Development of Contemporary HIV-1 Pseudovirus COCOM Panels for Improved Evaluation of Countermeasure Efficacy

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Walter Reed Army Institute of Research

Defense Health Agency
RESEARCH & DEVELOPMENT

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Disclaimers

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The study protocols were approved by the relevant Institutional Review Board(s) in compliance with all applicable Federal regulations governing the protection of human participants.

Bottom Line Up Front

- HIV remains a major threat to the warfighter
  - Monoclonal broadly neutralizing antibodies and vaccines are promising countermeasures
- HIV pseudovirus (PSV) neutralization assays assess function of monoclonal and vaccine elicited antibodies
  - PSV panels use HIV Envs isolated >20 years ago and **do not reflect currently circulating strains**

Characterized contemporary PSVs by COCOM

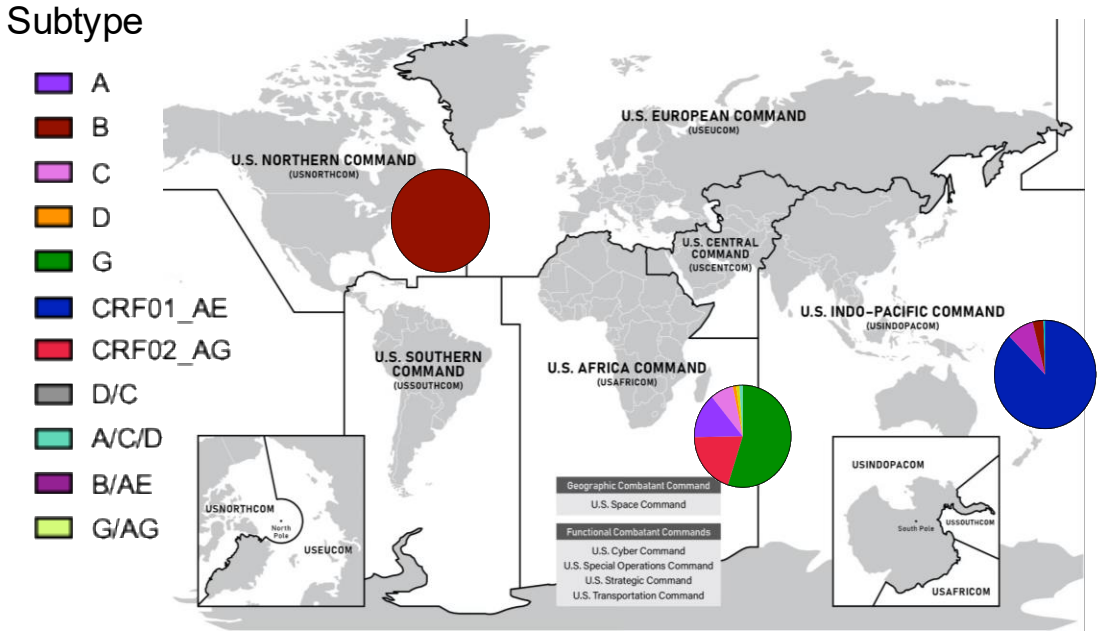

Figure modified from: Association of the United States Army (AUSA)

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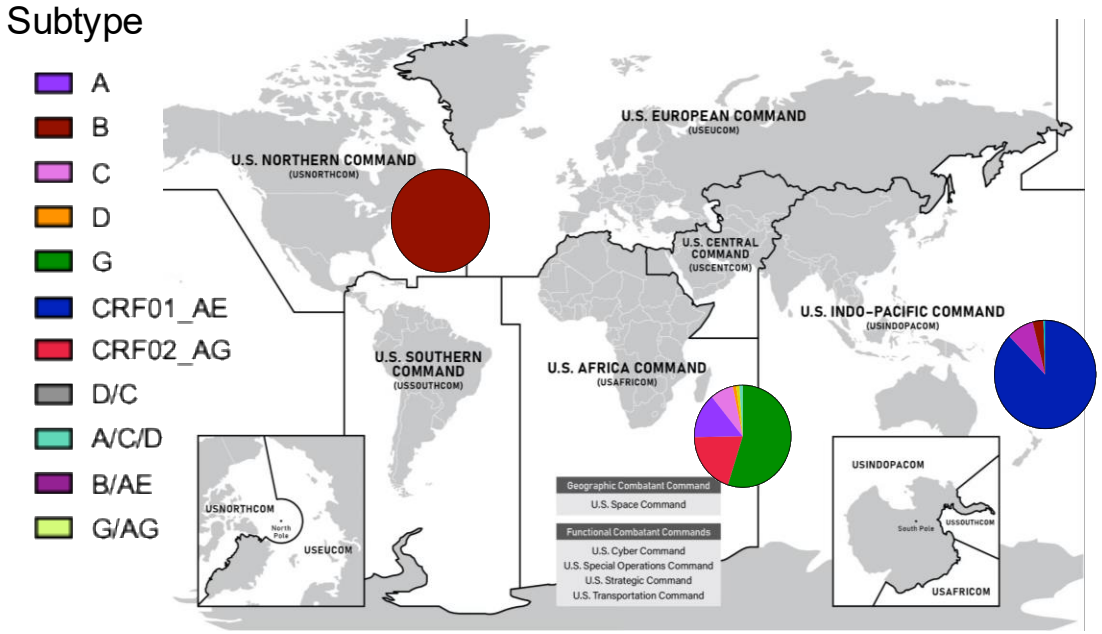


➢ Developing **contemporary COCOM-specific PSV panels** for improved evaluation of countermeasure efficacy

- ➢ Identify products effective against real-world circulating strains in key COCOMs
- ➢ Curate countermeasure administration to potential exposure

Figure modified from: Association of the United States Army (AUSA)

HIV is a threat to the warfighter and blood supply

- ~2,000 servicemembers living with HIV[1]
  - ~350 new infections a year[1]
- Regions of military interest have **increasing HIV transmission**
- Screening of blood products for HIV takes time and is imperfect
- Risks of **breakthrough contamination** are elevated in **high-volume**, **emergent transfusion** environments
  - Expected during large-scale combat operations
  - Rate of acquisition of HIV via HIV+ blood transfusion is **>90%**[2]

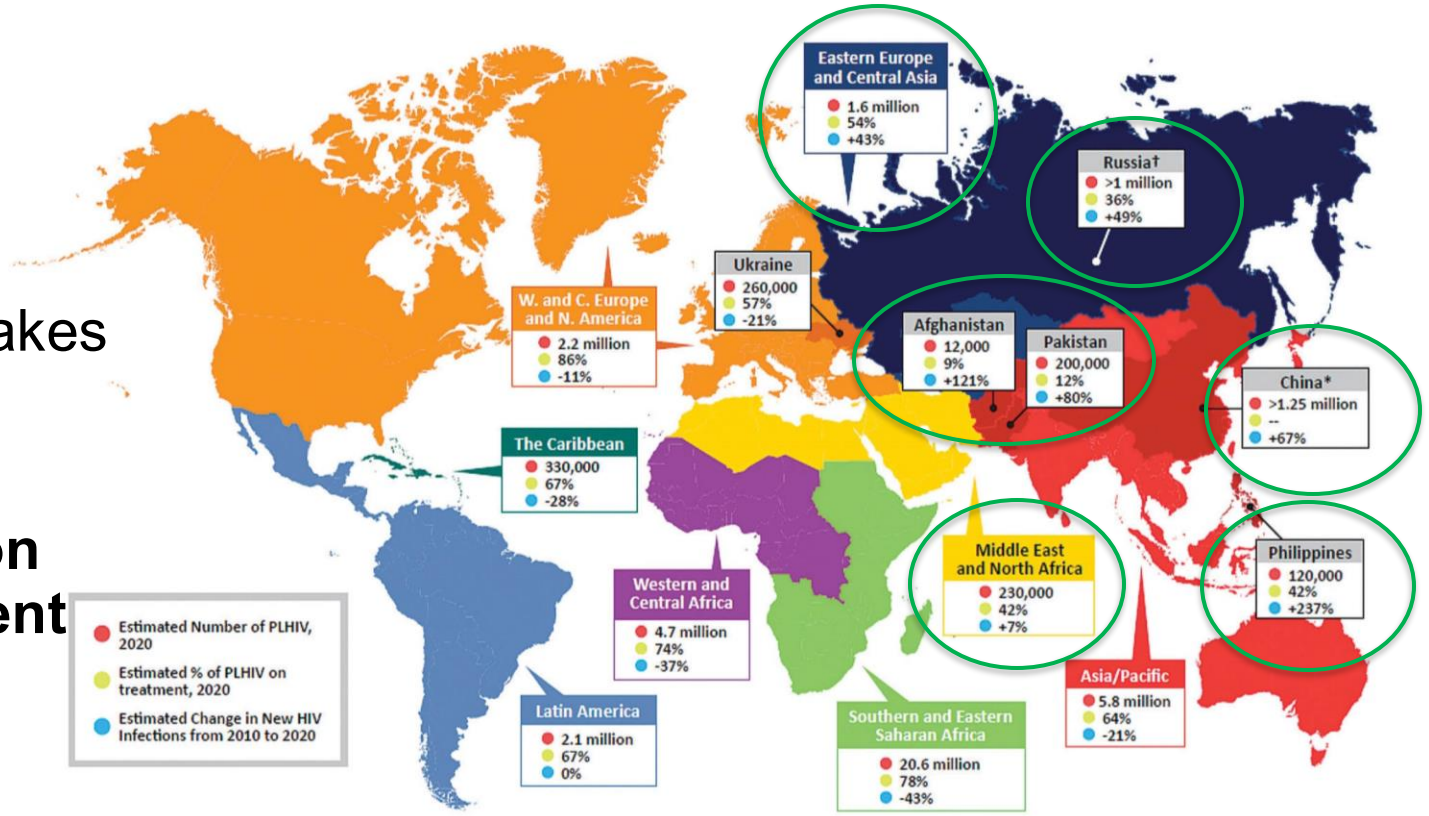
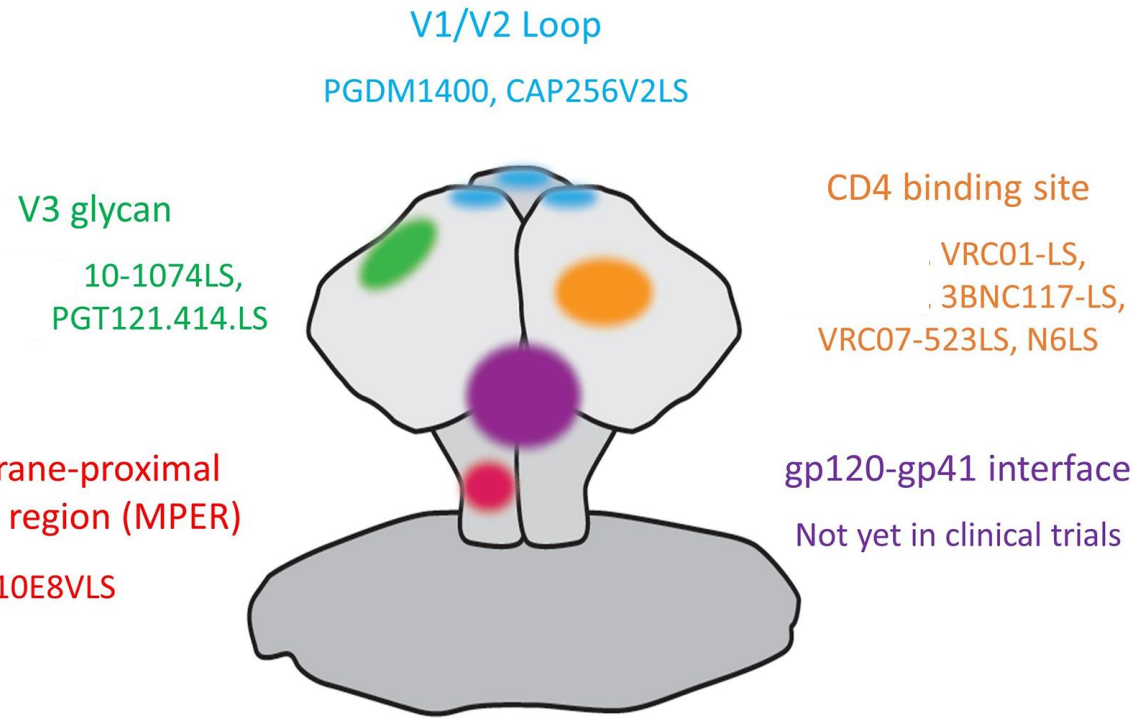


Figure modified from; 1. Cavanaugh et al., 2023. *Joint Force Quarterly.*
2. Scott & Wu, 2019. *Biosafety and Health.*

Neutralizing antibodies can protect against HIV acquisition

- Antibody mediated prevention trials
  - Neutralization is protective against HIV **only** when viruses are **sensitive to the antibody**[1]
- Env is the sole target of HIV neutralizing antibodies
  - Several neutralization epitopes that vary between strains
- Broadly neutralizing antibodies (**bNAbs**) targeting various epitopes are in clinical trials for HIV prevention and therapy

Examples of broadly neutralizing antibodies (bNAbs) in clinical trials:

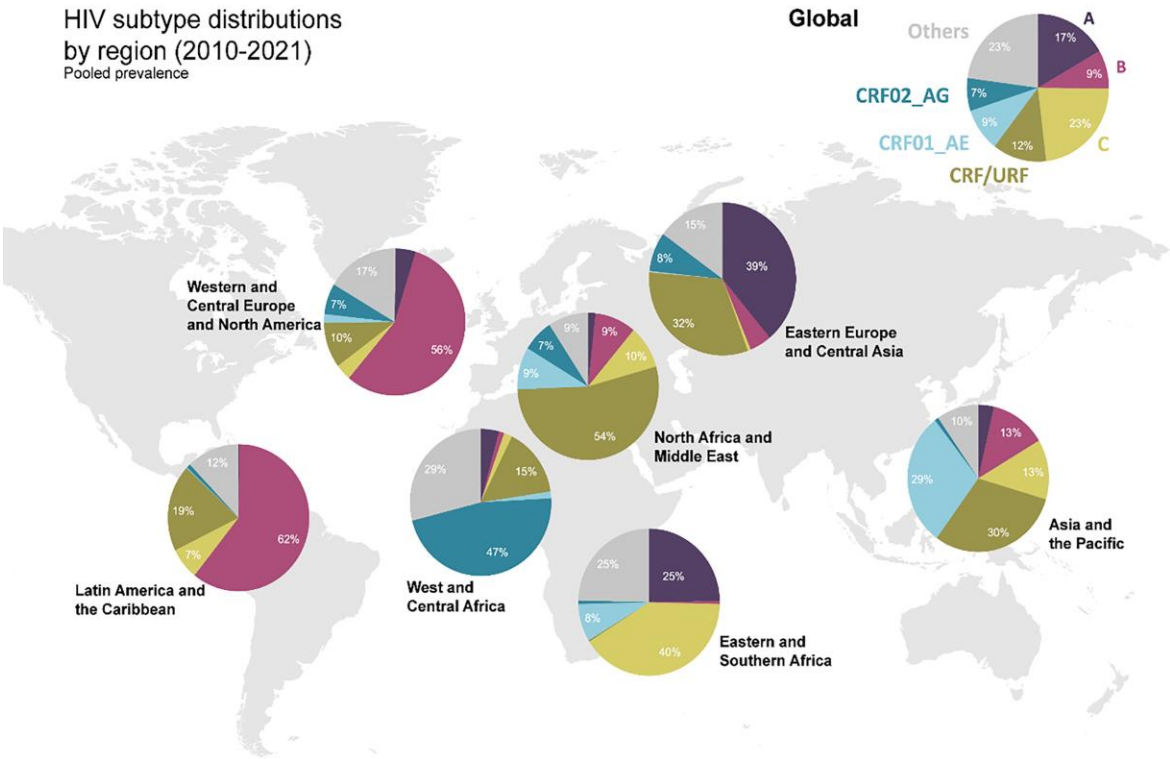


1. Corey et al., 2021. *NEJM.*

Figure modified from : Hsu, Mellors, & Vasan, 2021. *Front. In Immunol.*

HIV diversity poses a challenge for identifying effective countermeasures

- Subtypes vary in their sensitivity to bNAbs
- Multiple subtypes present in all regions
- It is important to know…
  1. Which contemporary strains the warfighter may be exposed to in a given COCOM
  2. What countermeasures are effective against circulating strains in those COCOMs

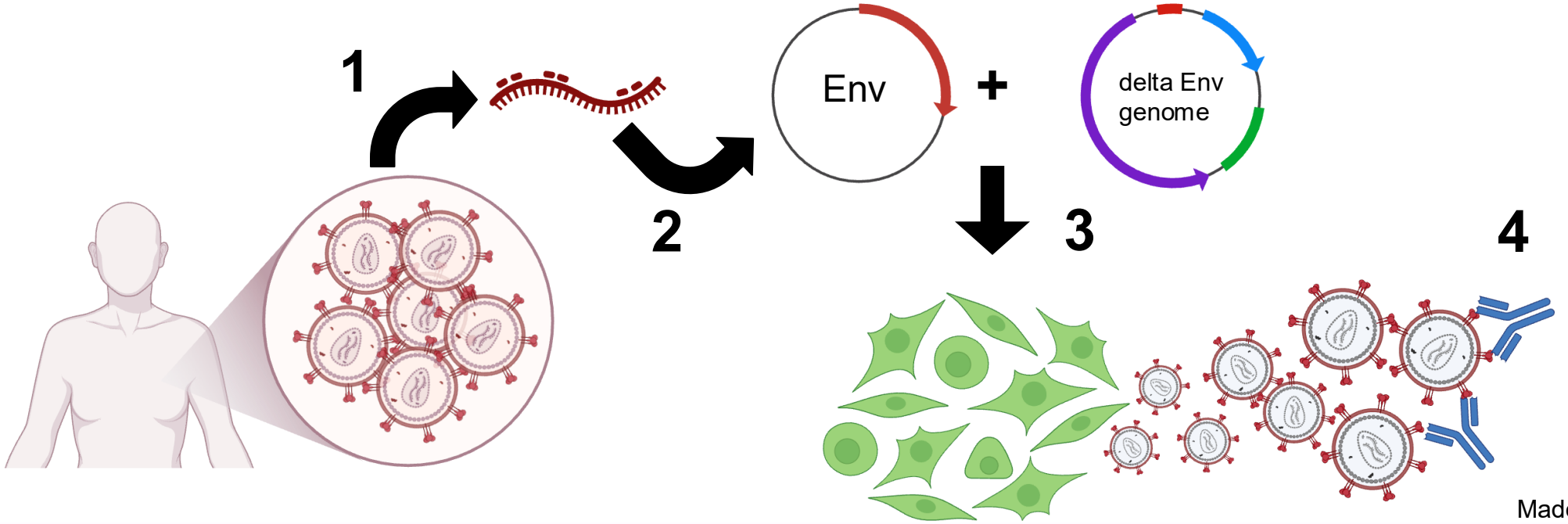


➢ **Solution: develop contemporary COCOM specific PSV panels**

Figure: Williams et al., 2023, *JID*

Approach to develop contemporary COCOM panels

1. Sequence HIV Env from people living with HIV in various COCOMs
2. Insert Env sequence into expression plasmid
3. Co-transfect plasmids with Env and Env-defective HIV genome to produce PSV
4. Characterize contemporary PSVs sensitivity to bNAbs



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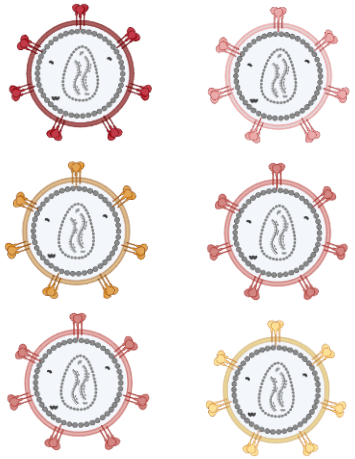
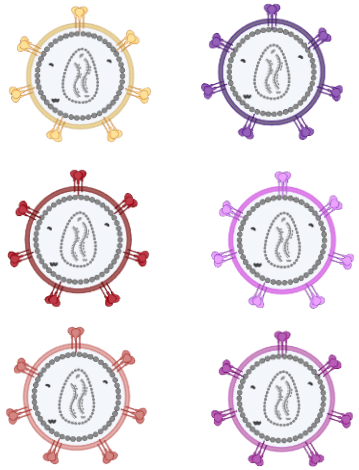
4. Characterize contemporary PSVs sensitivity to bNAbs
5. Assemble panels representative of genetic and antigenic variation present in COCOMs

NORTHCOM

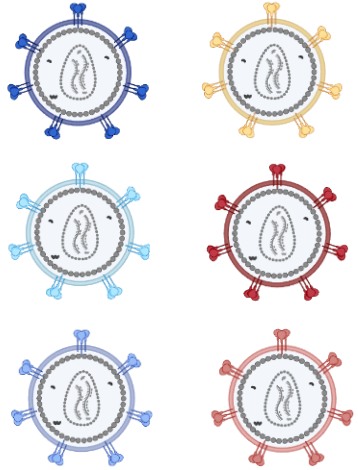


AFRICOM

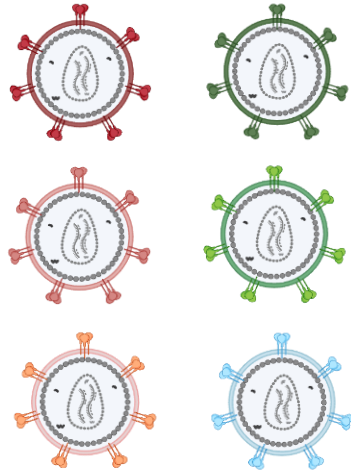
PACOM



CENTCOM



EUCOM



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311 contemporary strains have been sequenced and produced as PSVs

- HIV *Env* was sequenced from global participants enrolled in MHRP clinical trials and cohorts from 2007-2019
- 311 *Env* sequences have been produced as PSVs
  - Neutralization sensitivity testing is ongoing
  - 155 have been tested for sensitivity to ≥15 broadly neutralizing antibodies

Pseudoviruses being characterized				
Study	**Years**	**COCOM**	**Countries**	**Subtypes**
AFRICOS (RV329)	2007-2014	AFRICOM	Nigeria	G (73.5%, n=50), CRF02_AG (26.5%, n=18)
ECHO (RV217)	2009-2018	AFRICOM	Uganda, Kenya, Tanzania	A (56.5%, n=13), C (30.4%, n=7), D (4.3%, n=1), D/C (4.3%, n=1), A1/C/D (4.3%, n=1)
ECHO (RV217)	2009-2018	INDOPACOM	Thailand	AE (100%, n=20)
RV551	2017-2019	NORTHCOM	USA	B (100%, n=44)
SEARCH (RV254)	2009-current	INDOPACOM	Thailand	CRF01_AE (85.4%, n=134), B/AE (10.2%, n=15), B (3.8%, n=6), G/AG (<1%, n=1), additional PSVs coming soon
RV584	2025-current	AFRICOM	Tanzania	60 PSVs coming soon
RV505	2019-current	CENTCOM	Jordan	PSVs produced in future?
MOCHI	2024-current	INDOPACOM	Phillipines	PSVs produced in future?
RoGHITA	2025-current	EUCOM	Republic of Georgia	PSVs produced in future?

Produced PSV subtypes by COCOM

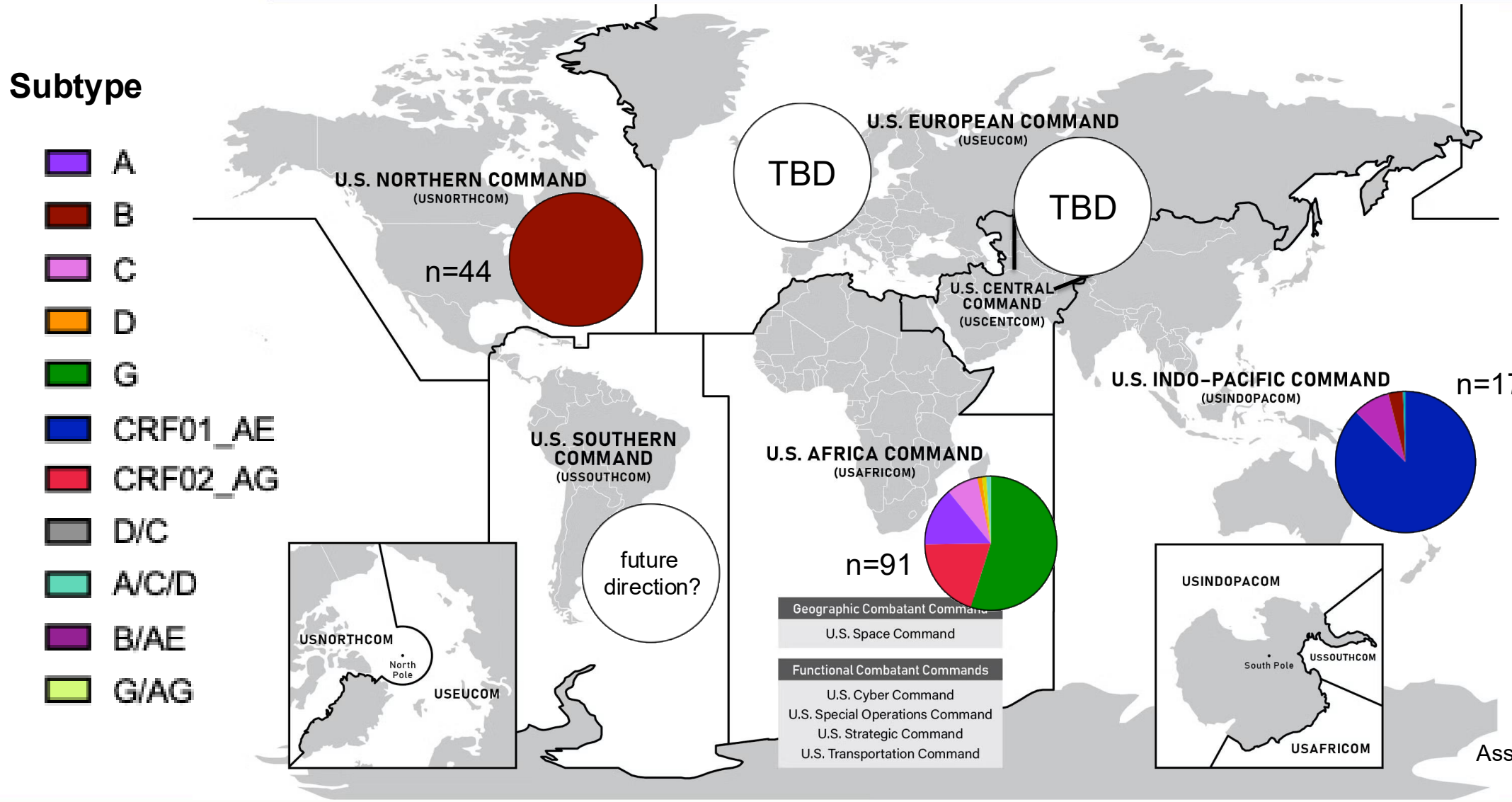
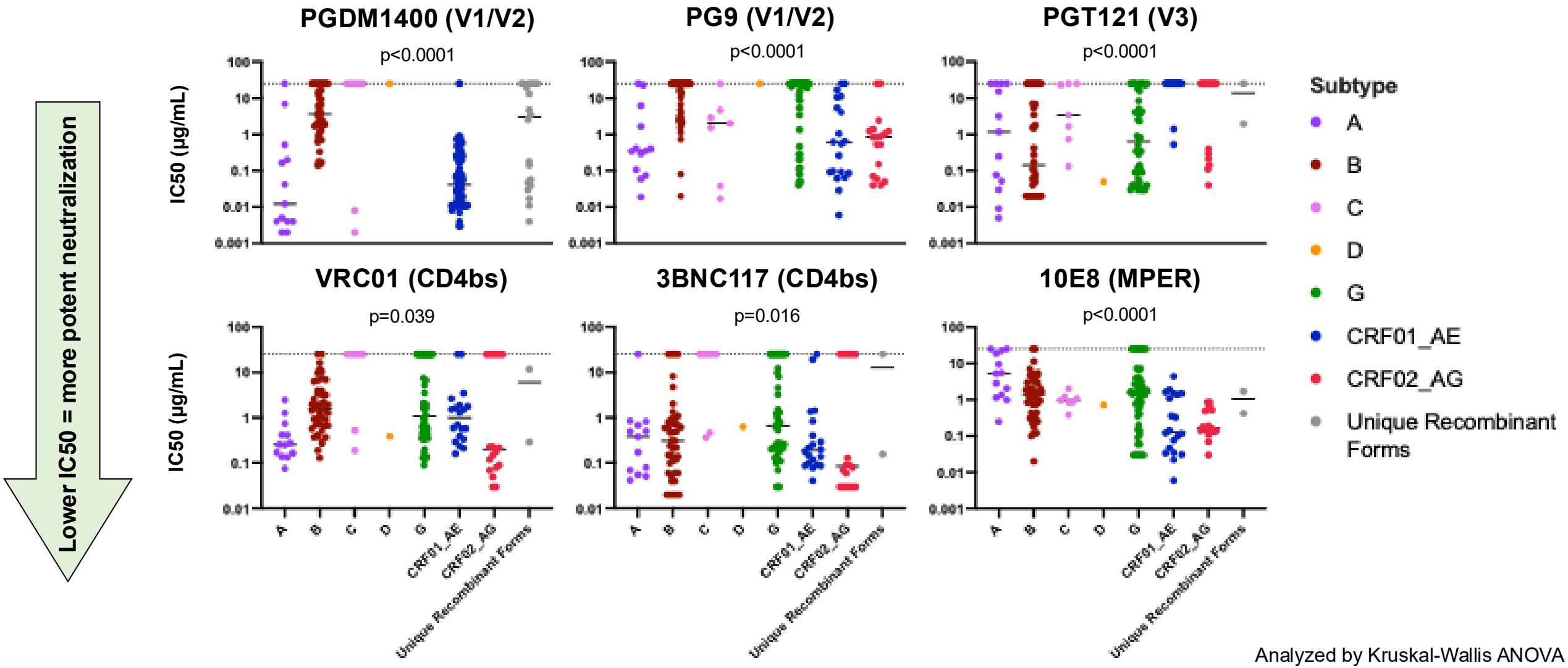


Figure modified from: Association of the United States Army (AUSA)

Contemporary subtypes have distinct neutralization profiles



Analyzed by Kruskal-Wallis ANOVA

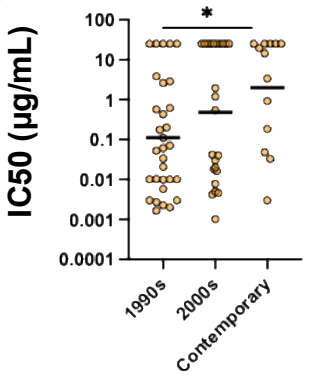
Decreased neutralization sensitivity over time across global subtypes

bNAb specificity
V1V2
V3
CD4bs
MPER

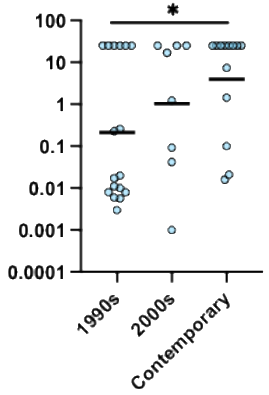
Lower IC50 = more potent neutralization

Subtype A

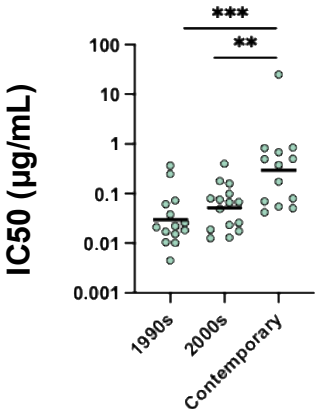
A. PG16



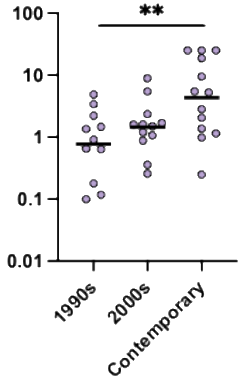
B. PGT126



C. 3BNC117

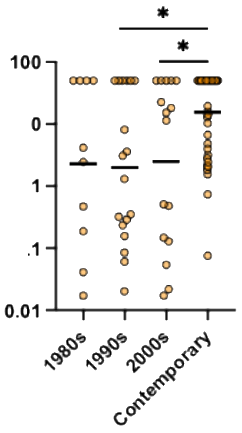


D. 10E8

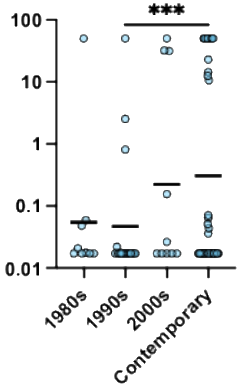


Subtype B

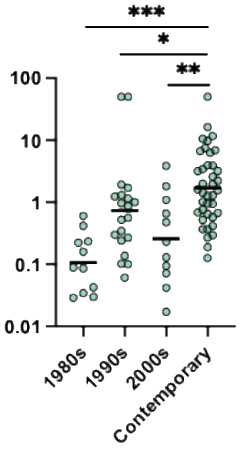
E. PG9



F. PGT128



G. VRC01



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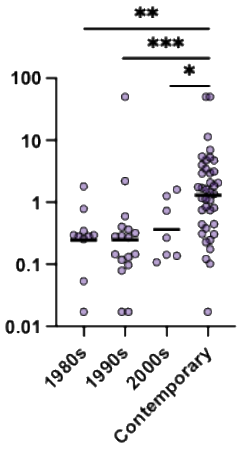
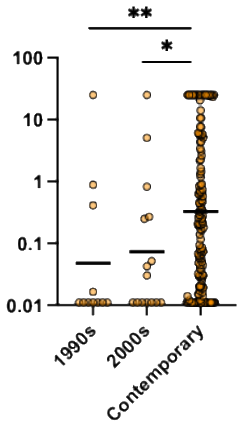
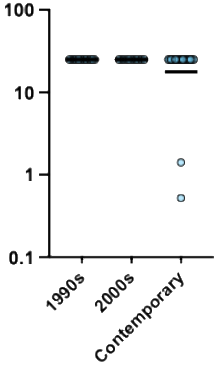


CRF01_AE

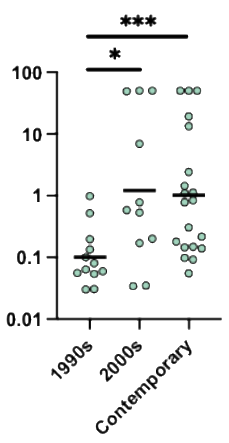
I. PGDM1400



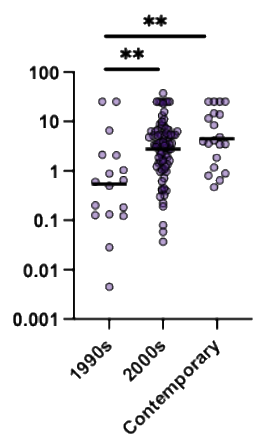
J. PGT121



K. 3BNC117



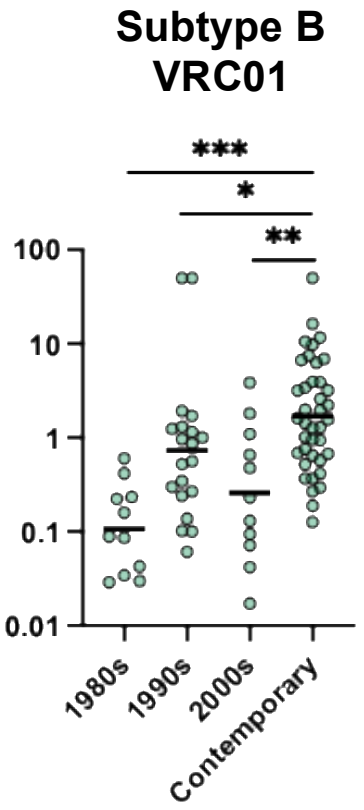
L. 2F5



Analyzed by Mann-Whitney t-test

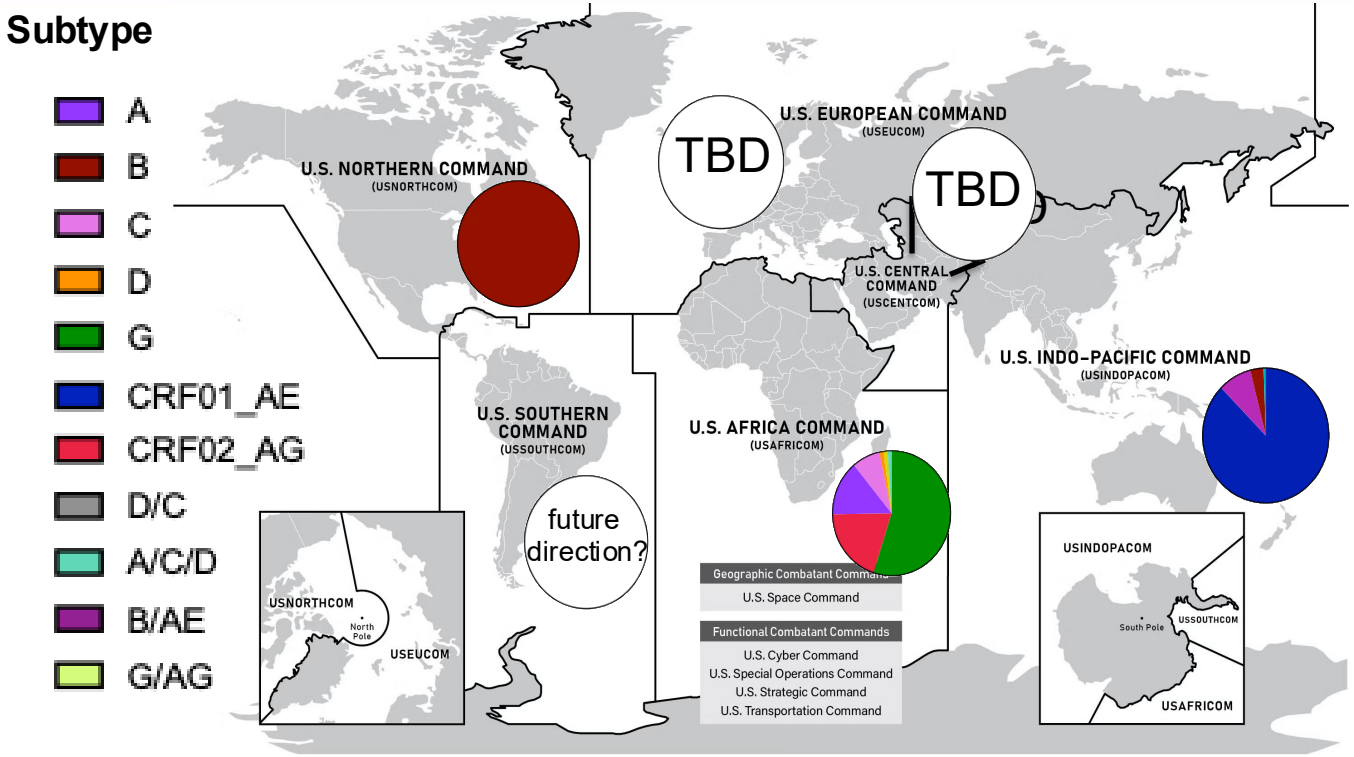
Conclusions

- Common existing PSV panels do not accurately represent the genetic and antigenic makeup of currently circulating strains of HIV
  - Lab assessment may not reflect real world efficacy
- Neutralization profiles of HIV vary significantly by subtype
  - Select countermeasures effective against subtypes the warfighter may be exposed to
- Contemporary HIV is less sensitive to neutralization by existing bNAbs
  - Importance of using contemporary strains and isolating novel, next-generation bNAbs
- *Contemporary COCOM PSV panels → improved identification of effective antibody-based countermeasures*



Future directions

- Continue producing novel PSVs and characterizing neutralization profile
  - CENTCOM
  - EUCOM
  - SOUTHCOM?
- Select 6-12 PSVs representative of the genetic and antigenic diversity within each COCOM for panels



- Utilize contemporary COCOM panels to evaluate monoclonal and vaccine elicited antibodies
  - **Identify products** with the **greatest real-world efficacy for the warfighter** based on currently circulating strains they may be exposed to while deployed

Figure modified from: Association of the United States Army (AUSA)

Acknowledgements

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