

# The DNA-MVA/HIVA Vaccine: Successes and Challenges

Megan Clark  
Human Biology 146

# Kenyan Sex Workers

- 1994-1999 Rowland-Jones studies
  - 71 highly exposed, persistently seronegative (HEPS) sex workers in Nairobi
- Cellular immunity?
  - Number of HIV-specific CTLs lower than HIV+ sex workers
  - BUT different epitope specificity
- Conclusion: Immunity relies on CTLs targeting right epitopes

# Vaccine design

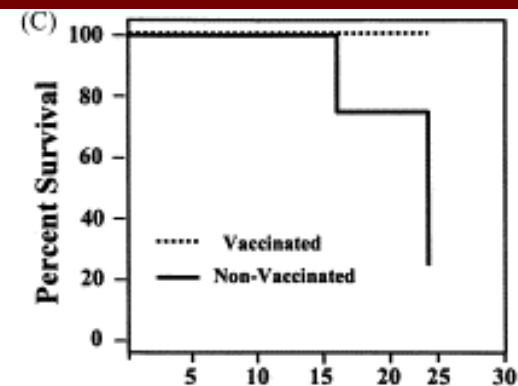
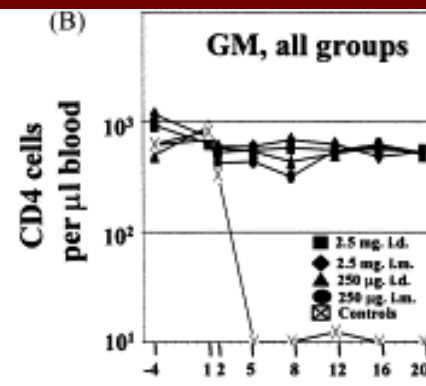
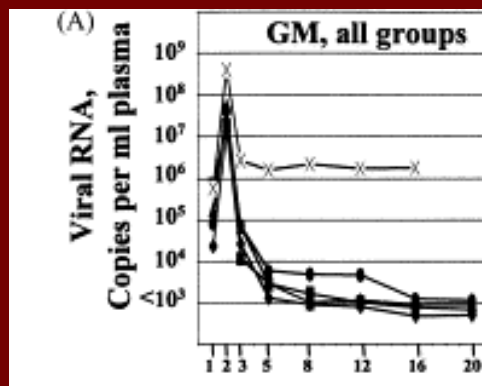
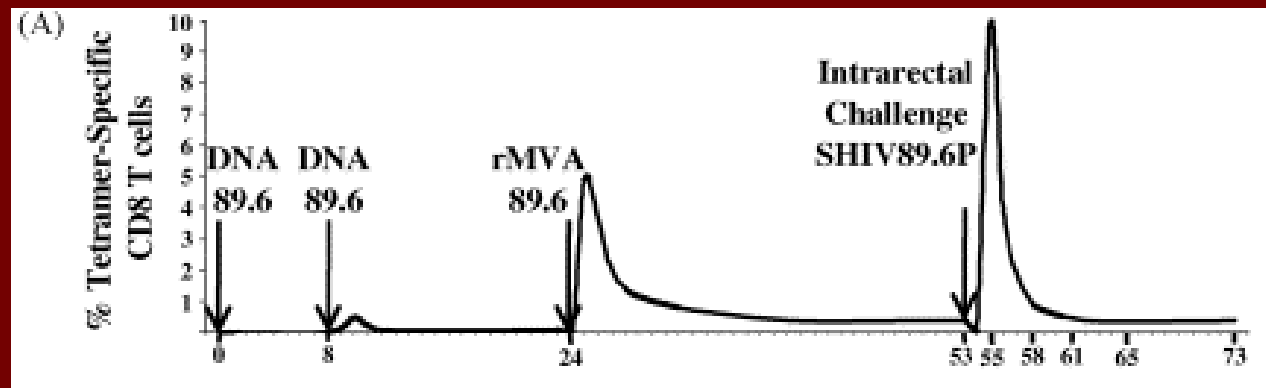
- What are the “right” epitopes?
  - Number of HEPs with CTLs specific to *env* increased with duration of uninfected exposure
  - HEPs tend to respond to *pol* and B18 *p24* while HIV+ workers do not
- Vaccine designed with:
  - clade A *gag* p24/p17 epitopes
  - string of ~25 clade A epitopes (*gag*, *pol*, *nef*, *env*)

# Vaccine design

- Goal: Make the body produce CTLs specific to “right” HIV epitopes
- 2 delivery methods
  - Directly inject DNA epitopes
  - Incorporate DNA epitopes into other vector
    - Modified vaccinia ankara (MVA) virus
    - Cellular response to MVA tricks body into also recognizing and responding to HIV epitopes
- Solution – Combine delivery methods
  - DNA prime with MVA boost
  - 10-100 times higher T-cell counts than either alone in macaques

# Vaccine Immunogenicity

- Amara, 2002 study – 24 macaques
  - 2 DNA prime with 1 MVA boost (SIV and HIV epitopes)



# Vaccine Immunogenicity

- Humans – phase I and I/II trials on each vaccine alone since 2001 in Oxford and Nairobi
- Preliminary data
  - HIV vaccine - 12/18 volunteers showed responses in ELISPOT assay
  - MVA vaccine – 4/5 volunteers showed responses in ELISPOT assay

# Vaccine safety

- Safety – Murine studies
  - DNA and MVA alone and in combination safe
  - No evidence of pharmacological effects
  - Genes cleared from all organs except injection sites by 5 weeks post-vaccination
- Published safety data from human phase I trials not yet available

# Challenge – Not true immunity

- Vaccine reduces pathogenicity (viral load)
- Doesn't produce sterilizing immunity
- Sex workers resistant, not immune
  - 12 seronegative workers who reduced or took a break from sex work became seropositive
  - Infection associated with switch in specificity
  - Suggests that repeated exposure to epitopes maintains resistance
- Implications – Regular boosting may be necessary.
  - More expensive
  - Many will miss their boosts

# Challenge – Viral escape and diversity

- Barouch, 2002 – vaccine study on 8 rhesus monkeys
  - 7 had successful disease reduction
  - 1 had successful reduction until week 24 when viral replication breakthrough occurred, led to disease and death
  - Findings – single nucleotide mutation in targeted *gag* epitope resulted in viral escape, vaccine failure
- HIV strain diversity – Will the vaccine produce resistance to other clades?
- Implications – Evolving boosts with old and new epitopes
  - Ex. Flu vaccine evolves with changing virus
  - Burden on research to keep up with virus

# Challenge – Mucosal Immunity

- Progression of infection:
  1. Sexual contact – virus enters mucus membrane
  2. Establishes lymphatic tissue virus reservoir
  3. Systemic virus replication begins
- If response is only systemic, won't block lymphatic reservoir (Pope and Haas, 2003)
- Mucosal response critical to protect against mucosal challenge in mice (Belyakov, 1998)
- Implication – Effective vaccine must elicit mucosal immunity to combat virus at initial contact

# Conclusions

- Promising vaccine based on animal and preliminary human data
- Even if no sterilizing immunity, reduction in viral load and replication
  - Slowed disease progression
  - Reduction in transmission
- Outlook – Phase III trials scheduled for 2004

# References

- Amara RR, Villinger F, Altman JD, et al. Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science* 2001; 292: 6974.
- Barouch DH, et.al. Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature*. 2002 Jan 17; 415(6869): 335-9.
- Belyakov IM, et. al. The importance of local mucosal HIV-specific CD8(+) cytotoxic T lymphocytes for resistance to mucosal viral transmission in mice and enhancement of resistance by local administration of IL-12. *J Clin Invest*. 1998 Dec 15; 102(12): 2072-81.
- Bird TG, Kaul R, et. al. HLA typing in a Kenyan cohort identifies novel class I alleles that restrict cytotoxic T-cell responses to local HIV-1 clades. *AIDS*. 2002 Sep 27; 16(14): 1899-904.
- Hanke T, McMichael AJ, et.al. Development of a DNA-MVA/HIVA vaccine for Kenya. *Vaccine*. 2002 May 6;20(15):1995-8.
- Heeney JL. The critical role of CD4+ T-cell help in immunity to HIV. *Vaccine* 2002; 20: 1961-63.
- IAVI Database of AIDS Vaccines in Human Trials: HIVA.  
<http://www.iavi.org/trialsdb/vaccinedetail.asp?i=7>.
- IAVI Database of AIDS Vaccines in Human Trials: MVA.HIVA.  
<http://www.iavi.org/trialsdb/vaccinedetail.asp?i=11>.
- International AIDS Vaccine Initiative. "IAVI R&D Agenda in Detail."  
<http://www.iavi.org/vaccinedev/agenda.htm>.
- Kaul R, Rowland-Jones SL, et. al. New insights into HIV-1 specific cytotoxic T-lymphocyte responses in exposed, persistently seronegative Kenyan sex workers. *Immunology Letters* 2001; 79: 3-13.
- Robinson HL, et. al. AIDS vaccines: heterologous prime/boost strategies for raising protective T-cell responses. *AIDS Rev* 2000; 2: 105-10.
- Rowland-Jones S, et. al. The role of cytotoxic T-cells in HIV infection. *Dev Biol Stand*. 1998;92:209-14.