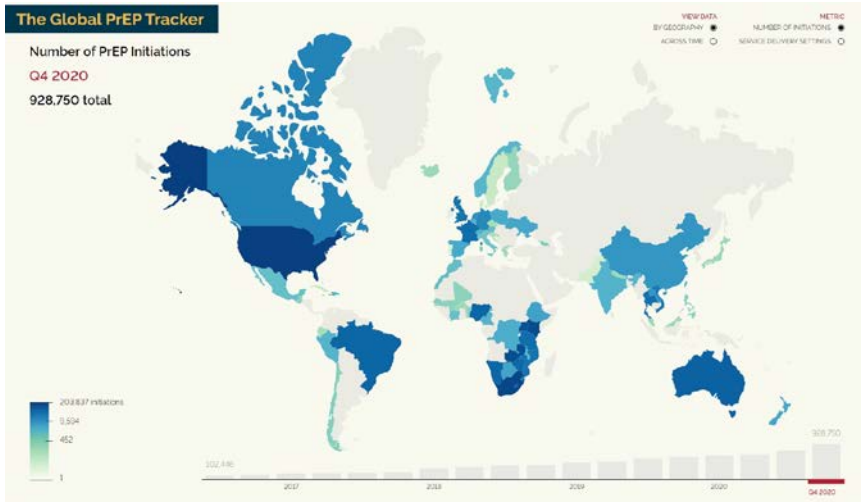
University of the Witwatersrand
WITS RHI

Sinead Delany-Moretlwe, MBBCh PhD
PDVAC, 15 April 2021

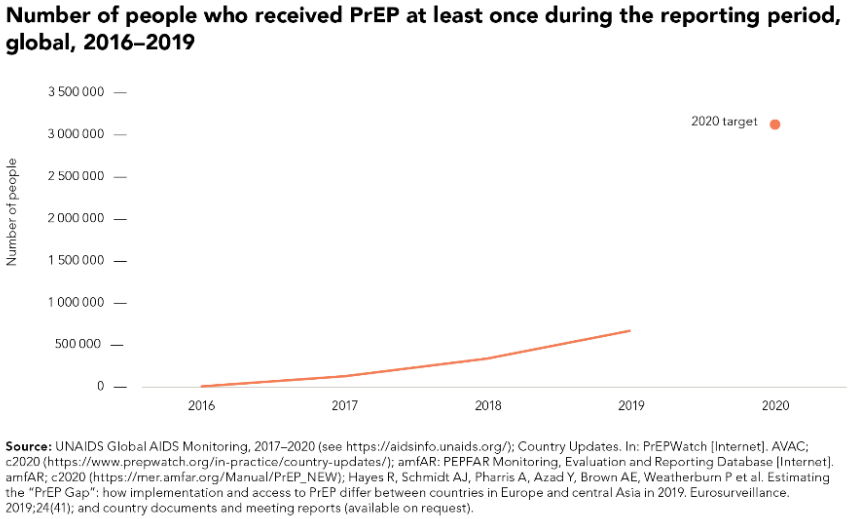
Global PrEP landscape – 8 years in

By Q4 2020, oral PrEP
Included in >70 country programmes
928,750 people on PrEP world wide

Goal: 3 million on PrEP by 2020



USA, South Africa, Kenya,
top 3 countries for PrEP initiations

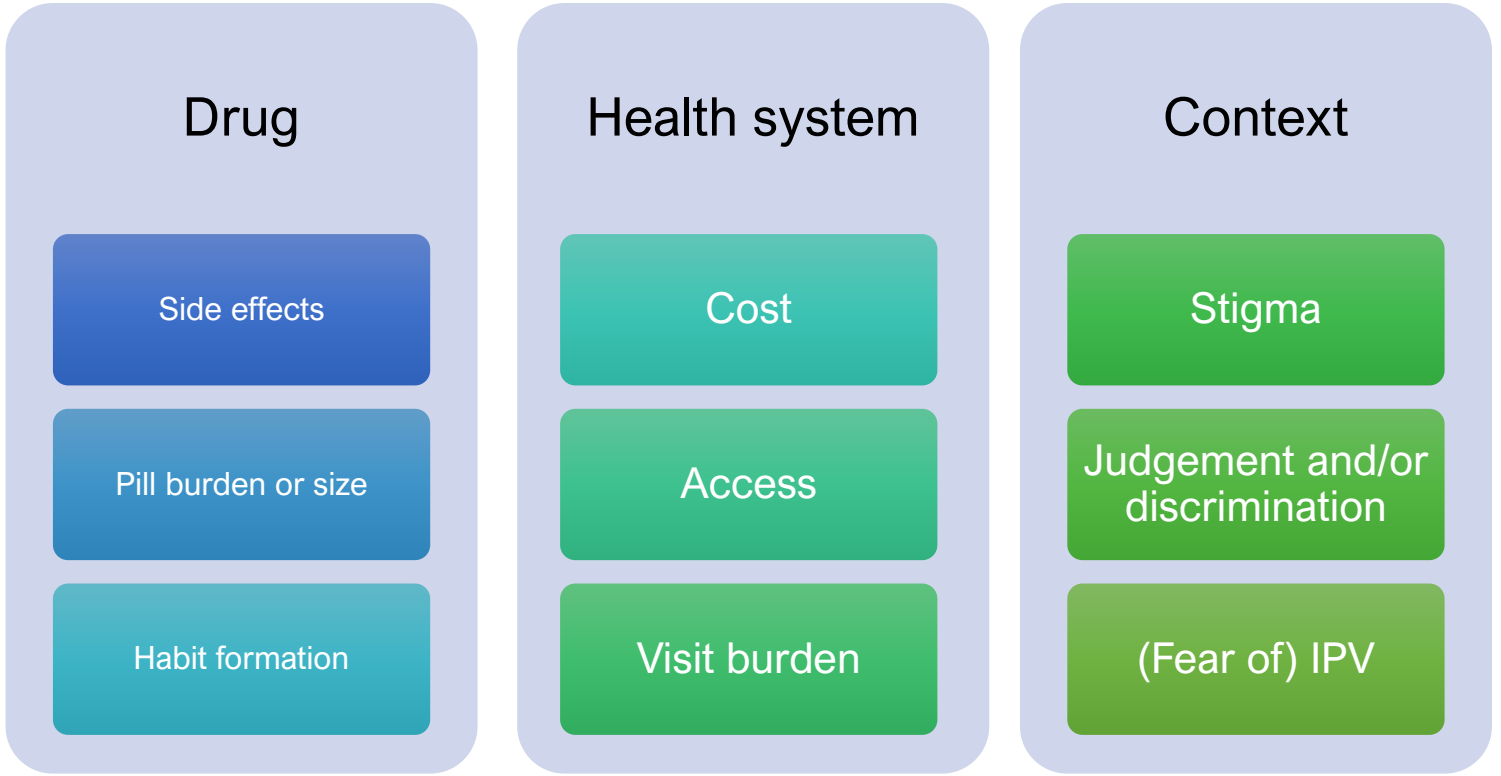


… but initiations do not translate to continued use. Systematic review found 1/3 discontinued by Month 1.

www.prepwatch.org; www.unaids.org;

Reasons for oral PrEP discontinuation

Consistent across populations and geographies



Long-acting products could overcome some of these barriers
Many people want discreet prevention products that require minimal daily effort

Zarwell, AIDS Behav 2020; Bargnighausen, Culture Health Sex 2020; Pillay, PLoS One, 2020 Rutstein, Lancet HIV, 2020;

Monthly dapivirine ring

- Flexible silicone vaginal ring developed by IPM
  - Self-inserted monthly
  - Dapirivine released over 30 days
- Low systemic absorption
- Two Ph 3 trials showed well-tolerated and reduced HIV risk in women by ~30%
- Open-label extension studies showed greater use with estimated ~50% risk reduction
- Favourable EMA opinion, July 2020
- Included in WHO clinical guidance, March 2021
- Paves the way for in-country approvals

Nel, NEJM 2016; Baeten, NEJM 2016; Baeten, IAS 2019; Nel, SA AIDS 2019

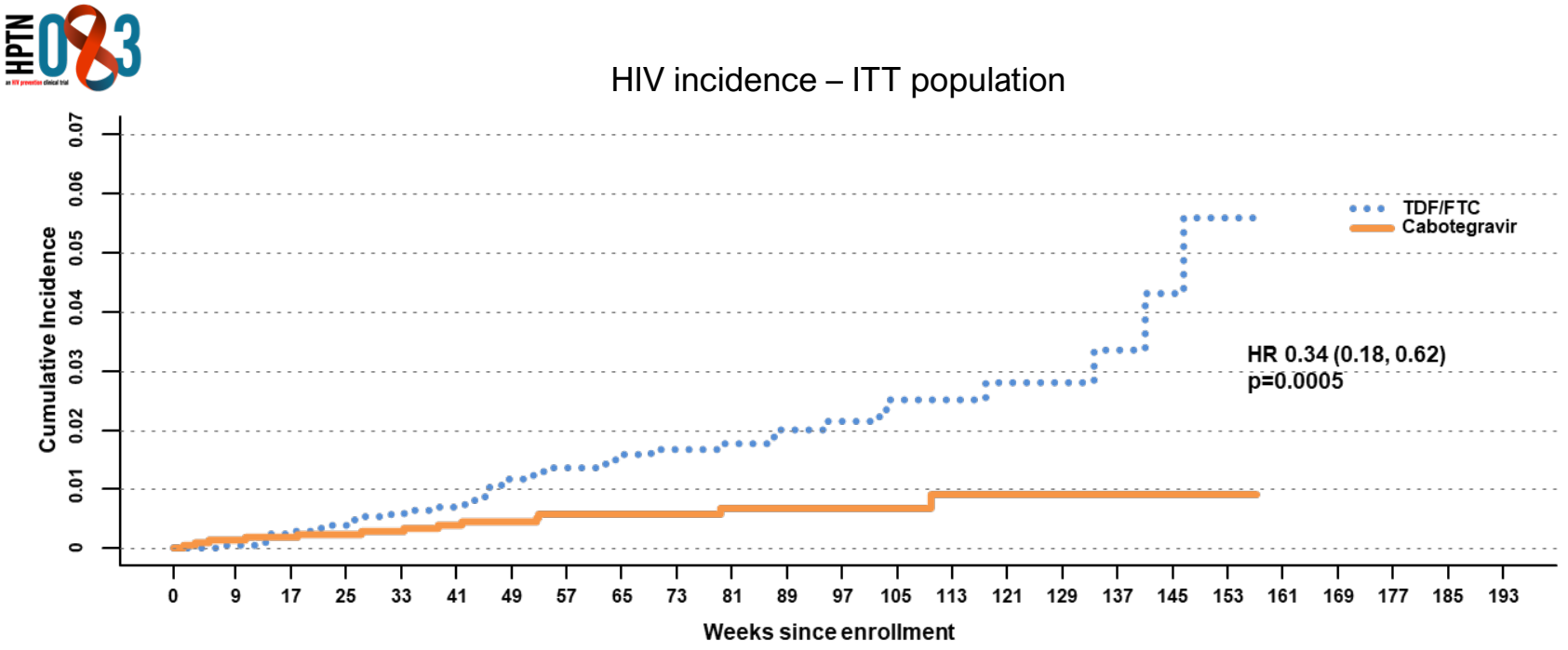
Monthly dapivirine ring – additional considerations

- Promising technology and an alternative prevention option for women
  - 90-day ring,
  - dapivirine-contraceptive ring
  - other ARV-based rings

- Additional data requirements
  - Adolescents - lowest adherence, but at highest risk for HIV
  - Resistance in seroconverters
  - Pregnant and breastfeeding women - additional safety studies ongoing

- Cost and cost effectiveness
  - Unit cost $9/ring
  - Countries currently considering relative CE given other long-acting options

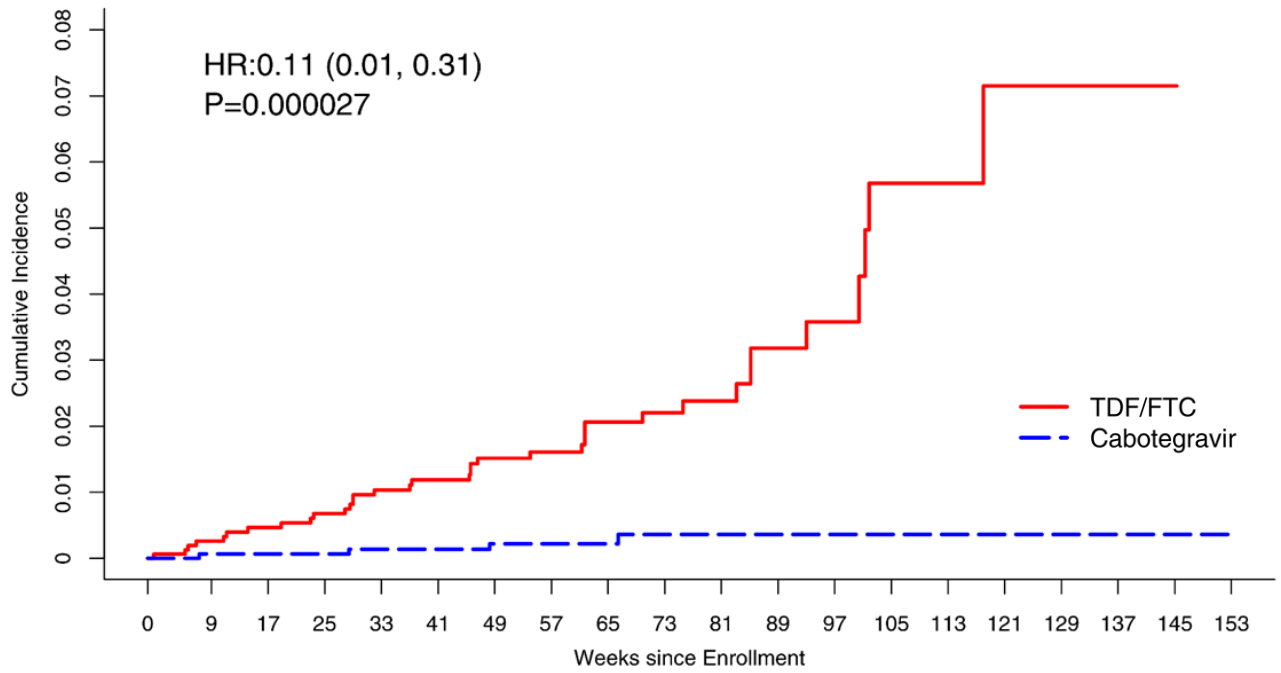
Long-acting injectable cabotegravir – MSM and TGW (N=4566)



- Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY
- Adherence subset plasma TFV > 40 ng/ml 75%
- Grade 2+ ISR, pyrexia, ↑ blood glucose, nasopharyngitis CAB>TDF/FTC
- 2.2% discontinued d/t ISR
- No evidence of weight gain associated with CAB LA

Landovitz RJ et al. AIDS 2020, #OAXLB0101;

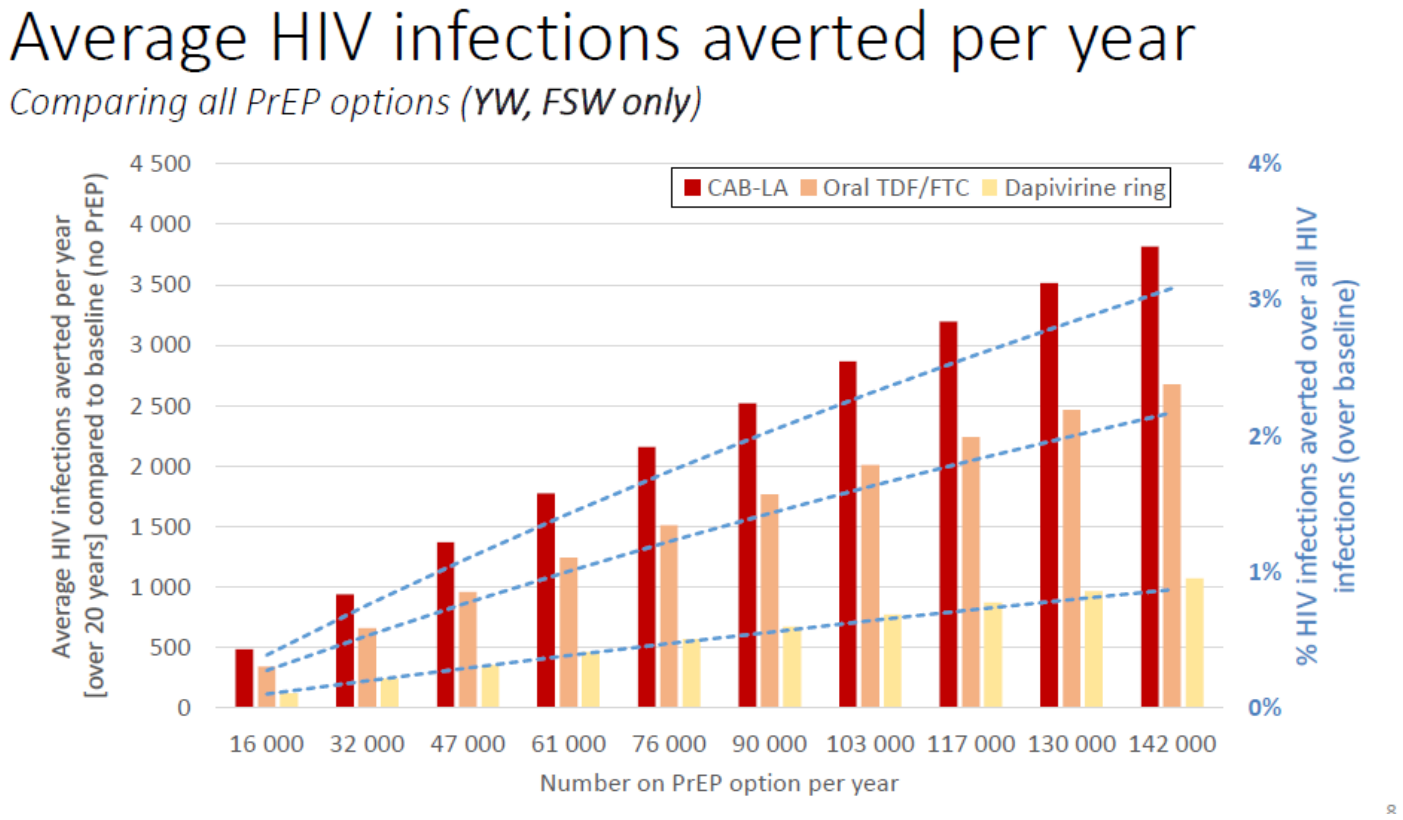
Long-acting injectable cabotegravir - ciswomen (N=3224)



- Pooled incidence 1.03 (0.73, 1.4) per 100 person-years
- Adherence subset TFV > 40 ng/ml 46%
- Grade 2+ ISR CAB>TDF/FTC
- No discontinuations associated with ISR
- No evidence of weight gain

Delany-Moretlwe, HIV R4P #LB1479

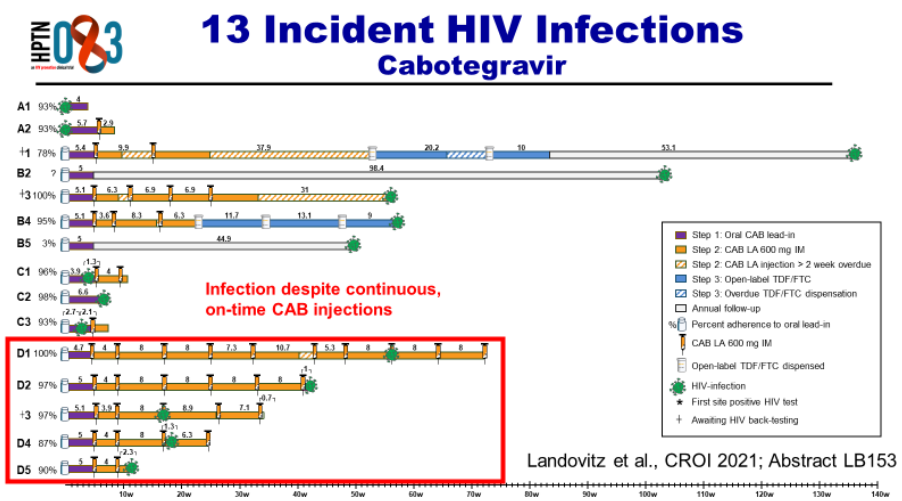
Long acting injectable cabotegravir – considerations

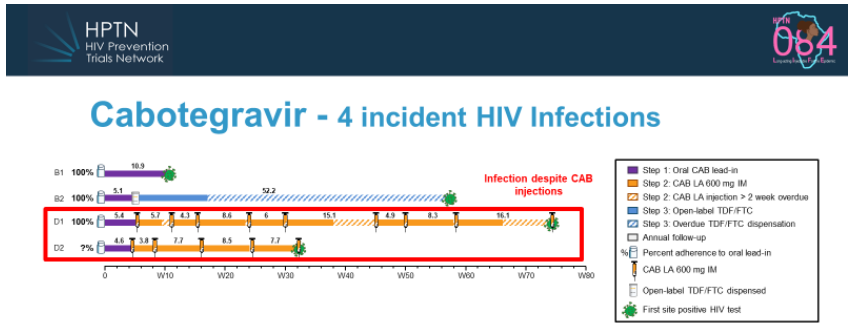


Long-acting option that provide protection for high risk populations
Safe and well tolerated
Potential to be cost-effective even at higher price given prevention benefit
Potential to be developed as a multi-purpose prevention product with contraceptive

Jamieson, SA NDOH HIV Prevention workshop 2021

Long-acting cabotegravir - unknowns

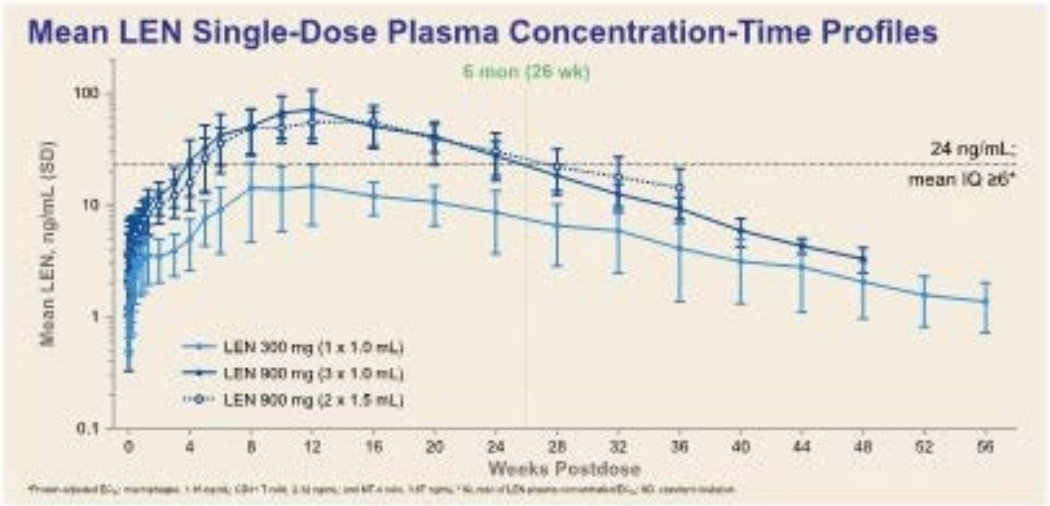




- **Concerns about resistance**
  - PK tail was primary concern but not supported by evidence from trials
    - May be more of an issue in programmes
  - Delays in diagnosis with standard testing approaches
    - HIV RNA testing? cost?
  - Breakthrough infections associated with resistance
    - Drug concentrations at site of infection? Rectal vs vaginal compartment
    - Pts did suppress on other regimens but concerns where DTG first-line
- Need more data!
- Also need more data on pregnancy and breastfeeding – planned for OLE

Other LA injectables
Lenacapavir: capsid inhibitor

- Lenacapavir GS-6207 first-in-class capsid inhibitor
- Oral and SC formulations
- Sustained delivery formulation supports 6-monthly dosing
  - Ph I HIV negative pts single dose
  - LEN 900 mg SC maintained target concentrations for 26 weeks



- Emerging data highlighting potential for resistance concerns given LA
- Also drug interaction considerations
- Trial results expected 2023/4, will allow active dosing in pregnancy

Begley, IAS 2020; Link Nature 2020;Lutz, CROI 2021

Monthly oral pills: Islatravir

- Islatravir: Nucleoside reverse transcriptase translocation inhibitor
- Long half-life, potent antiviral, good tissue concentrations in genital tissue
- Shorter PK tail after cessation
- Phase III trial dose confirmed in phase II studies
- Phase III trials planned to start in 2021, results 2023/4
- In cisgender women trial, will allow active dosing in pregnancy

- Issues to consider
  - Will a monthly oral pill be acceptable?
  - What advantages will an oral pill have to have over existing options?
    - Eg cost, ease of administration/delivery, HIV diagnosis, resistance and treatment options
  - If oral ISL effective, will inform development of implant delivered annually
  - Could by co-formulated with contraceptive

Subcutaneous implants

- Simple insertion and removal
- Long-acting ~ 1 year
- More consistent and predictable drug release
- Can be combined with contraception
- Several potent antiretrovirals for evaluation
  - E.g. TAF, CAB LA, ISL

- Safety?
- Acceptability?
- Health system capacity?
- Cost

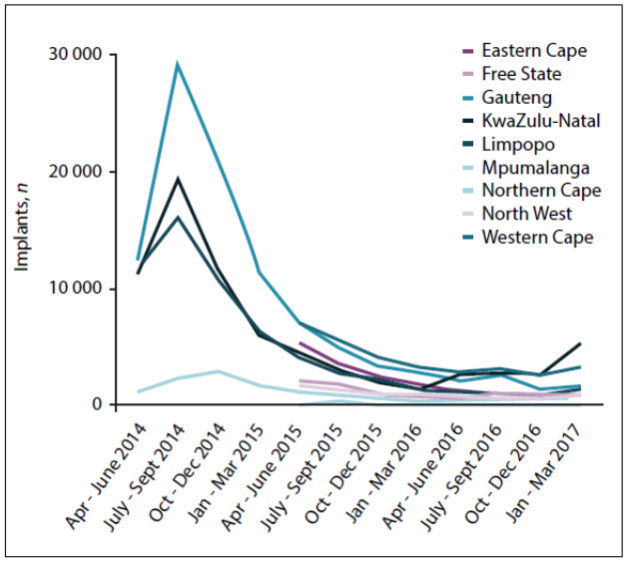


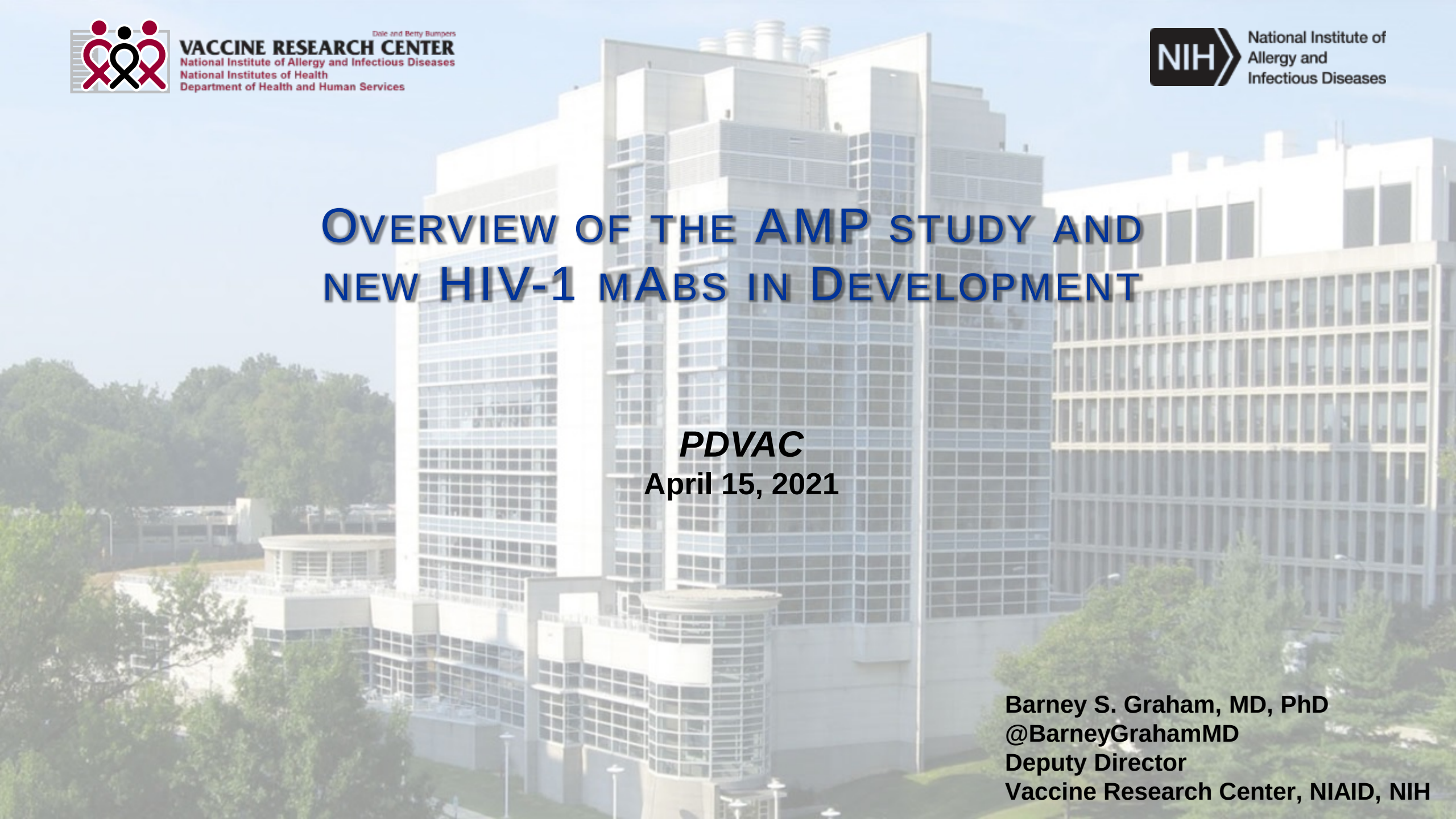
Fig. 1. Implant insertions in SA by province (April 2014 - March 2017).[26] *(No data are available for the Eastern Cape, the Free State, Mpumalanga, North West and the Western Cape before April - June 2015.)*

Summary

- Increasing number of PrEP options
- An expanded set of options has the potential to increase HIV prevention coverage and have a public health impact
- New HIV prevention options will need
  - Similar/better effectiveness
  - Similar or better safety profile
  - For use in adolescents, pregnant and b/f women
  - Potential to combine as a multi-purpose product
  - Not interfere with current HIV diagnostic algorithms
  - Minimal resistance concerns
  - To be acceptable
  - Cost and cost-effectiveness
  - Be delivered within constrained health systems
    - Reduced requirements for specialist skills or infrastructure
- Time and more data will address many of current unknowns

Acknowledgements

- Raphael Landovitz
- Beatriz Grinszteyn
- Mina Hosseinpour
- Charles Flexner
- HPTN



Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

National Institute of Allergy and Infectious Diseases

Overview of the AMP study and new HIV-1 mAbs in Development

PDVAC

April 15, 2021

Barney S. Graham, MD, PhD
@BarneyGrahamMD
Deputy Director
Vaccine Research Center, NIAID, NIH

AMP Studies

Phase 2b Proof-of-Concept Trials (Harmonized Protocols) Designed to Test the Efficacy of VRC01 Antibody to Prevent HIV Acquisition

AMP = Antibody Mediated Prevention

HVTN 704/HPTN 085

(MSM and TG in the Americas & Europe)

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

4600 volunteers total

HVTN 703/HPTN 081

(Women in sub-Saharan Africa)

AMP
STUDY

Slide Courtesy: Larry Corey

Study Schema

IV Infusions

End point

Infusion number (visit week)												
Treatment	1 (W0)	2 (W8)	3 (W16)	4 (W24)	5 (W32)	6 (W40)	7 (W48)	8 (W56)	9 (W64)	10 (W72)	W80*	W104**
VRC01 10 mg/kg	+	+	+	+	+	+	+	+	+	+	-	-
VRC01 30 mg/kg	+	+	+	+	+	+	+	+	+	+	-	-
Control	+	+	+	+	+	+	+	+	+	+	-	-

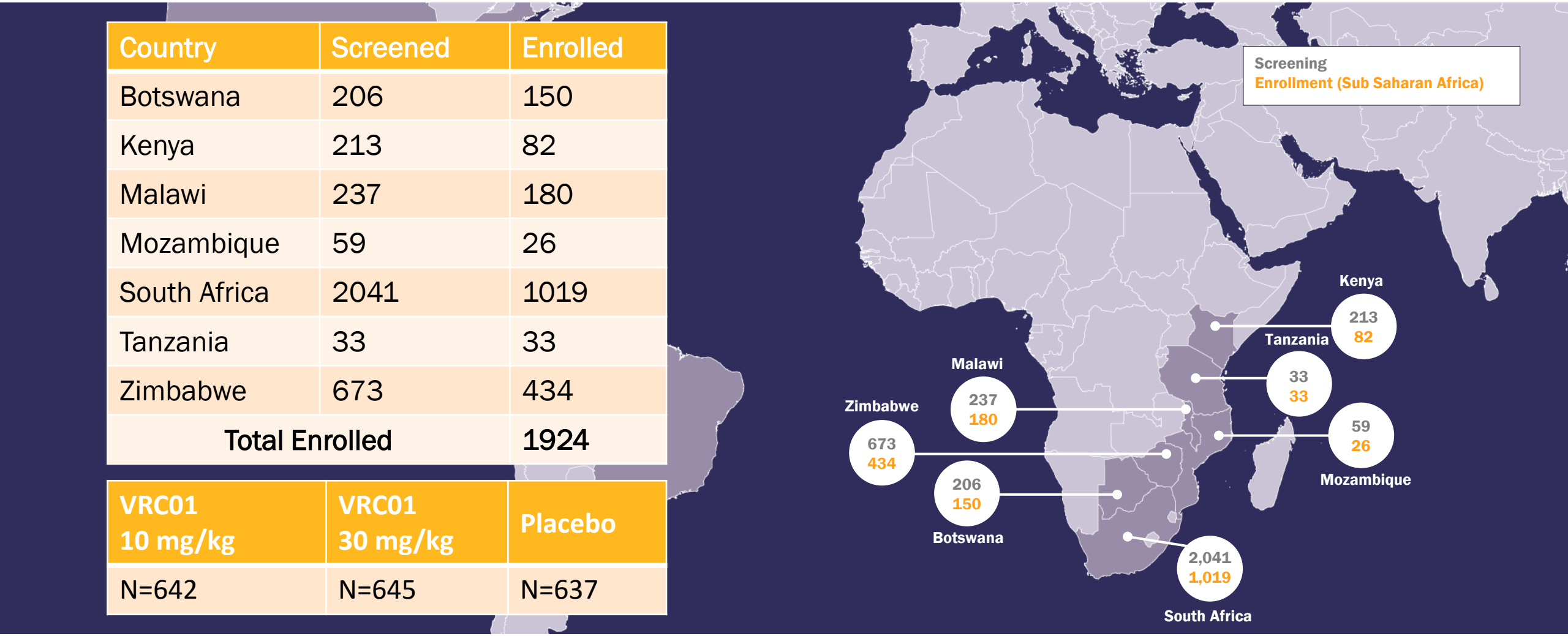
*Week 80: last study visit to evaluate efficacy
**Week 104: final study visit to evaluate safety and tolerability

Slide Courtesy: Larry Corey

HVTN 703/HPTN 081 Enrollments

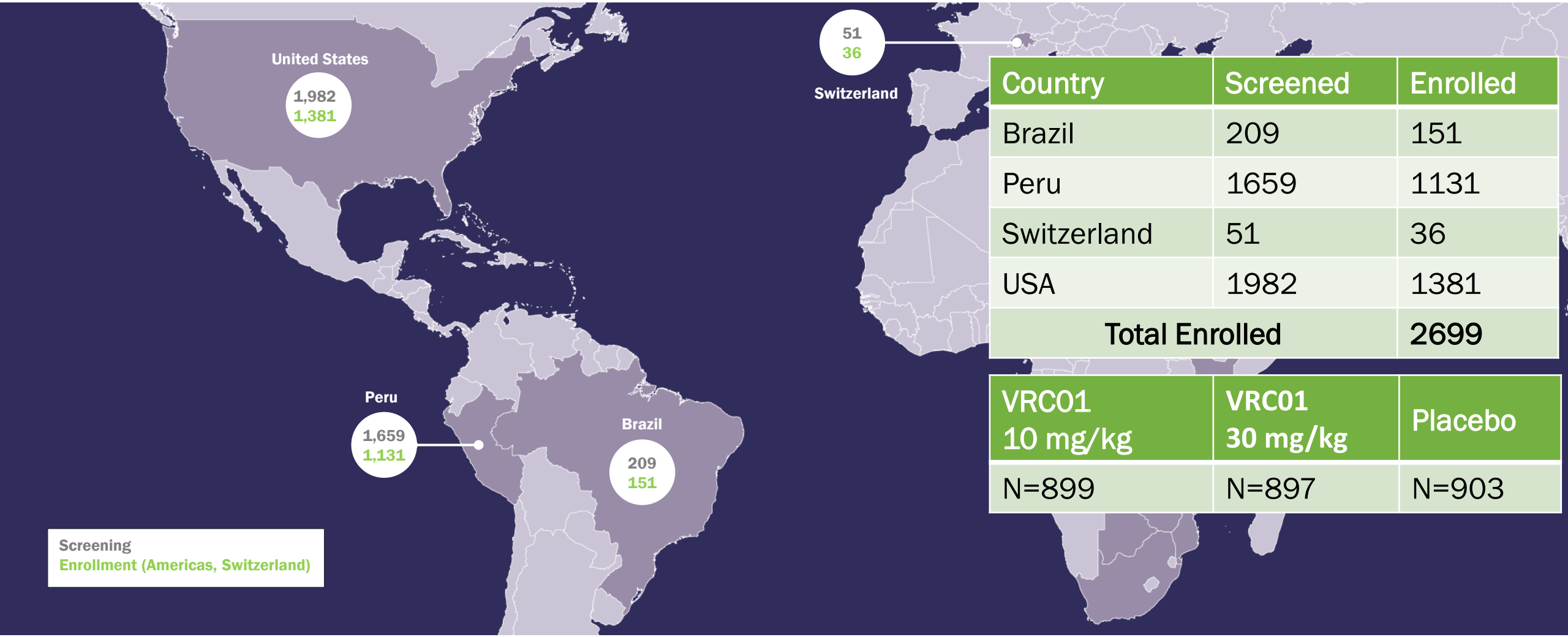
Country	Screened	Enrolled
Botswana	206	150
Kenya	213	82
Malawi	237	180
Mozambique	59	26
South Africa	2041	1019
Tanzania	33	33
Zimbabwe	673	434
Total Enrolled		**1924**

VRC01 10 mg/kg	VRC01 30 mg/kg	Placebo
N=642	N=645	N=637



Slide Courtesy: Larry Corey

HVTN 704/HPTN 085 Enrollments



Country	Screened	Enrolled
Brazil	209	151
Peru	1659	1131
Switzerland	51	36
USA	1982	1381
Total Enrolled		**2699**

VRC01 10 mg/kg	VRC01 30 mg/kg	Placebo
N=899	N=897	N=903

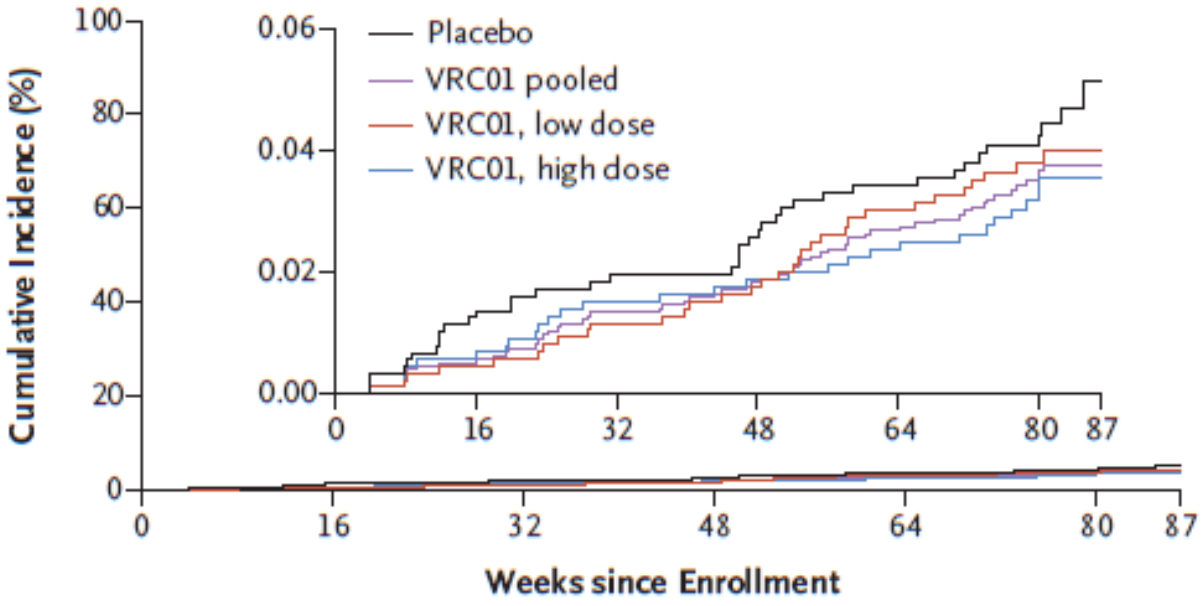
Slide Courtesy: Larry Corey

Efficacy at Week 80

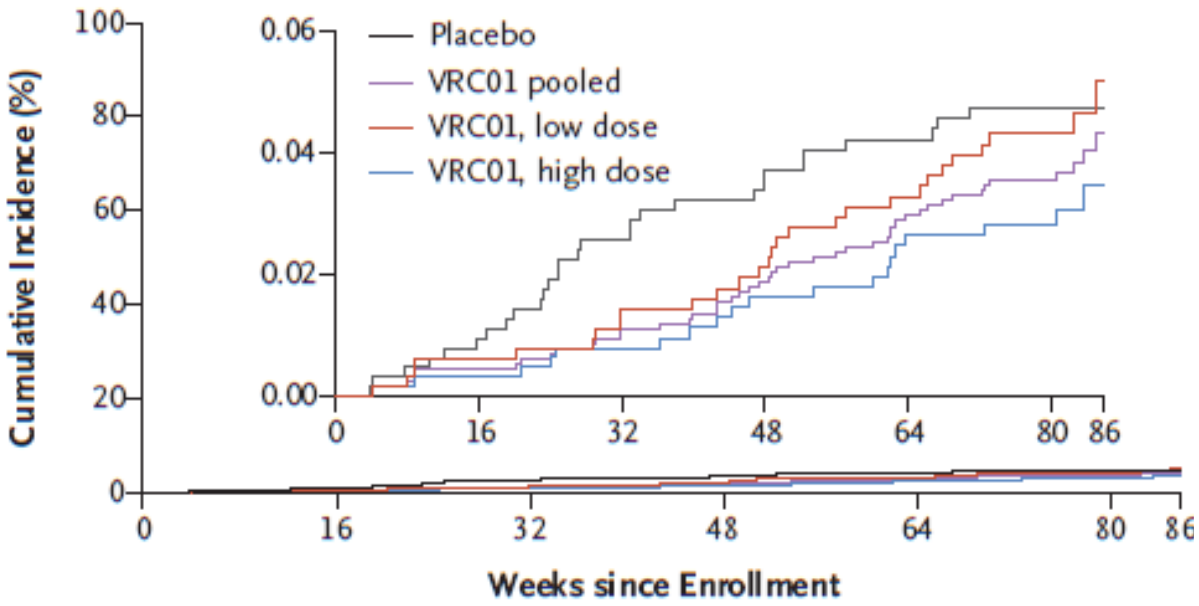
	Total Primary Endpoints	Endpoints 10 mg/kg	Endpoints 3 mg/kg	Endpoints Placebo	Estimated Cumulative Efficacy	95% Confidence Interval	2-sided P-value
HVTN 704/HPTN 085	98	32	28	38	26.6%	(-11.7% to 51.8%)	0.15
HVTN 703/HPTN 081	77	29	19	29	8.8%	(-45.1% to 42.6%)	0.70
Pooled AMP Trials	175	61	47	67	18.1%	(-12.2% to 40.2%)	0.21

Dose-Dependent Efficacy Diminished Over Time

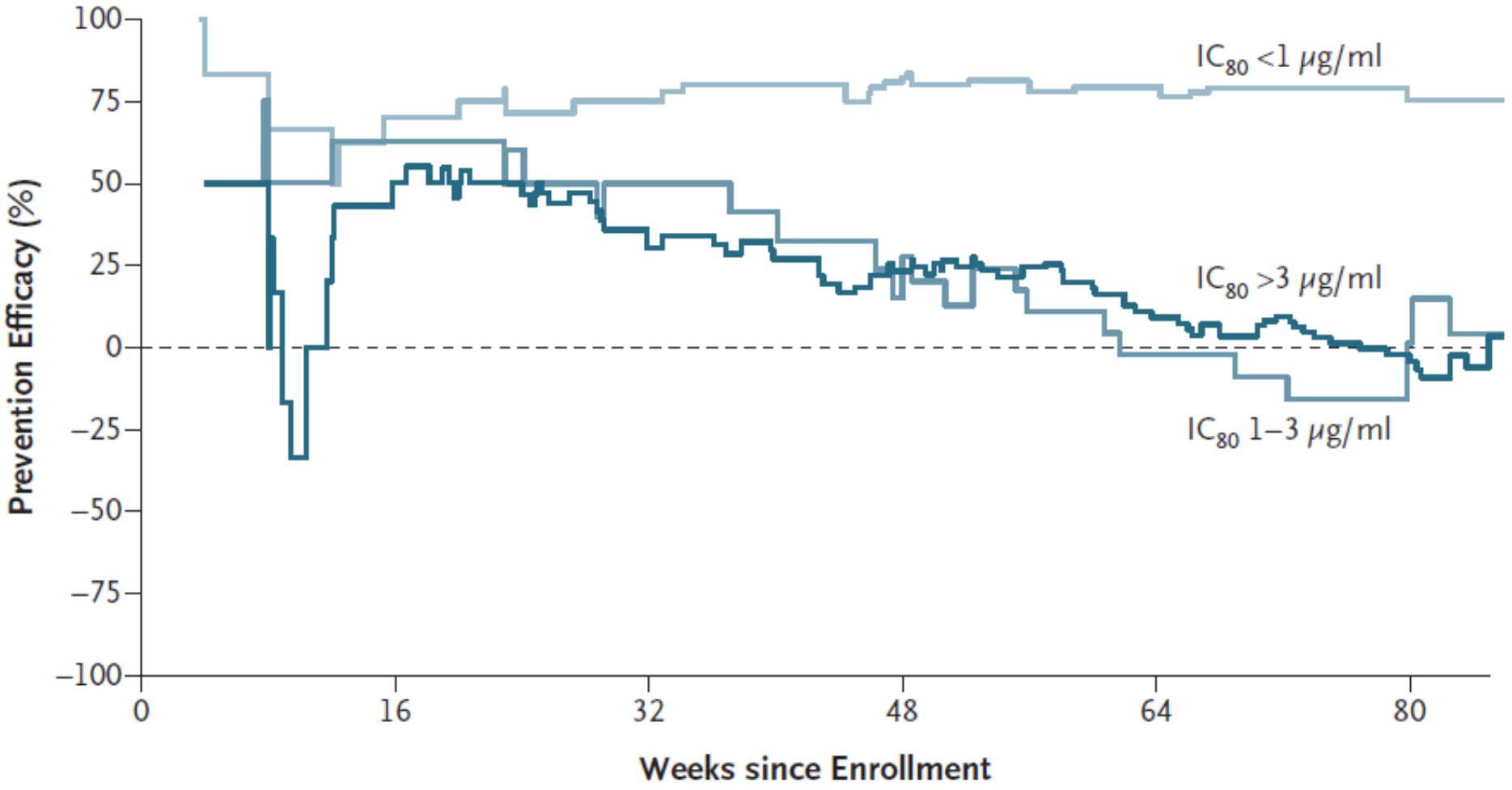
HVTN 704/HPTN 085



HVTN 703/HPTN 081

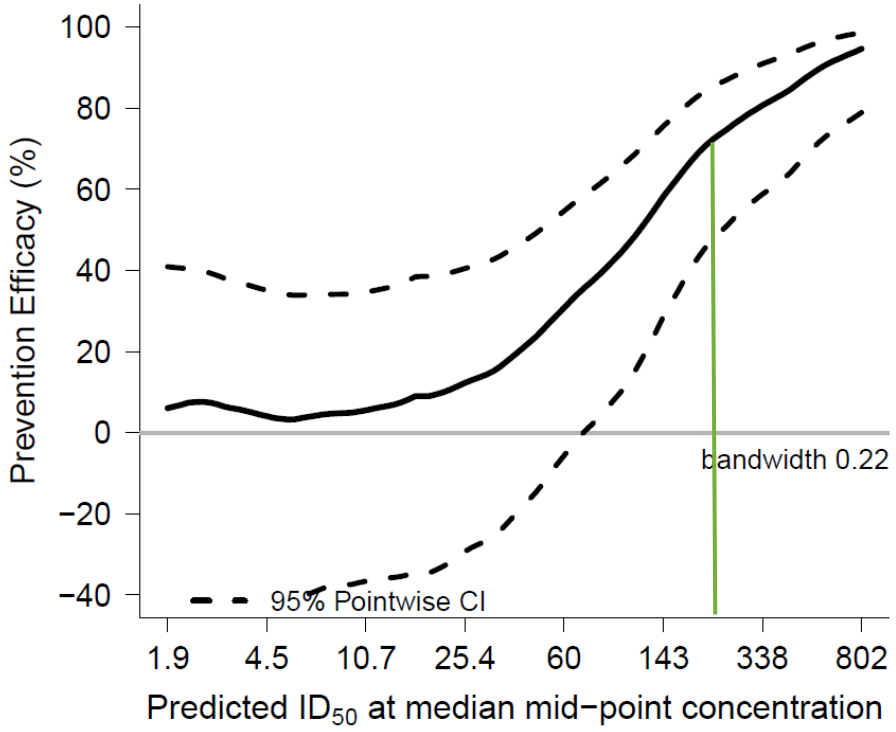


Sieve Analysis: Efficacy Against Sensitive Viruses

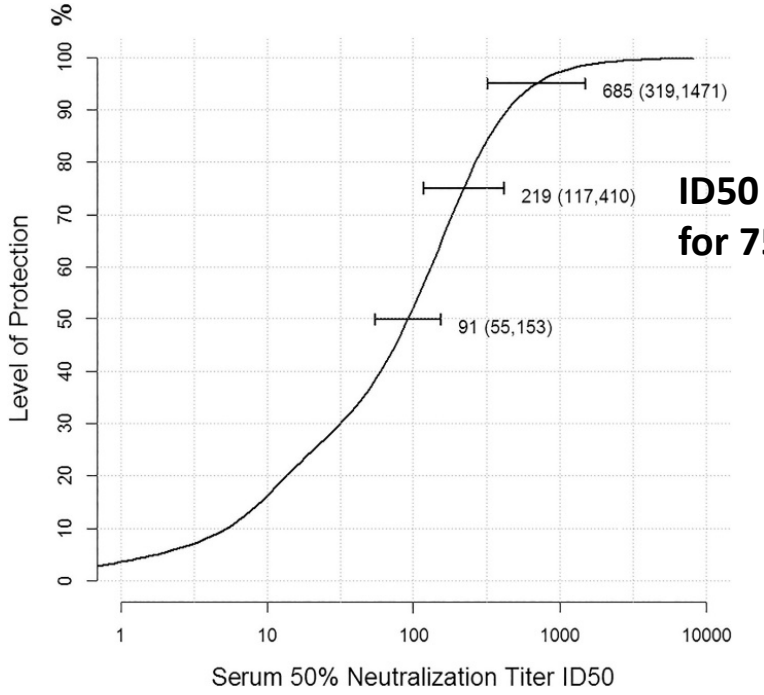


Estimation of Serum Neutralization Titers for Prevention Efficacy at Week 80

ID_{50} ~ 1:250 for 75% PE



Pegu et al. (2019) meta-analysis of N=274 NHPs receiving a single bnAb



ID50 219 for 75% PE

Peter Gilbert, Ying Huang, Michal Juraska

Selected Broadly Neutralizing mAbs

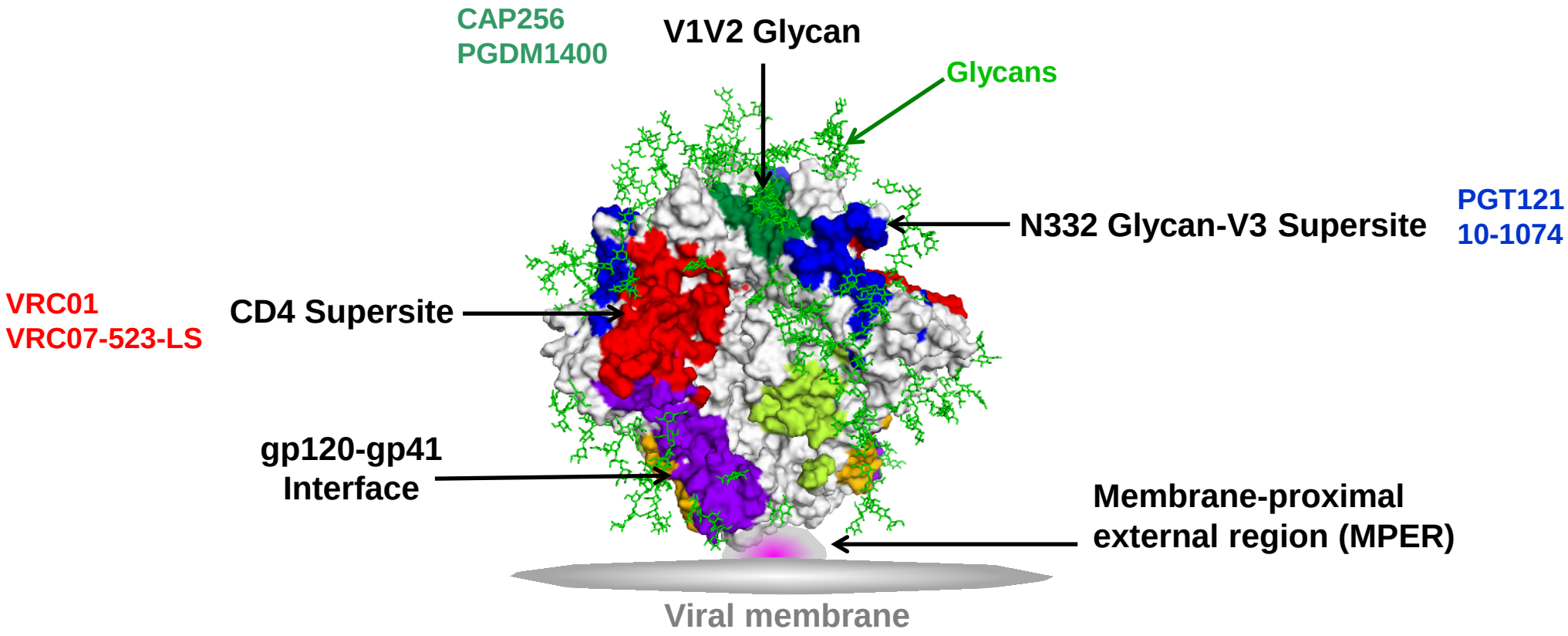
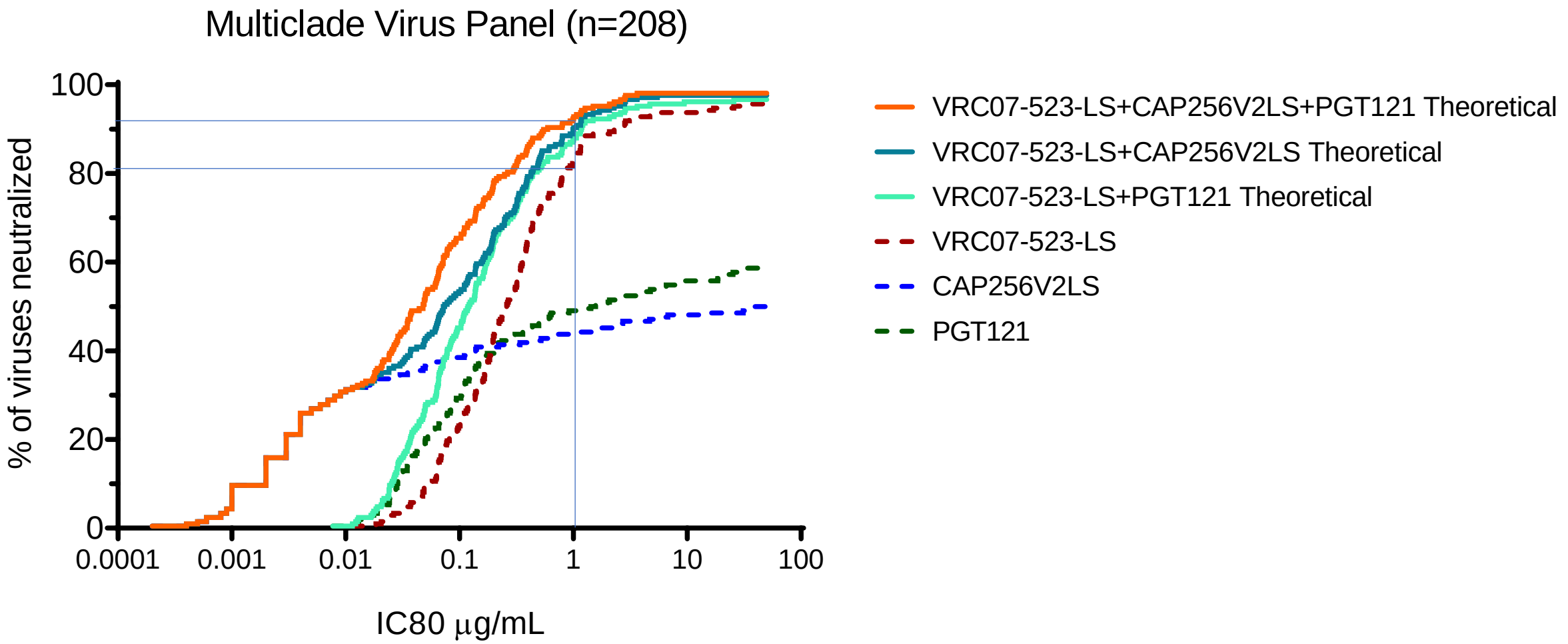


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

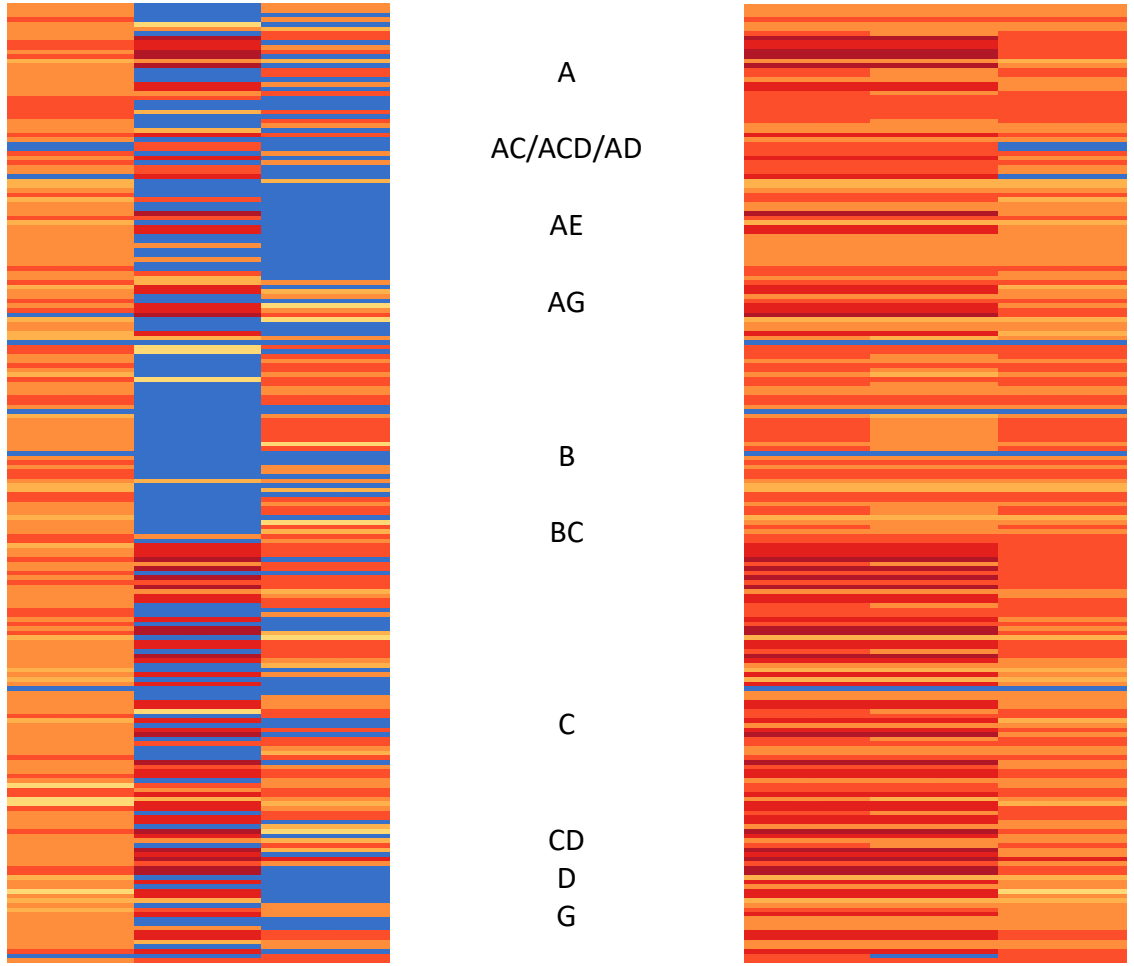
Theoretical Combinations of VRC07-523-LS with PGT121 and/or CAP256V2LS

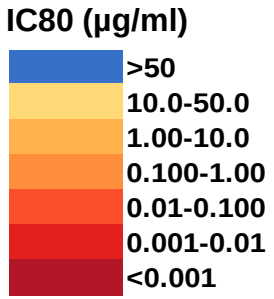
double and triple combinations



Multiclade Virus Panel

Theoretical Combinations of VRC07-523-LS with PGT121 and/or CAP256V2LS





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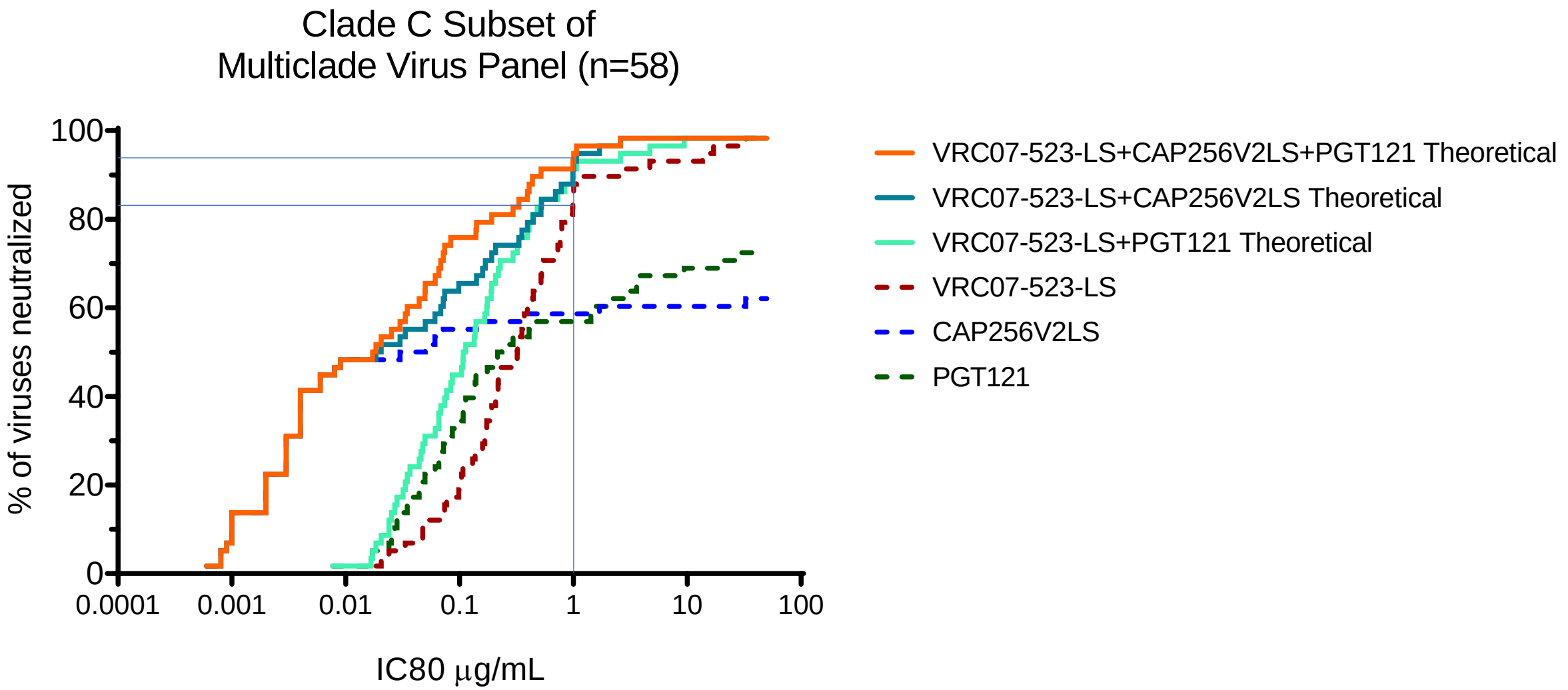
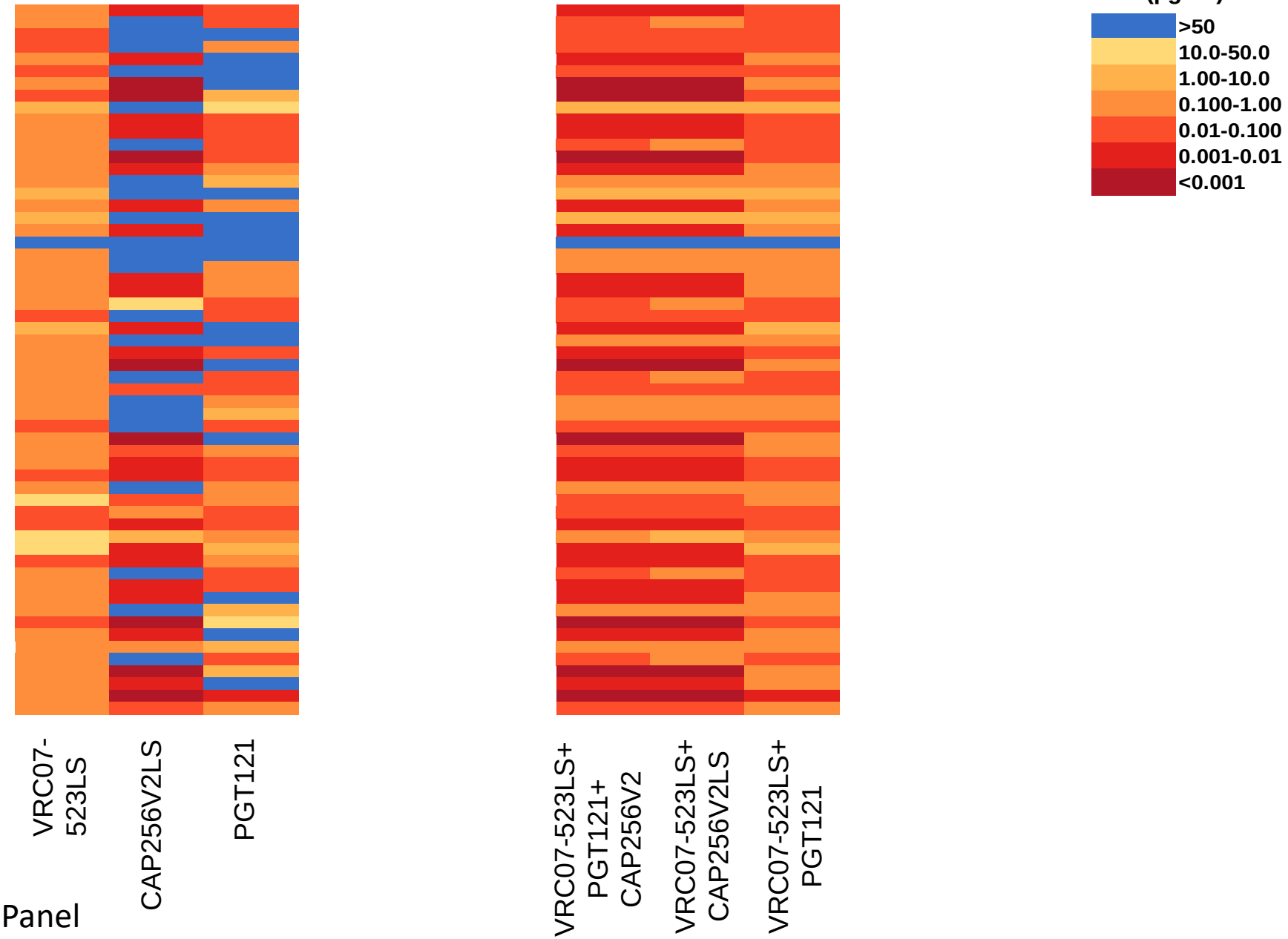
double and triple combinations



Clade C Subset of Multiclade Virus Panel

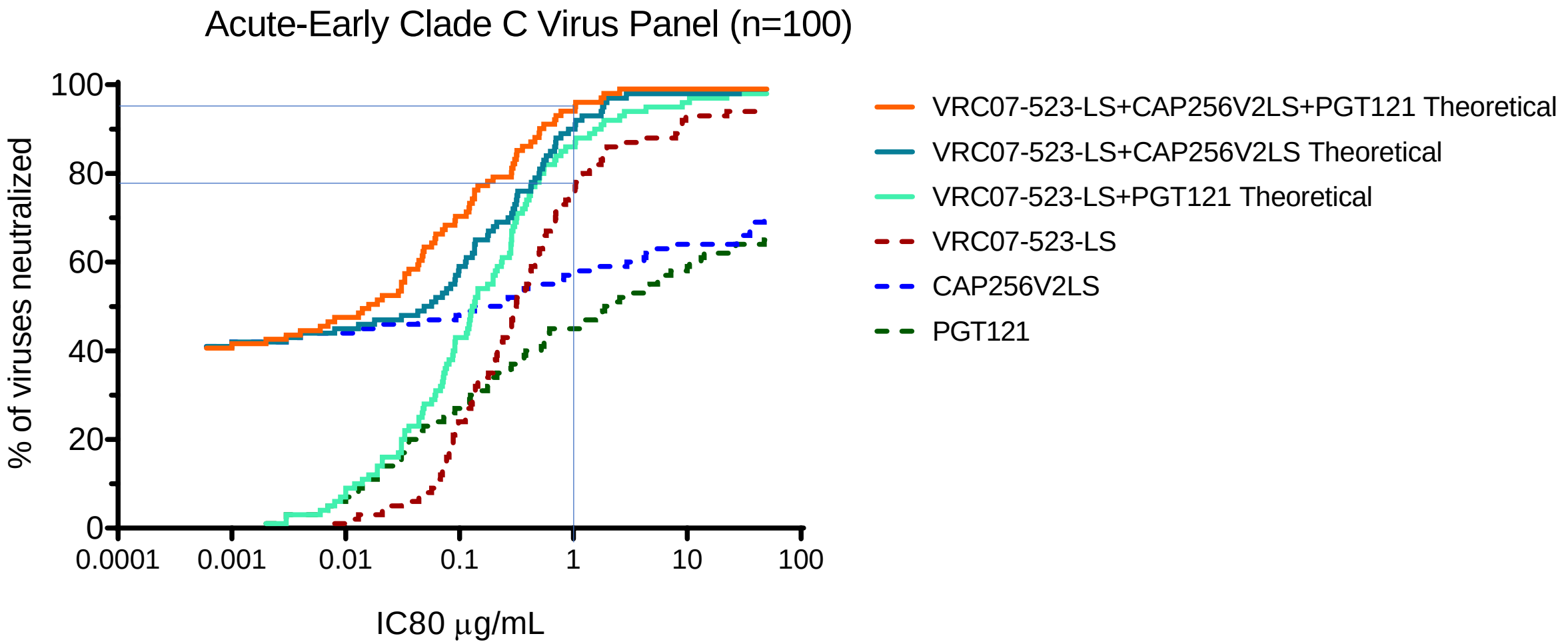
Theoretical Combinations of VRC07-523-LS with PGT121 and/or CAP256V2LS - Clade C



Clade C Subset of Multiclade Virus Panel

Theoretical Combinations of VRC07-523-LS with PGT121 and/or CAP256V2LS

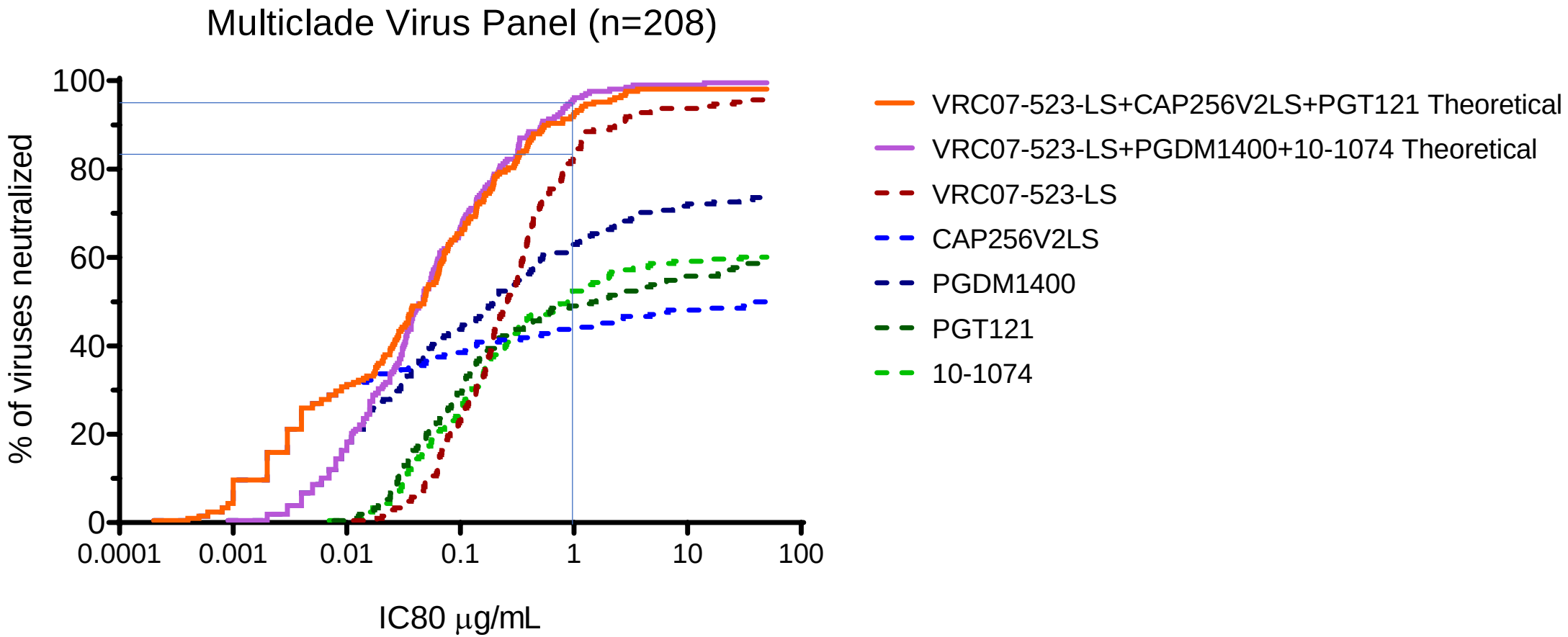
double and triple combinations



Acute-Early Clade C Virus Panel

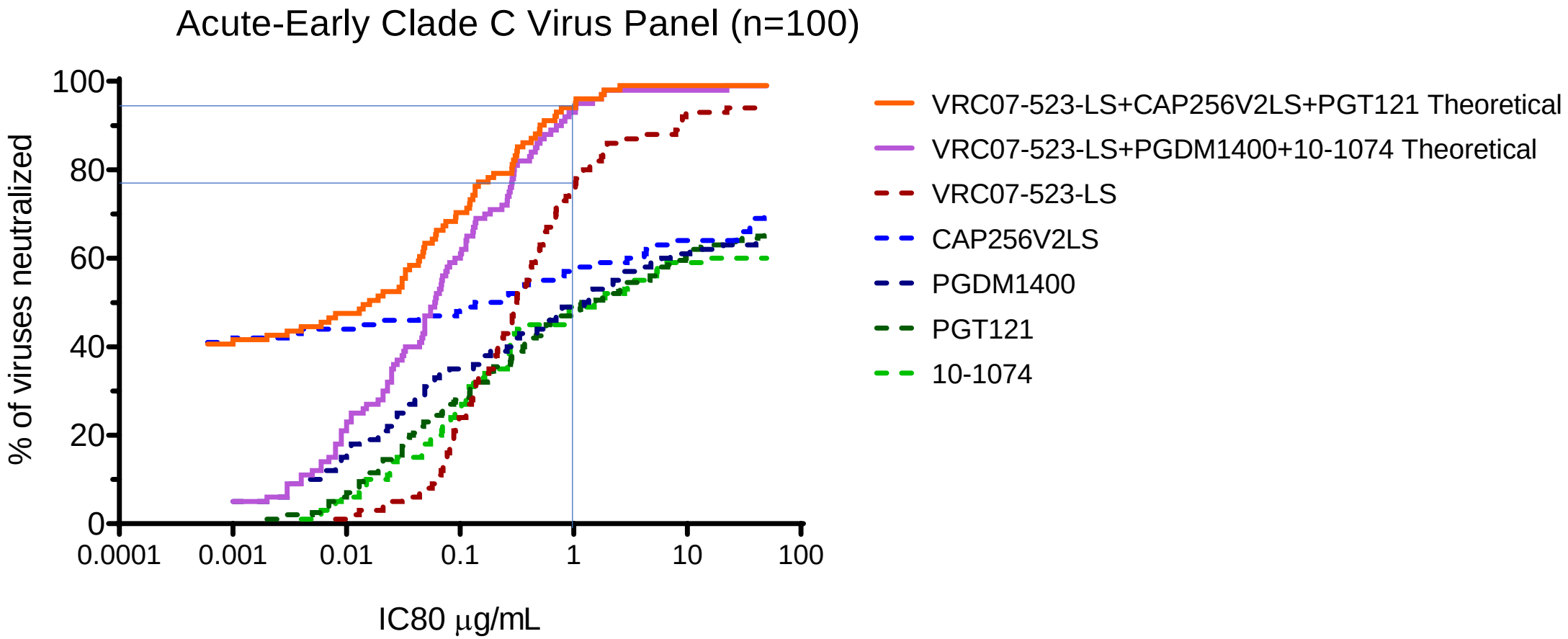
Note: Data shown are from a subpanel of 100 viruses;
CAP256V2 data are not fully titrated out; potency may be overestimated.

Theoretical Combinations of VRC07-523-LS with CAP256V2+PGT121 or PGDM1400+10-1074



Multiclade Virus Panel

Theoretical Combinations of VRC07-523-LS with CAP256V2+PGT121 or PGDM1400+10-1074



Acute-Early Clade C Virus Panel

Note: Data are shown for a subpanel of 100 viruses.
CAP256V2 data are not fully titrated out; potency may be overestimated.

Conclusions

- mAb prophylaxis for HIV is feasible
- mAb potency of <1 µg/ml IC_{80} is needed for effectiveness
- Achieving ~1:250 IC_{50} serum NT activity is needed for ~75% PE

Acknowledgements

Vaccine Research Center

VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

VRC01 IgG1
100 mg/ml

VRC PIs and Program Heads

John Mascola, Rick Koup, Julie Ledgerwood, Nancy Sullivan, Peter Kwong, Robert Seder, Daniel Douek, Mario Roederer, Adrian McDermott, Jason Gall, Ruth Woodward, Eli Boritz, Kevin Carlton, Sandra Vazquez; VRC VPP staff; David Lindsay and VCMP staff

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Michal Juraska
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Elena Giorgi

David Montefiori
Nono Mkhize
Carolyn Williamson
Jim Mullins
Georgia Tomaras
John Hural

HVTN 704/HPTN 085 Protocol Team Acknowledgements

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- Nyaradzo Mgodi

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- NIAID/DAIDS

NIH National Institute of Allergy and Infectious Diseases

HIV VACCINE TRIALS NETWORK

HPTN HIV Prevention Trials Network

HVTN 703/HPTN 081 Protocol Team Acknowledgements

Chair
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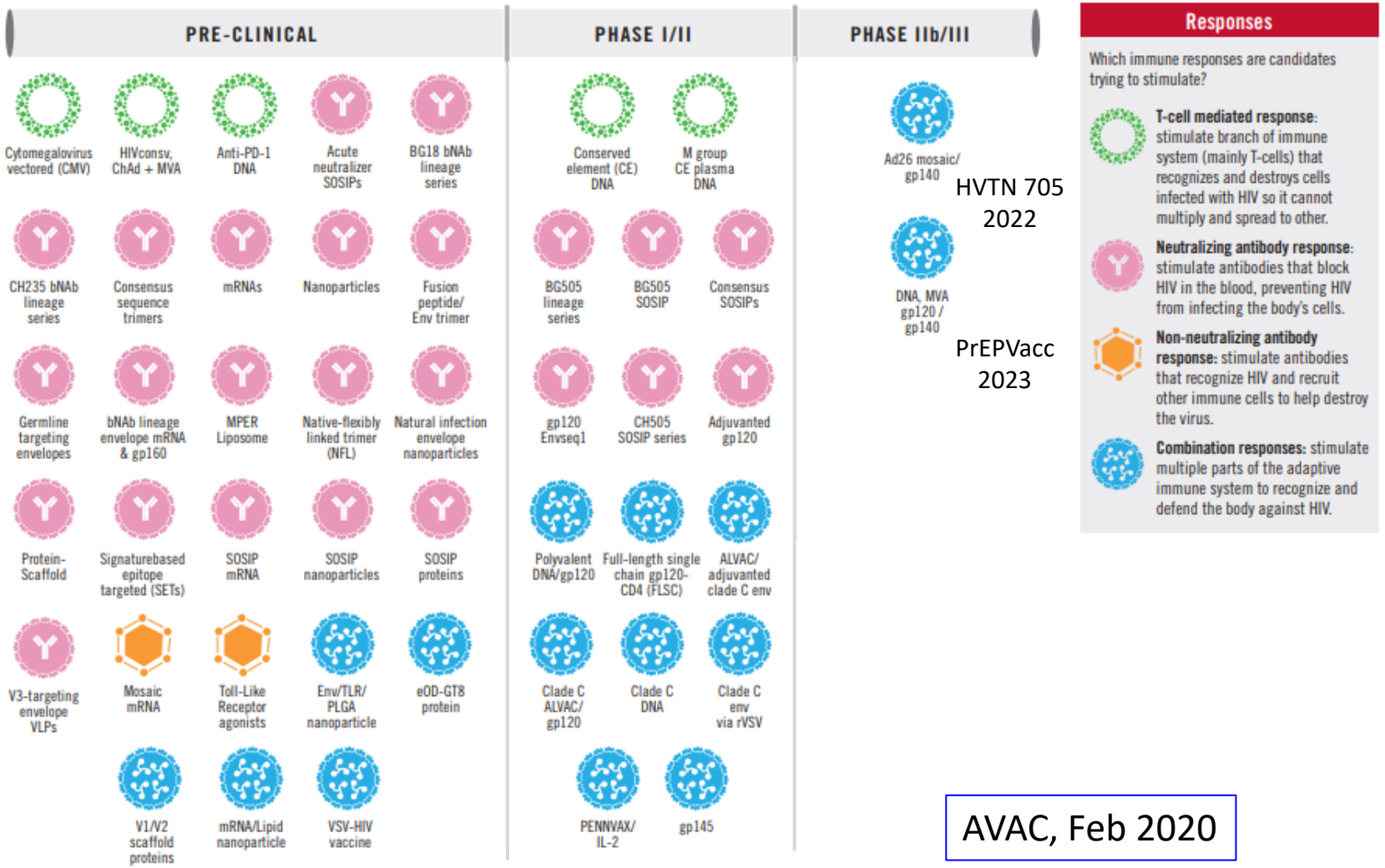
Thank you to the study participants and CAB and community members!

HIV vaccine update

Jerome Kim

International Vaccine Institute

HIV Vaccine pipeline



AVAC, Feb 2020

Efficacy trials of HIV vaccines

No efficacy

VAX003	IDU	gp120 B/E
VAX004	Mixed	gp120 B/B’
Step* / Phambili	Mixed	Ad5 gag/pol/nef
HVTN 505*	MSM	DNA/Ad5
HVTN 702	Heterosexual	ALVAC C + gp120 C/C’

Efficacy

RV144	Heterosexual	ALVAC E + gp120 B/E

*Excess infections in vaccinated group, futility

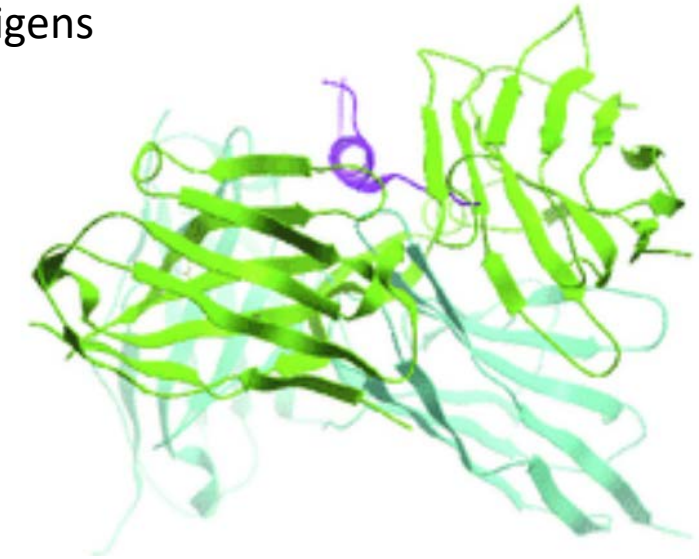
The challenges remain…and HVTN 705 uses Ad26

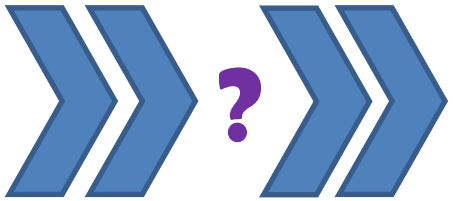
Challenge	Approach
Sequence diversity	Broadly neutralizing antibody, T cells, mosaics, non-neutralizing antibody
Cryptic epitopes and glycosylation	Broadly neutralizing antibody
High mutation rate	Broadly neutralizing antibody, T cells
Integration	T cells

PG9 (somewhat) broadly neutralizing anti-V1V2 Ab

- Iterative germline targeted immunogen design, B-cell lineage based design
- Stabilized trimers of founder strains
- Scaffolded antigens
- CMV vectors

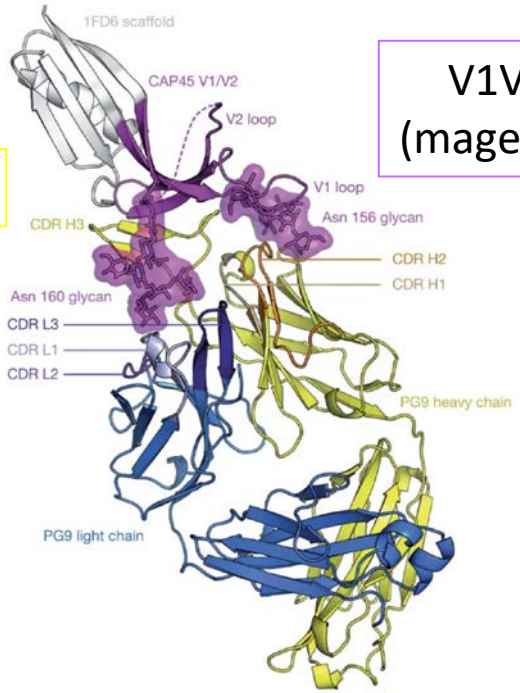
CH58 anti-V2 ab from RV144





CDR H3

V1V2 (magenta)



PG9

Value Proposition for Monoclonal Antibodies

Or

We have ARVs for prevention; what more do we want?

Susan Buchbinder, MD

San Francisco Department of Public Health

April 15, 2021

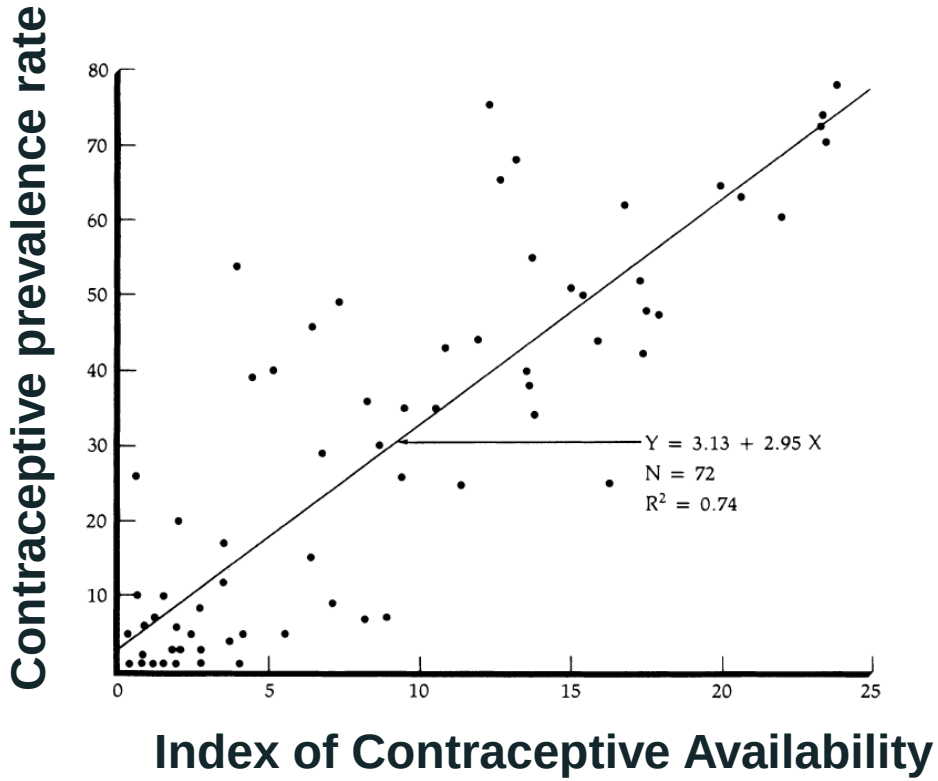
Seven reasons why mAbs may be an important component of our prevention toolbox

1. Diversify our portfolio

- **We don’t know what will happen with the current long-acting ARVs in testing**
  - Could be an issue with safety or efficacy in trials and in roll-out
    - Example: COVID vaccines, having different approaches is proving to be very important
- **Don’t know what uptake of or adherence to any of the new agents will be**
  - Will adherence to monthly pill taking be any better than daily is?
  - Will people go to the clinic for q2 month injections? Will providers be able to provide this?
  - Will people be willing to get implants?

2. Choice matters – no one size fits all

- **WHO systematic review (231 articles) showed *increased choice* associated with:**
  - **Increased contraceptive uptake**
  - **Increased persistence** on chosen method
  - **Better health outcomes**
- **12% increase in contraceptive prevalence for each additional method**
- **Similar to contraceptive needs → different people have different HIV prevention needs at different times**



Gray et al RHRU 2006; Jain AK Stud Fam Planning 1989

3. Keeping all treatment options open

- **All ARVs being developed for PrEP are also being developed for treatment**
- **We need to keep as many treatment options open as possible, as people develop resistance over time, and having more options for alternative regimens is important**
- **In HPTN 083, 6/16 persons in the CAB-LA arm with HIV infection developed INSTI resistance**
  - INSTIs are the first line backbone of treatment throughout much of the world; this could limit treatment options not just for this particular drug, but for a class of drugs
- **Don’t need to worry about resistance causing limits to treatment options when using mAbs.**

4. Avoiding toxicity associated with ARVs

- **ARVs often have some tolerability and/or toxicity associated with them**
  - Tolerability often rate limiting for patients
  - May be particularly true for a prevention rather than a treatment indication
  - Can be a perceived toxicity

- **Toxicity not always immediately evident**
  - E.g., Weight gain with various INSTIs, TAF
  - E.g., Temporary hold on DTG when question of increased neural tube defects

5. Providing privacy, avoiding stigma

- **Keeping pills, going to clinic every 2 months, or having an implant may not be discrete enough for some potential PrEP users who want utmost privacy**

- **Every 6 month injections may be a better regimen to keep use of PrEP discrete**

6. Added benefit of helping the HIV vaccine field

- **Learning what/how much is needed in mAbs may help provide targets for active immunization program**

- **Helps keep people interested in HIV vaccine field as movement is made in the mAb field**

7. Solving the access issue for HIV mAbs will help develop access for mAbs against other diseases

- **HIV research has paved the way for many innovations in research design, implementation, advocacy, and access**

- **Working on building access to mAbs against HIV will catalyze development of regulatory, manufacturing, and business models to serve as a template for mAbs against other diseases**

Overview of preferred product characteristics

- Developed in collaboration with IAVI and the WHO HIV vaccines and monoclonal antibodies working group
- The PPC was presented to a broad range of stakeholders (43 participants, including industry) at a virtual meeting in November 2020, comments have been incorporated in this version.
- Next steps: Gather input from PDVAC and post for public consultation with broad outreach
- **Parameters** (red for discussion):
  - ❑ Indication for use
  - ❑ **Target populations**
  - ❑ Access and Affordability
  - ❑ Safety
  - ❑ **Efficacy**
  - ❑ Formulation and presentation
  - ❑ **Dose regimen**
  - ❑ Co- administration
  - ❑ **Route of Administration**
  - ❑ Product stability and storage
  - ❑ Registration, prequalification and programmatic suitability

Characteristics

Indication for use

Preferred Characteristic	Notes
Prevention of HIV-1 infection in confirmed HIV-negative individuals Prevention of HIV-1 infection in neonates and infants with HIV exposure	Treatment or curative indications are out of scope of this PPC.

Characteristics (to discuss)

Target populations (& *delivery strategies*)

- ❑ There are multiple target populations at risk, that generally reside in different contexts and/or settings. The optimal product attributes to enable access and delivery these various settings may differ.
- ❑ Should we prioritise particular risk groups within the PPC or where appropriate, stratify the preferred attributes by risk group and associated setting and potential delivery strategy?
- ❑ What would be the delivery strategy for different target populations: e.g: in line with ARV delivery, routine vaccination schedule, contraceptives, other. (How) do these different strategies impact the preferred product attributes?

Preferred Characteristic	Notes
Persons at high-risk of HIV infection and their sexual partners including:	
Men who have sex with men, male and female sex workers, people who inject drugs and their injection partners, transgender individuals, and incarcerated populations	Key populations and their sexual partners account for more than 60% of new infections globally and therefore are critical to HIV prevention efforts.
Serodiscordant couples	As a complement to effective antiretroviral therapy (ART), which can prevent HIV transmission to partners, continued efforts to strengthen pre-exposure prophylaxis options are needed to support serodiscordant couples.
Neonates and infants with HIV exposure	Given bNAbs' potentially long half-life, they may be effective in supporting Prevention of Mother to Child Transmission (PMTCT) implementation.
Pregnant and breastfeeding women in high prevalence settings	Identifying prevention products that are appropriate for use during conception, pregnancy, and while breastfeeding is also important.
Adolescents and cisgender men and women in high prevalence settings	Adolescent girls and young women (AGYW) account for 3 out of every 4 new infections in sub-Saharan Africa—the epicenter of the HIV epidemic—and therefore are priority in prevention efforts.
Other target populations at high risk may be considered based on local epidemiology.	Additional research is needed to determine the potential role of bnAbs in post-exposure prophylaxis for those facing sexual exposure or occupational risk (eg. from needle-stick or other nosocomial exposure).

Characteristics (to discuss)

Efficacy

- ❑ Note that we have not indicated a target efficacy value in the PPC table
- ❑ WHO/UNAIDS ethical guidelines for HIV prevention trials limit placebo-controlled trials (all arms should have access to the WHO standard prevention package. This limits the ability to measure absolute efficacy of new interventions, complicating efficacy target-setting, measurement of endpoints and size of trials. Is guidance needed here on clinical trial design for developers? Not necessarily in the PPC but highlighted in a separate article that highlight research priorities etc?

Preferred Characteristic	Notes
Efficacy trial with standard of prevention incorporated. Evidence of broad coverage of genetic diversity of HIV-1 across geographies, populations, and modes of transmission Antibody combinations and/or multi-specific formats, with antibodies targeting different epitopes in a complementary manner to achieve broad protection and to prevent viral escape Efficacy maintained with repeated use.	Efficacy trial design should conform to relevant regulatory standards and be conducted with reference to *UNAIDS/WHO Ethical Considerations in HIV Prevention Trials*. As outlined in this guidance document, researchers and trial sponsors should ensure access to a package of recommended prevention methods. Alternative trial designs may be needed to establish the value of specific agents for HIV prevention in the context of evolving standards of prevention. Further regulatory guidance on alternative trial designs is needed. Trials should also conform to *WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology*. Programmatic benefits -- such as less frequent administration, increased acceptability, or improved safety -- may be considered alongside efficacy. Evaluation of sustained protection with repeated use based on long-term follow-up studies and post-introduction surveillance. High breadth of protection will be key to support sustained use across diverse geographies. Population level data will be important in determining whether there is selection for resistance to specific antibodies over time.

Characteristics (to discuss)

Dose regimen (& *duration of protection*)

- ❑ Longer-acting mAbs could potentially achieve up to 5-6 months protection. Long-acting ARVs for HIV prophylaxis on the market or pending licensure offer dosing on a monthly or bi-monthly basis. There are longer-acting products in development.
- ❑ Experts consulted expressed that durations of 2 months or greater would be considered if there were other favourable attributes (e.g., superior safety or effectiveness, tolerability, acceptability, ease of access, affordable cost and supply chain considerations, or aligning dosing schedule with other care-seeking timepoints, such as injectable contraceptives.
- ❑ Are we in agreement?

Preferred Characteristic	Notes
Administration every 6 months or longer preferred. Fixed, non-weight-based dosing is preferred, with appropriate fixed dosing presentations for: • Adolescents/adults • Infants • Neonates Co-formulation of combination products preferred. Single site, single injection preferred but not required.	Durations of 3 months and longer would be considered, in the context of other favorable attributes (e.g., superior safety or effectiveness, tolerability, acceptability, ease of access, affordable cost, and supply chain benefits, compared to other available options). Pharmacokinetic studies demonstrating half-life sufficient to support schedule of administration needed.

Characteristic (to discuss)

Route of Administration (& *amount of mAb required*)

- ❑ Large amounts of mAb(s) are not possible to deliver via SC or IM routes. Lower amounts of mAb(s) could be achieved through increasing potency, binding affinity and engineered antibodies, which could potentially support SC or IM administration, or mRNA delivery.
- ❑ Should development of these be highlighted as research priorities?
- ❑ Are we agreed that we will not include intravenous administration as a preferred delivery route, since the focus of WHO PPCs is LMIC populations?

Preferred Characteristic	Notes
Subcutaneous or intramuscular injection	Per defined criteria for prequalification, WHO specifies that an intravenous route of administration is not broadly suitable for programmatic implementation in LMIC settings

Other issues to discuss

Research priorities

- ❑ Should we publish a perspectives article highlighting research priorities needed to advance mAbs for HIV prevention, to be published soon after the PPC?

- ❑ Examples
  - Development of use case scenarios?
  - Development of full value assessment?
  - Alternative clinical trial designs
  - Prioritization of mAbs with increased potency, breadth of protection, mRNA delivery?
  - Alternative production platforms to reduce CoGs?
  - Establishment of a WHO prequalification pathway?

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- Susan Buchbinder, HIV Prevention Research in the San Francisco Department of Public Health, USA
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- Nelly Mugo, Kenya Medical Research Institute (KEMRI)
- Pontiano Kaleebu, Uganda Virus Research Institute (UVRI)
- Yiming Shao (PDVAC member)
- Sunil Solomon, Johns Hopkins University School of Medicine, USA
- Helen Rees, Wits Reproductive Health and HIV Institute (WRHI) – co-chair
- Mitchell Warren, AVAC Global Advocacy for HIV prevention

IAVI, Wellcome Trust, USAID, WHO colleagues, participants at the stakeholder consultation held in Nov 2020

Other Characteristics

Access and affordability

Preferred Characteristic	Notes
Product and health systems delivery costs should be affordable and cost-effective in LMIC settings.	Cost should be considered relative to efficacy and impact vis-a-vis comparable products. Further evidence on the cost-effectiveness, acceptability, and full value proposition of bnAbs, including from a LMIC perspective, is needed. Manufacturers should plan for how to make products broadly available, particularly in countries and in populations in which they will be tested.

Safety

Preferred Characteristic	Notes
Should have a favorable and acceptable safety and reactogenicity profile. Safe to use in pregnancy & breastfeeding Safe in older adolescents (15-19 years) Safe in infants	In clinical trials, single and repeat bNAb administrations of anti-HIV-1 antibody combinations have generally been well tolerated with infrequent adverse events reported. Transplacental transfer should be factored in safety evaluations. Monitoring for clinically relevant anti-drug antibodies in clinical trials is important.

Characteristics

Formulation and Presentation

Preferred Characteristic	Notes
WHO defined recommendations on presentation, packaging, storage volume and disposal should be met, where applicable to mAbs A single vial product preferred For infants, 0.5 ml per dose preferred For children aged 5 years or younger 1 ml per dose or less preferred.	For volumes >2 mL, multiple injections are typically used. However, in clinical studies, target injection volumes of as high as 3 ml have been well tolerated and may be preferred over multiple injections. Further evaluation of preferences with respect to injection frequency, volume, and site is needed.

Characteristics

Co- administration

Preferred Characteristic	Notes
Non-interference with HIV vaccines, if available	Concomitant administration of bnAbs for HIV prevention are expected to not interfere with immune responses to non-HIV vaccines.

Characteristics

Product stability and storage

Preferred Characteristic	Notes
At a minimum mAbs should be stable at refrigerated condition (2° to 8°C); a controlled temperature chain (CTC) product is preferred. Storage footprint should be minimized.	A room temperature, lyophilized product may be preferable. However, technical and implementation considerations, including preferences for ready-to-use formats, must be factored into formulation decisions.

Registration, prequalification and programmatic suitability

Preferred Characteristic	Notes
WHO prequalification preferred	WHO prequalification is often used as a reliance mechanism to support licensure in LMIC settings and can enable procurement through UN agencies and other global mechanisms. Additionally, WHO prequalification can facilitate broad registration through the *Collaborative Procedure for Accelerated Registration of Prequalified FPPs procedure.* Close cooperation and coordination with WHO and with national and international regulatory authorities is of high importance. Product attributes that support programmatic implementation and adherence— such as extended duration of protection and tolerability— hold the potential to lower delivery costs and improve the real-world effectiveness of HIV prevention products. There may be benefits in aligning dosing schedule with other care-seeking timepoints, such as injectable contraceptives. Engagement to understand the product preferences and needs of local decision makers and end users is important.

Thank you!

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