HPTN
HIV Prevention
Trials Network

AMP
STUDY

Antibody Mediated HIV Prevention

The AMP Studies

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UZ UCSF
Saving lives through innovative research strategies

Disclosures

- **No financial disclosures**

Passive Antibody Protection

- Long history of use of antibodies against viral infections
- Passive Antibody Prevention of HIV/SHIV in NHP for over 20 years
  - Polyclonal IgG protects Chimps from HIV infection
  - Polyclonal IgG protects against SHIV challenge
  - Use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
  - Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)
- NHP studies tell us that physiologically achievable levels of mAb could prevent HIV-1 infection
- **There are no human data regarding passive protection by HIV-1 monoclonal antibodies**

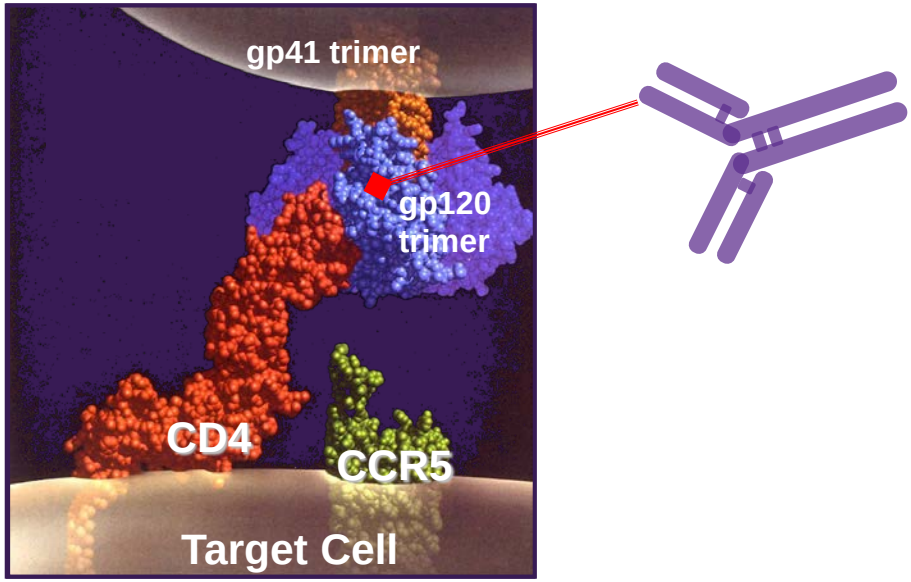
Can Antibodies be used to Prevent HIV in Humans?

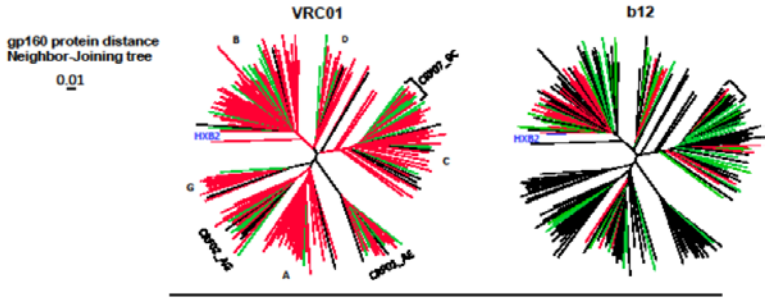
Many Unanswered Questions

- Can antibodies prevent HIV-infection in humans?
- What level of mAb is needed to protect?
- Where and how does the mAb work:
  - lumen, epithelial surface,
  - mucosal or lymphoid tissue
- Are Fc-mediated effector functions (ADCC, ADCVI) needed for protection?

Adapted from J Mascola CROI 2016

VRC01





Virus clade	Number of viruses	IC_{50} < 50 µg/ml		IC_{50} < 1 µg/ml	
		VRC01	b12	VRC01	b12
A	22	100%	45%	95%	23%
B	49	96%	63%	80%	39%
C	38	87%	47%	66%	13%
D	8	88%	63%	50%	25%
CRF01_AE	18	89%	6%	61%	0%
CRF02_AG	16	81%	19%	56%	0%
G	10	90%	0%	90%	0%
CRF07_BC	11	100%	27%	45%	9%
Other	18	83%	33%	78%	6%
Total	190	91%	41%	72%	17%

- CD4bs is functionally conserved
- Neutralizes 80 - 90% of diverse viruses, all clades

— IC_{50} < 1 µg/ml
— IC_{50} 1-50 µg/ml
— IC_{50} > 50 µg/ml

VRC01: Safety and Tolerability

- Studied in Phase 1 trials: VRC601, VRC602, HVTN104
  - **VRC 601*** : dose escalation and PK study of IV and SC in HIV infected individuals
  - **VRC 602****: dose escalation and PK study of IV and SC in HIV uninfected individuals
  - **HVTN 104**: safety and PK study of VRC01 in HIV uninfected individuals
- >100 participants; >250 IV infusions of VRC01
- Overall, safe and well-tolerated

*Lynch RM et al.Sci Transl Med.2015 Dec 23;7(319):319
**Ledgerwood et al. Clinical and experimental immunology, 2015, Vol.182(3), p.289-301.

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AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:

HVTN 704/HPTN 085

(2700 MSM and TG in the Americas)

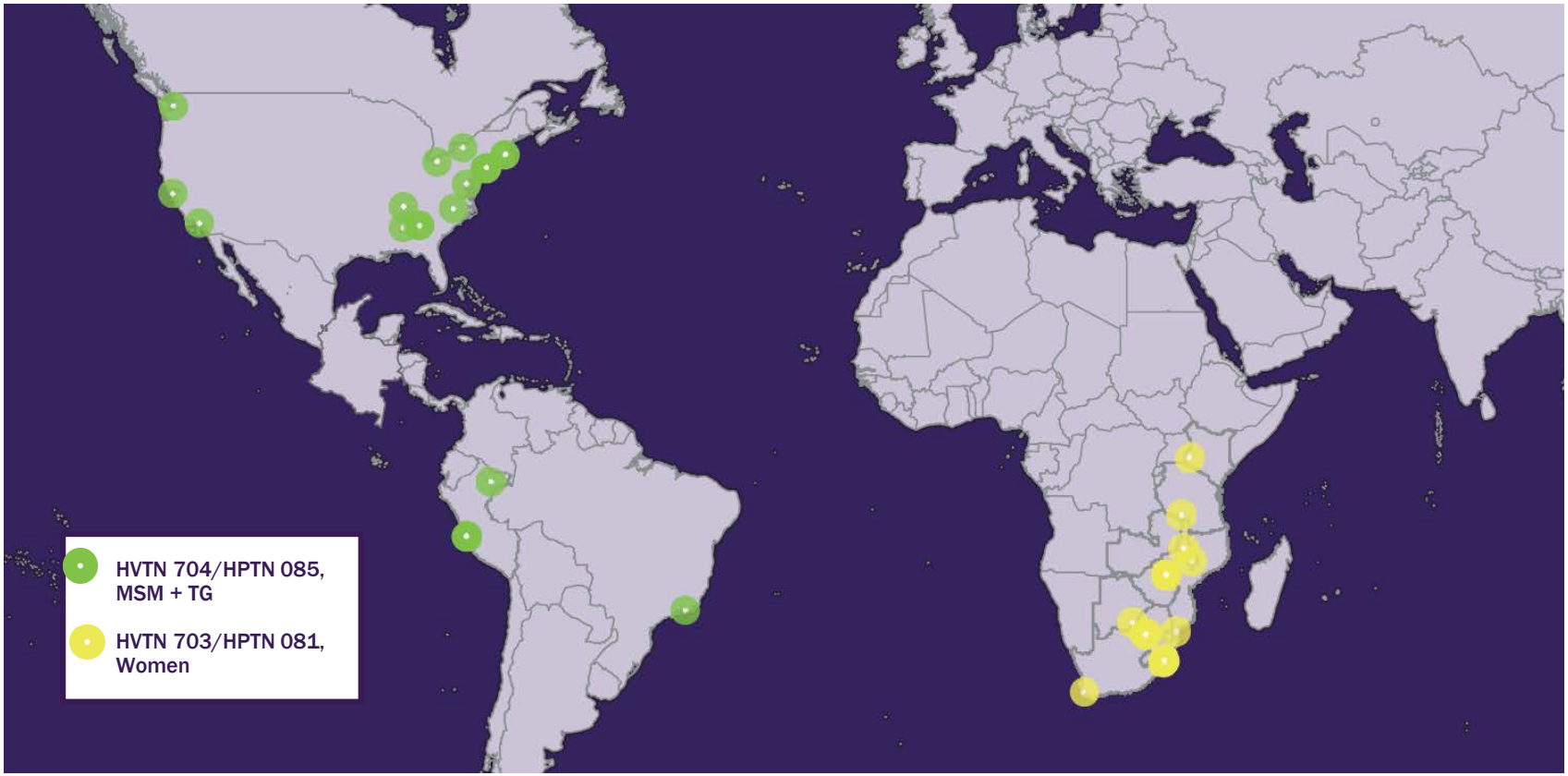
HVTN 703/HPTN 081

(1500 Women in sub-Saharan Africa)

HIV Prevention Trials Network

HIV VACCINE
TRIALS NETWORK

AMP Sites



AMP Study Objectives

PRIMARY

- **Safety & Tolerability of VRC01 infusion**
  - Reactogenicity, AEs, SAEs, discontinuation rates
- **Efficacy to prevent HIV infection**
  - HIV infection by Week 80 in those HIV-negative at enrollment

SECONDARY

- **Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy and to provide insight into mechanistic correlates of protection**
  - Serum VRC01 concentration
  - Serum mAb mediated neutralization and Fc effector functions to panels of HIV-1 Envs
  - Breakthrough HIV viral sequences in infected people
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants

AMP Study Objectives

- To determine whether and how the can prevent HIV infection
- To develop a marker(s) of VRC01 that correlates with the level of protection against HIV infection
- To provide insight into the mechanistic correlates of protection

Application: Help design candidate HIV vaccines and define immunogenicity study endpoints in Phase I/II trials for evaluating these candidate vaccines

MSM+TG AMP Schema: HVTN 704/HPTN 085

			Infusion schedule (Weeks) [A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80♦	W92†
Group 1	VRC01 10 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		
	Total:	2700 (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 control)												

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.
† Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 450 enrolled participants. Infusions for those 450 participants will continue while the interim safety assessment is conducted. Following enrollment of the 450th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete, reviewed by the DSMB, and submitted to the US FDA. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory.

SSA Women AMP Schema: HVTN 703/HPTN 081

			Infusion schedule (Weeks) [A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80♦	W92†
Group 1	VRC01 10 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	500	C	C	C	C	C	C	C	C	C	C		
	Total:	1500 (500 VRC01 30 mg/kg; 500 VRC01 10 mg/kg; 500 control)												

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.
† Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 300 enrolled participants. Infusions for those 300 participants will continue while the interim safety assessment is conducted. Following enrollment of the 300th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete and reviewed by the DSMB. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory. Data from VRC01 administration in HVTN 704/HPTN 085 may inform the safety assessment in HVTN 703/HPTN 081.

The AMP Study Highlights

- Placebo controlled trial of VRC01 mAb (IV), given on Q2 month schedule, 2 harmonized trials

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	500	1400	10 infusions total & Infusions every 8 weeks
VRC01 30 mg/kg	900	500	1400	
Control	900	500	1400	
Total	2700	1500	4200	**Study duration: ~22 months**

Primary Endpoint – HIV-1 Infection

- Week 80
- Diagnosed via the HVTN algorithm
- Independent adjudication committee confirms each HIV-1 infection endpoint within 24-hour turn-around

Select Eligibility Criteria

- **General and Demographic Criteria**
- **18-50 years of age**
- **HIV-Related Criteria: HIV uninfected**
- **Risk behavior related criteria:**
  - In the Americas: male or TG who has had condomless anal intercourse with ≥ 1 male or TG partner(s) or any anal intercourse with ≥ 2 male or TG partners
  - In Africa: female who has had vaginal or anal intercourse with a male partner in the past 6 months
  - All volunteers in a mutually monogamous relationship with an HIV(-) partner for > 1 year are excluded.
- **Volunteers with clinically significant medical conditions are excluded**

AMP Study Procedures

- **IV:** receive an IV over a 30-60 minute period every 8 weeks (10 times total)
- **Blood Draw:** get a blood draw at the clinic every 4 weeks (includes an HIV test)
- **STI Testing**: get STI testing at enrolment and Q6 months thereafter
- **Questionnaires:** complete questionnaires about sexual behavior & general health every 4-8 weeks
- **Comprehensive HIV Prevention Package**

STUDY DURATION: about 22 months

AMP Monitoring

- Monitoring for harm, non-efficacy, high efficacy
- Monitoring for futility to assess prevention efficacy
- Safety assessment/slow down once enrollment reaches n=450 participants/300 participants

What Happens with Success?

- **We define the level of plasma mAb needed to protect against infection (e.g., 5 - 10 ug/ml)**
- **Translate that into:**
  - Single dose administration of mAbs to achieve this level
  - Incentive to develop next generation mAb (more potent, longer half life)
  - Options for genetic immunization to provide medium to long-term protective antibody levels
  - Knowledge that neutralizing mAb can protect will guide vaccine field

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Site Activation Status - HVTN 704/HPTN 085
Study Opened March 31, 2016

Sites activated (67%)	• Nashville, San Francisco, Philadelphia, Birmingham, Columbia-NYBC, Columbia-P&S, Rochester, Seattle, Atlanta–Hope Clinic, Boston-Brigham, Boston-Fenway, Cleveland, Columbia–Harlem, Chapel Hill, LA, Washington DC/GWU
Sites not activated	• Atlanta–Ponce de Leon, Columbia–Bronx, New Jersey
Activation n/a training June 5-10	• Iquitos, Lima-Barranco CRS, Lima-San Miguel CRS, Lima Via Libre CRS, Rio-IPEC-Fiocruz CRS

HIV Prevention Trials Network

HIV VACCINE
TRIALS NETWORK

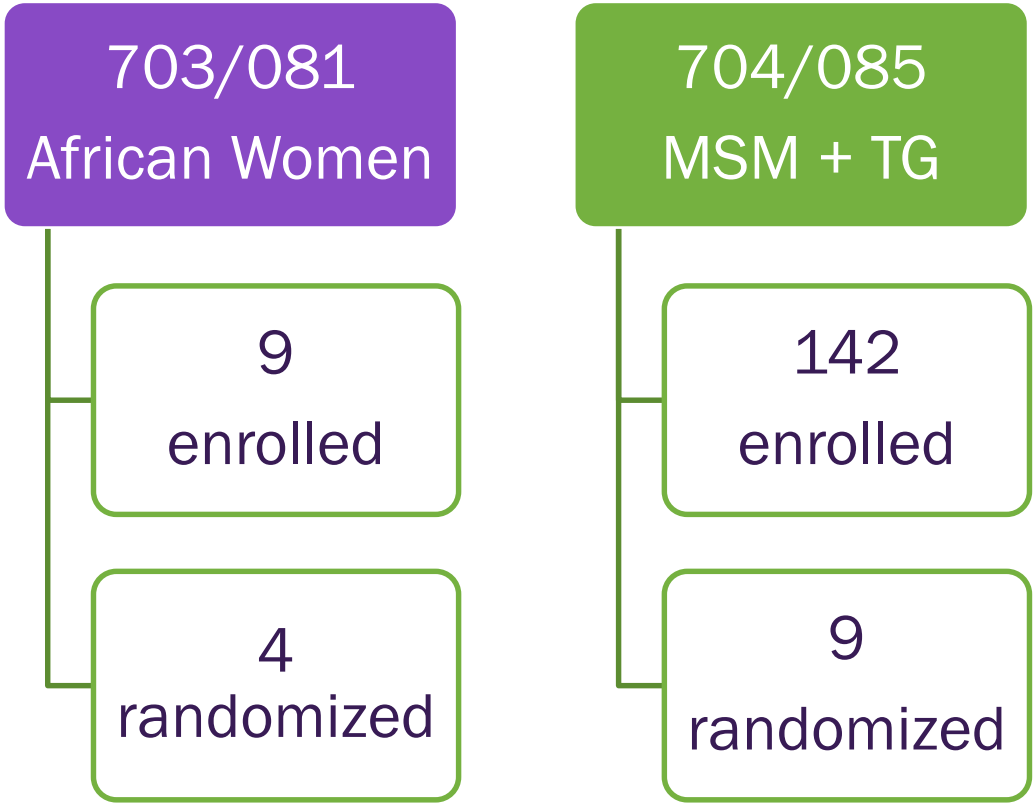
AMP 1 - OUR FIRST PARTICIPANT

Activation Status - HVTN 703/HPTN 081

Study Opened May 9, 2016

Sites activated (20%)	• Soweto CRS, eThekwini CRS, Vulindlela CRS
Sites not activated	• Groote Schuur CRS, Chatsworth CRS, Gabarone, Parirenyatwa CRS, Seke South CRS, Spilhaus CRS, WRHI CRS, Kisumu CRS
Activation n/a training August 1-5	• *Blantyre CRS, Lilongwe, Maputo CRS, Mbeya CRS*

Enrollment Updates as of 13 June 2016



Conclusions – Why Antibodies?

Px Option		Current Status
	Vaginal gel	❑ Results of FACTS 001 from Q1 2015
	Rectal gel	❑ First phase II just finished
	Vaginal ring	❑ Two phase IIIs
	Oral PrEP	❑ WHO recommends for all at substantial risk as of Sept 2015
	Long-acting Injectable ARV	❑ Phase II studies; will there be a phase III in 2017
	Preventive vaccines	❑ P5 – licensure: Research trials launch in 2016 ❑ Janssen Ad26/mosaic, early stages
	Antibodies	❑ HVTN/HPTN with VRC01

Conclusions – Why Antibodies?

- Reasonable likelihood that antibodies will work
- Likely to be safe and well tolerated (human mAbs)
- Potential that single shot – confer long lasting protection
- If we achieve clinical efficacy, mAbs could be developed for larger scale use
- **Goal:** A single shot injectable antibody product given one every 3 - 4 months, that safely and effectively protects high risk individuals from HIV-1 infection

Thank you

Some of this slide set was adapted from versions created by Dr. J Mascola, Dr S Karuna and Dr. S Edupuganti

AMP Protocol Team

- Chairs: Larry Corey & Mike Cohen
- co-Chairs: Sri Edupuganti & Nyaradzo Mgodi
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- Communications Representatives: Jim Maynard & Eric Miller
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- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab

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