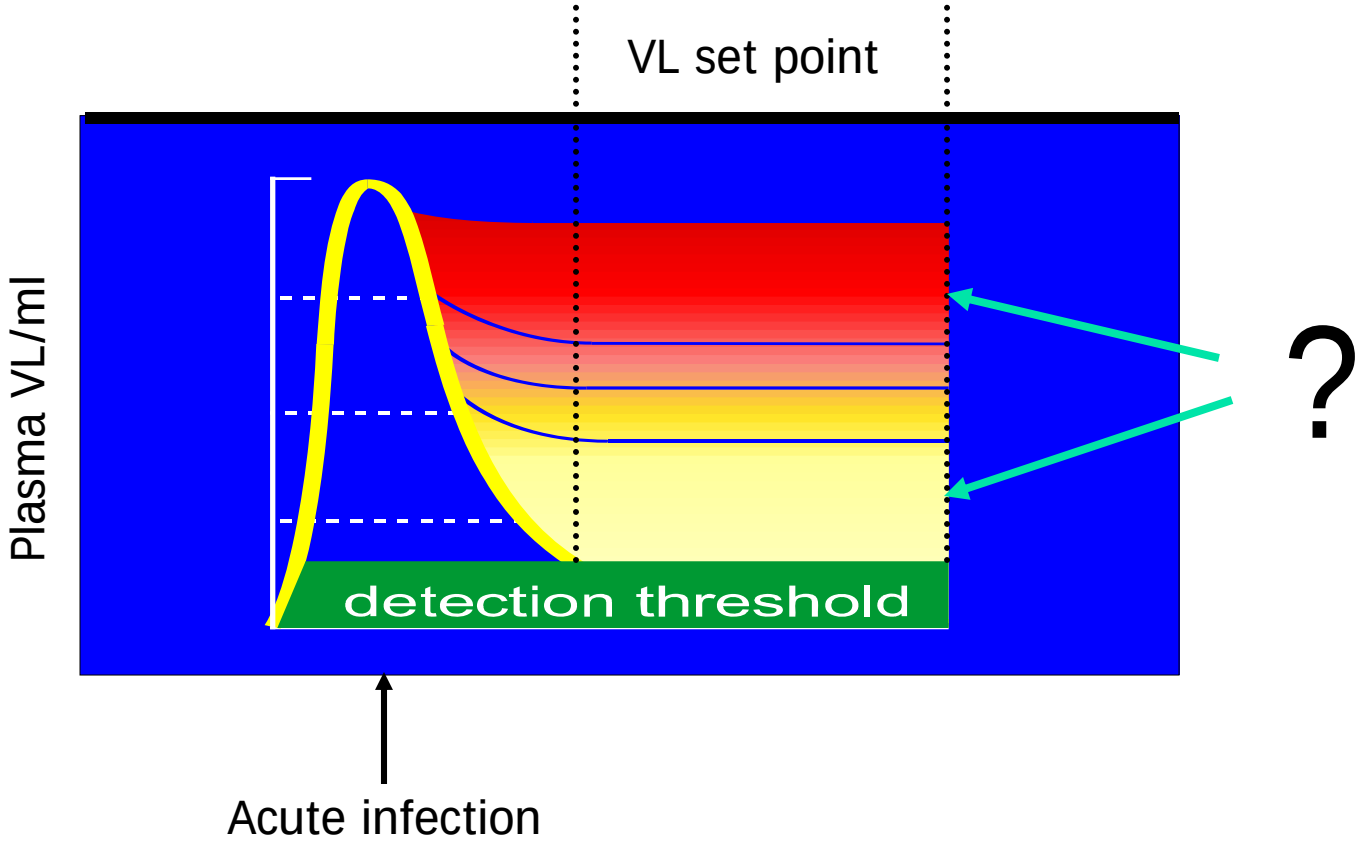
Donor HIV-1 Gag but not Nef CTL escape mutations lower viral load set point in newly infected recipients

Paul Goepfert
University of Alabama at Birmingham
Division of Infectious Diseases and International Health
August 23, 2007

What determines HIV-1 viral load?

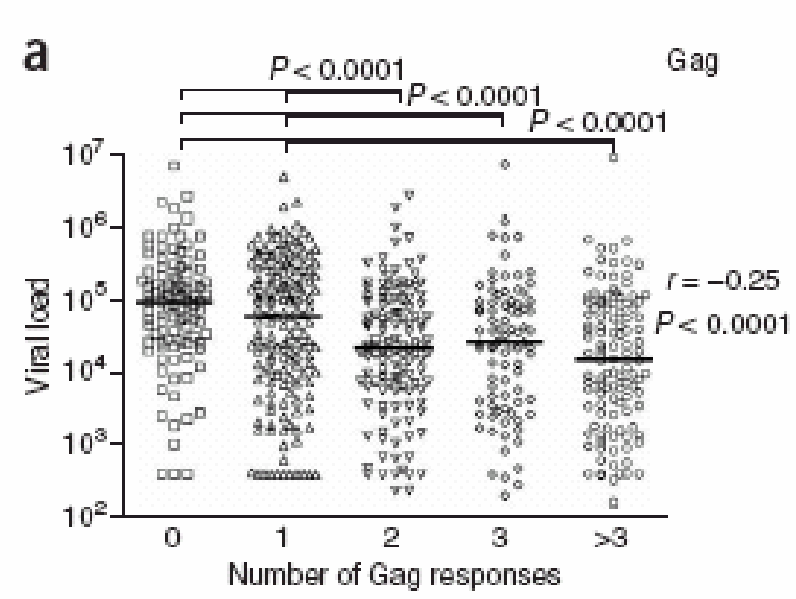


nature medicine

CD8+ T-cell responses to different HIV proteins have discordant associations with viral load

Photini Kiepiela[1], Kholiswa Ngumbela[1], Christina Thobakgale[1], Dhanwanthie Ramduth[1], Isobella Honeyborne[2], Eshia Moodley[1], Shabashini Reddy[1], Chantal de Pierres[1], Zenele Mncube[1], Nompumelelo Mkhwanazi[1], Karen Bishop[1], Mary van der Stok[1], Kriebashnie Nair[1], Nasreen Khan[1], Hayley Crawford[2], Rebecca Payne[2], Alasdair Leslie[2], Julia Prado[2], Andrew Prendergast[2], John Frater[2], Noel McCarthy[3], Christian Brander[4], Gerald H Learn[5], David Nickle[5], Christine Rousseau[5], Hoosen Coovadia[1], James I Mullins[5], David Heckerman[6], Bruce D Walker[1,4,7] & Philip Goulder[1,2,4]

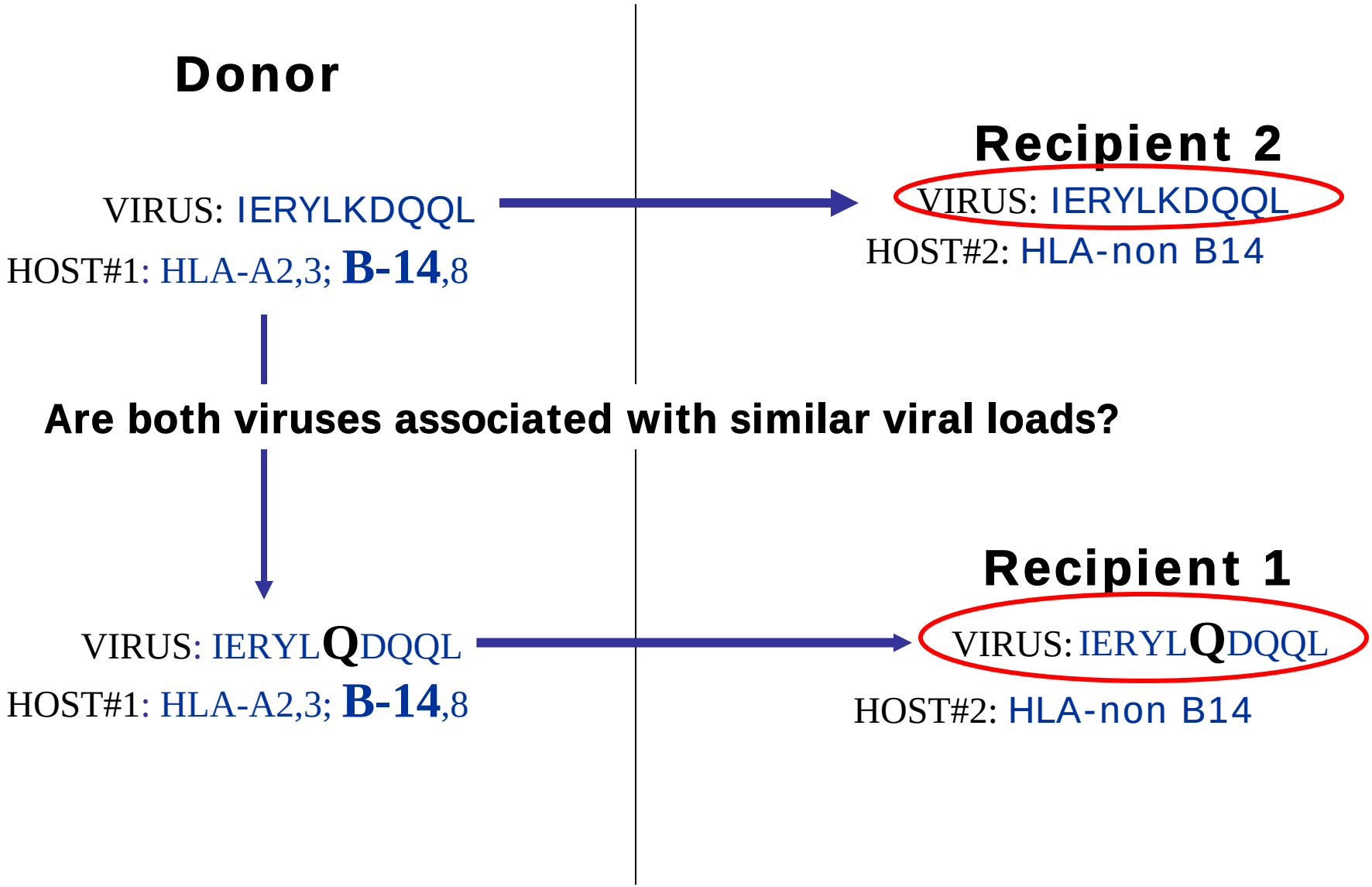
Received 8 August; accepted 8 November; published online 17 December 2006; doi:10.1038/nm1520



Why is Gag targeting better

- Better quality response?
- Gag mutations poorly tolerated by the virus?

Studying HIV-Linked Transmission Pairs



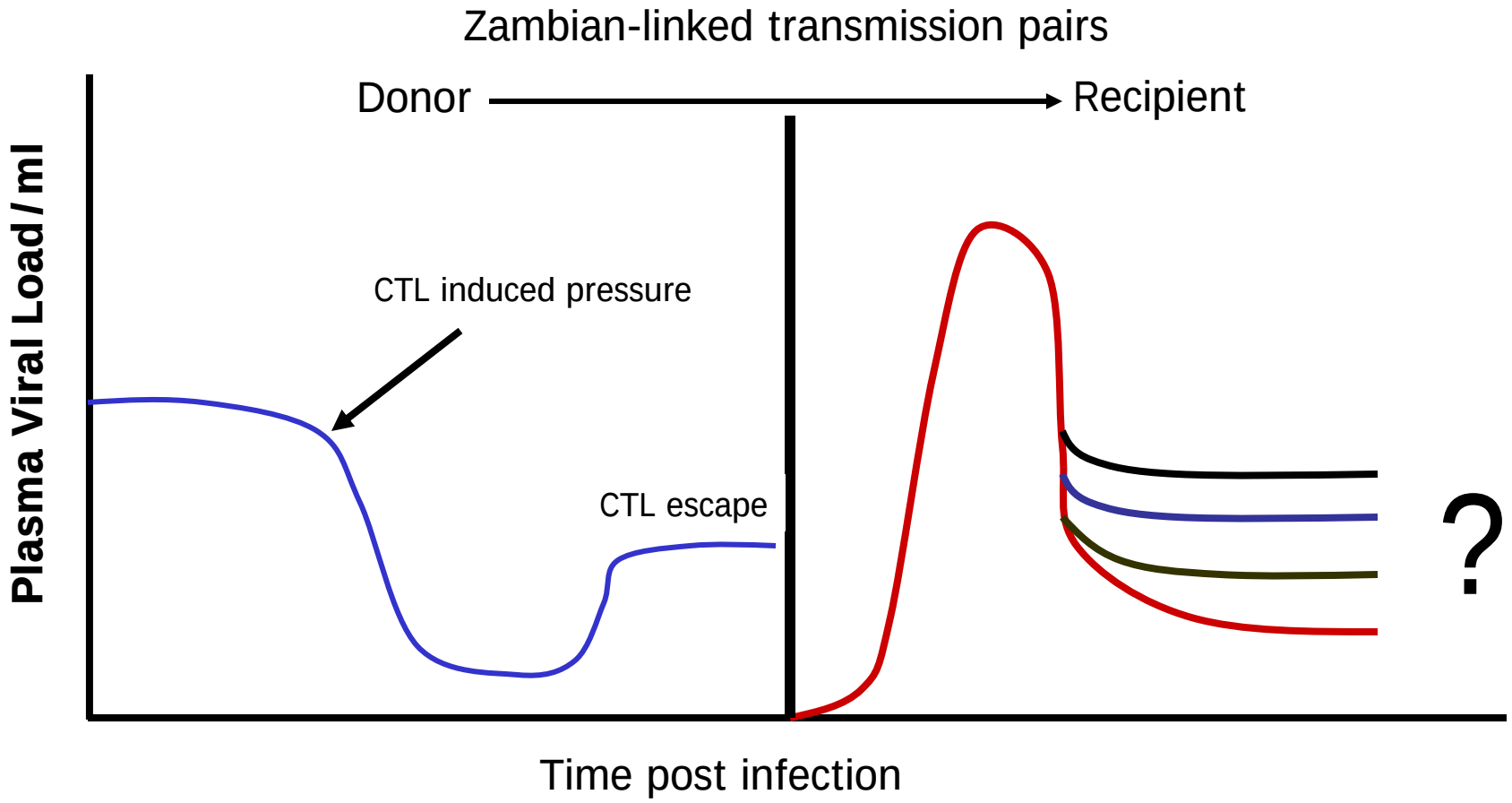
Methods 1

- Determine HLA-I associated HIV polymorphisms for clade C infection
  - 680 South Africans with chronic infection (ART naïve)
  - HLA class I typing
  - *gag* and *nef* sequencing
  - Limit to those within or flanking known CTL epitopes

HIV-1 mutations associated with HLA-I alleles in chronically infected South Africans

HIV-1 subregion	Common mutations (shaded) within known CTL epitopes	Specific HLA-I association
Gag-p17	---RLRPGGKKHY—-	**B***4201, p= 7.6×10^{-11}; q=0.19
Gag-p24	--ISPRTLNAW---	**B***57, p= 2.5×10^{-14}; q=0.00
	---ISPRTLNAW---	**B***57, p= 1.6×10^{-8}; q=0.05
	---KAFSPEVIPMF-	**B***57, p= 1.4×10^{-15}; q=0.00
	-TPQDLNTML---	**B***8101, p= 3.2×10^{-5}; q=0.06
	---TPQDLNTML---	**B***8101, p= 3.21×10^{-5}; q=0.06
	---TPQDLNTML---	**B***8101, p= 3.9×10^{-7}; q=0.05
	---TSTLQEQIAW--	**B***57/5801, p= 3.7×10^{-15}; q=0.00
	---TSTLQEQIAW--	**B***57, p= 1.7×10^{-5}; q=0.05
	---DRFFKTLRA---	**B***14, p= 2.6×10^{-11}; q=0.03
	---YVDRFFKTL---	**Cw***0304, p= 0.0002; q=0.07
	---QATQDVKNW---	**B***5801, p= 3.9×10^{-7}; q=0.05
	---QATQDVKNW---	**B***44, p= 3.0×10^{-9}; q=0.033
	---GPSHKARVL---	**B***0702, p= 0.001; q=0.15
Nef	---EEVGFPVRPQV-	**B***4501, p= 8.3×10^{-9}; q=0.00
	---FPVRPQVPL---	**B***0702, p= 9.4×10^{-13}; q=0.00
	---RPQVPLRPM---	**B***8101, p= 1.9×10^{-10}; q=0.00
	---VPLRPMTY----	**B***35, p= 9.9×10^{-8}; q=0.00
	---KAAFDLSFF---	**B***5801, p= 7.3×10^{-6}; q=0.07
	---KRQEILDLWVY-	**Cw***0701, p= 7.8×10^{-7}; q=0.00
	---QEILDLWVY---	**B***18, p= 1.3×10^{-7}, q=0.00
	---GPGVRYPLTF--	**B***35, p=6.3×10^{-6}; q=0.00
	---RYPLTFGW----	**A***2402, p= 0.0001; q=0.20
	---RYPLTFGW---	**A***2301, p= 6.8×10^{-12}; q=0.00

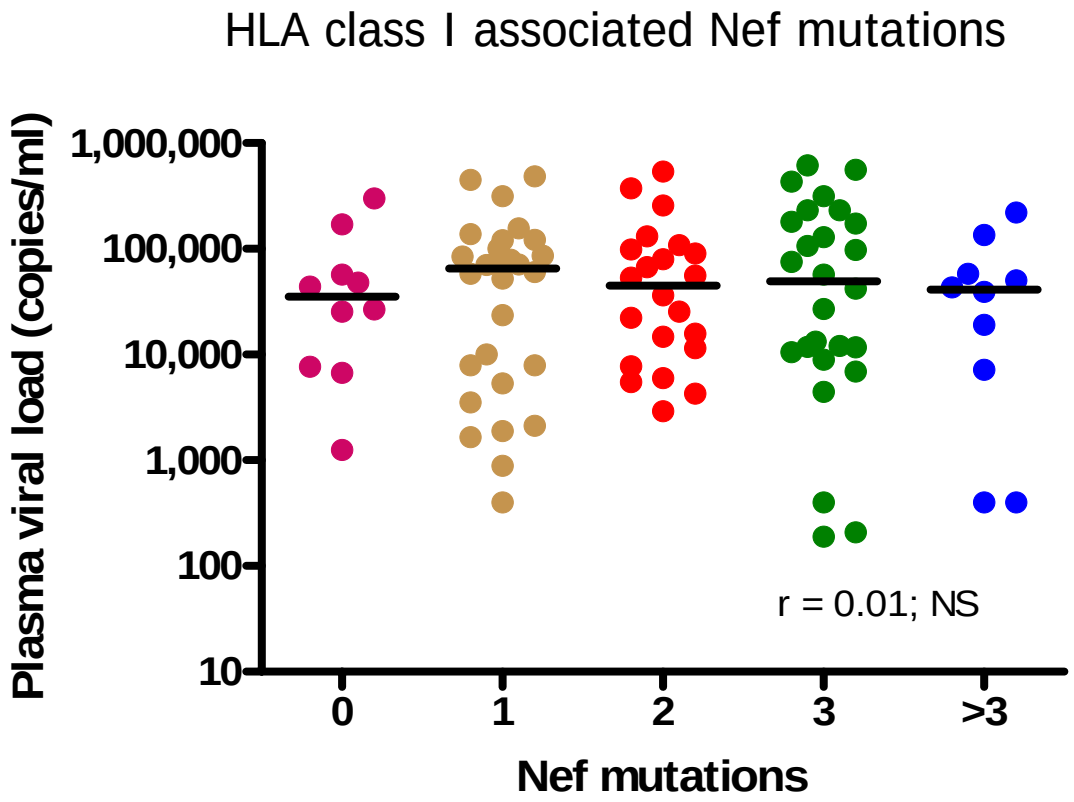
Determination of *in vivo* viral fitness



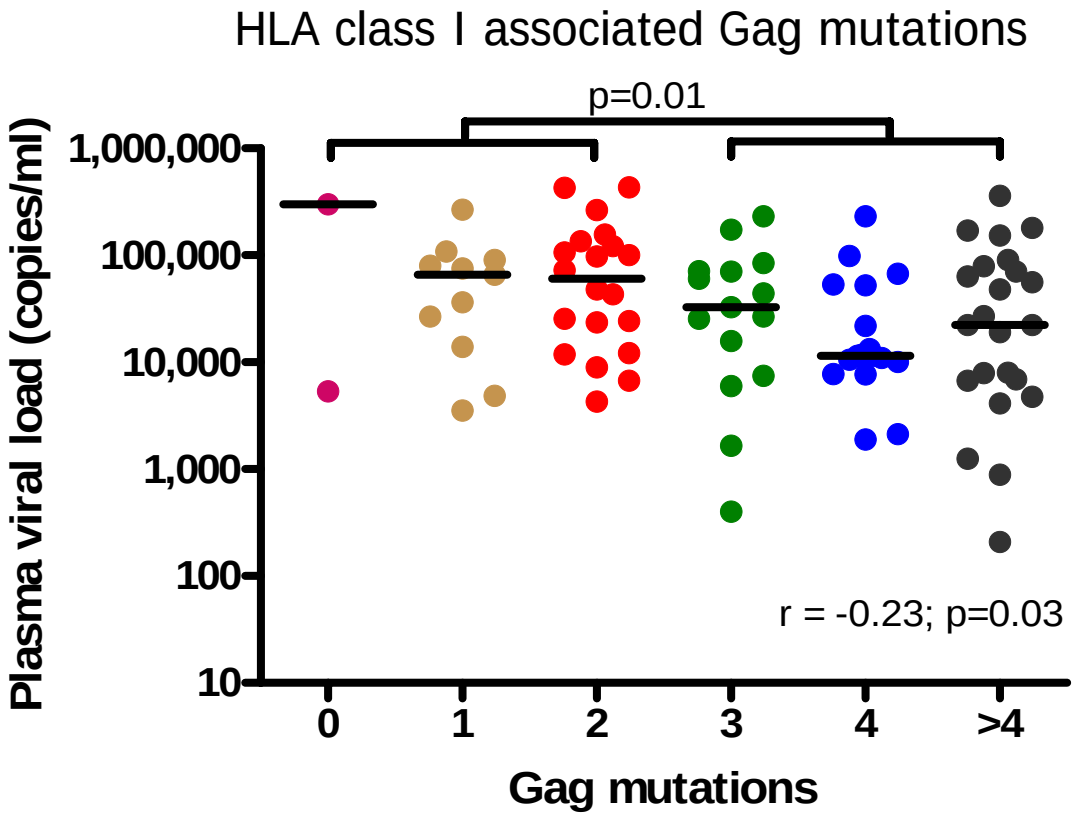
Methods 2

- Determine whether “CTL escape mutations” impact viral replication *in vivo*
  - 88 Zambian transmission pairs
  - HLA class I typing
  - *gag* and *nef* sequencing
  - Determine transmitted virus
  - VL in recipients 3-6 months post transmission
  - Analyze data according to presence of Gag or Nef mutations

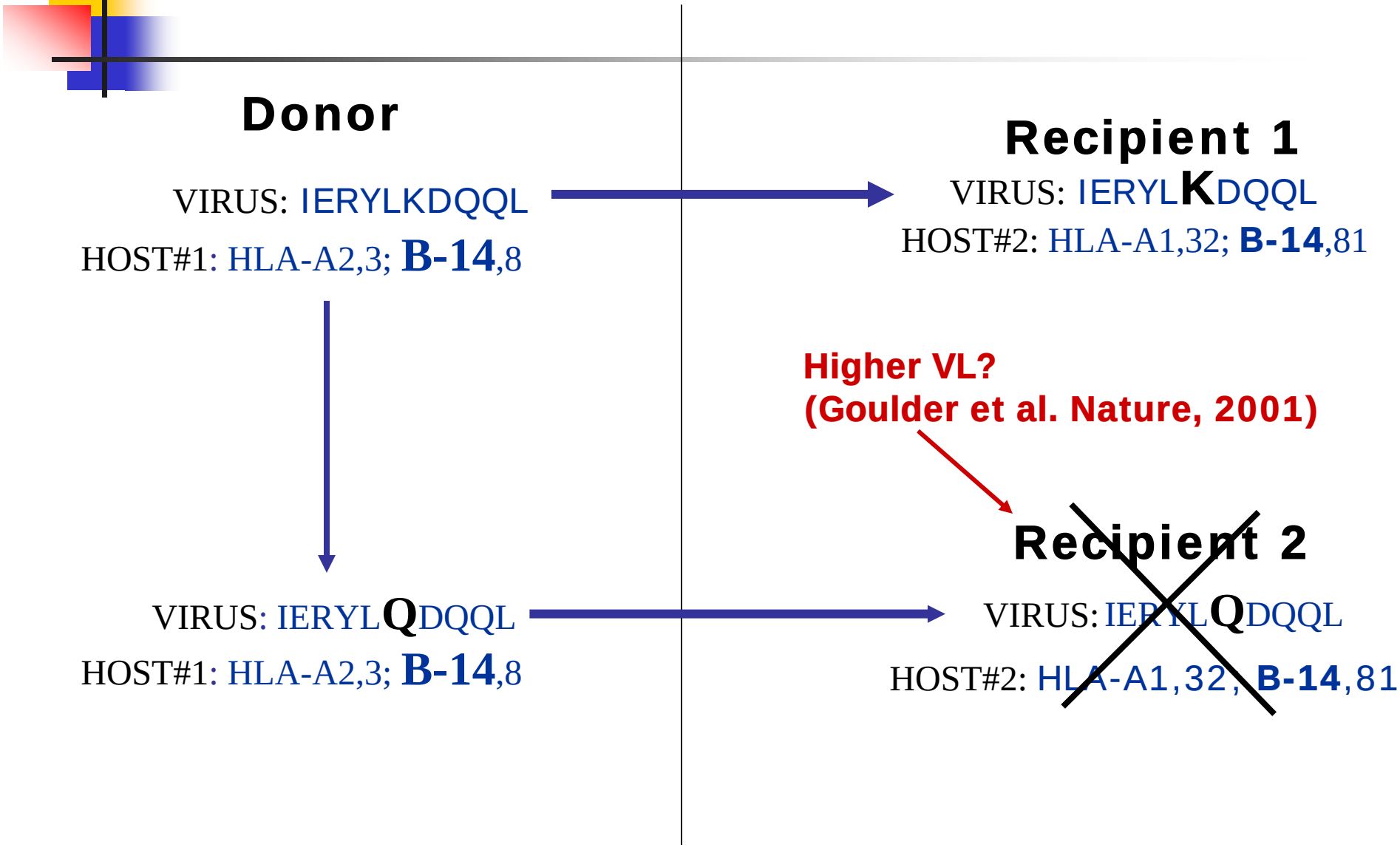
Nef CTL escape mutations have no effect on plasma viral load



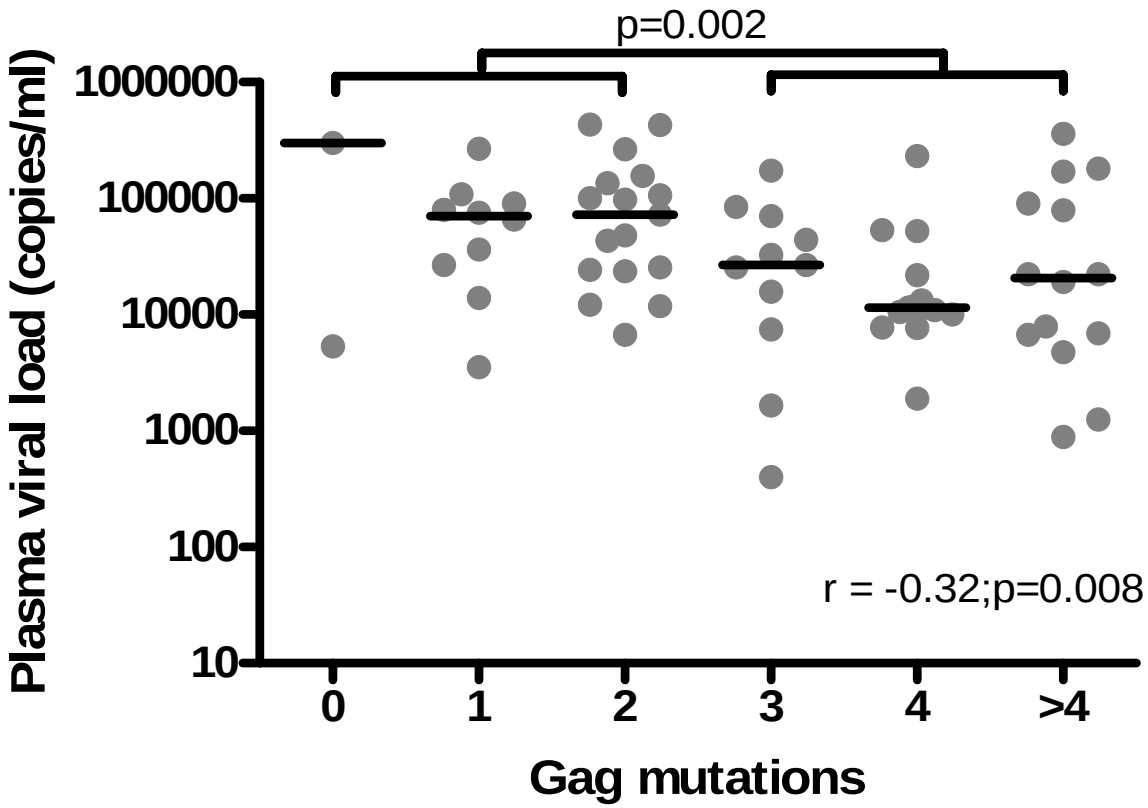
Gag CTL escape mutations induce a viral fitness cost



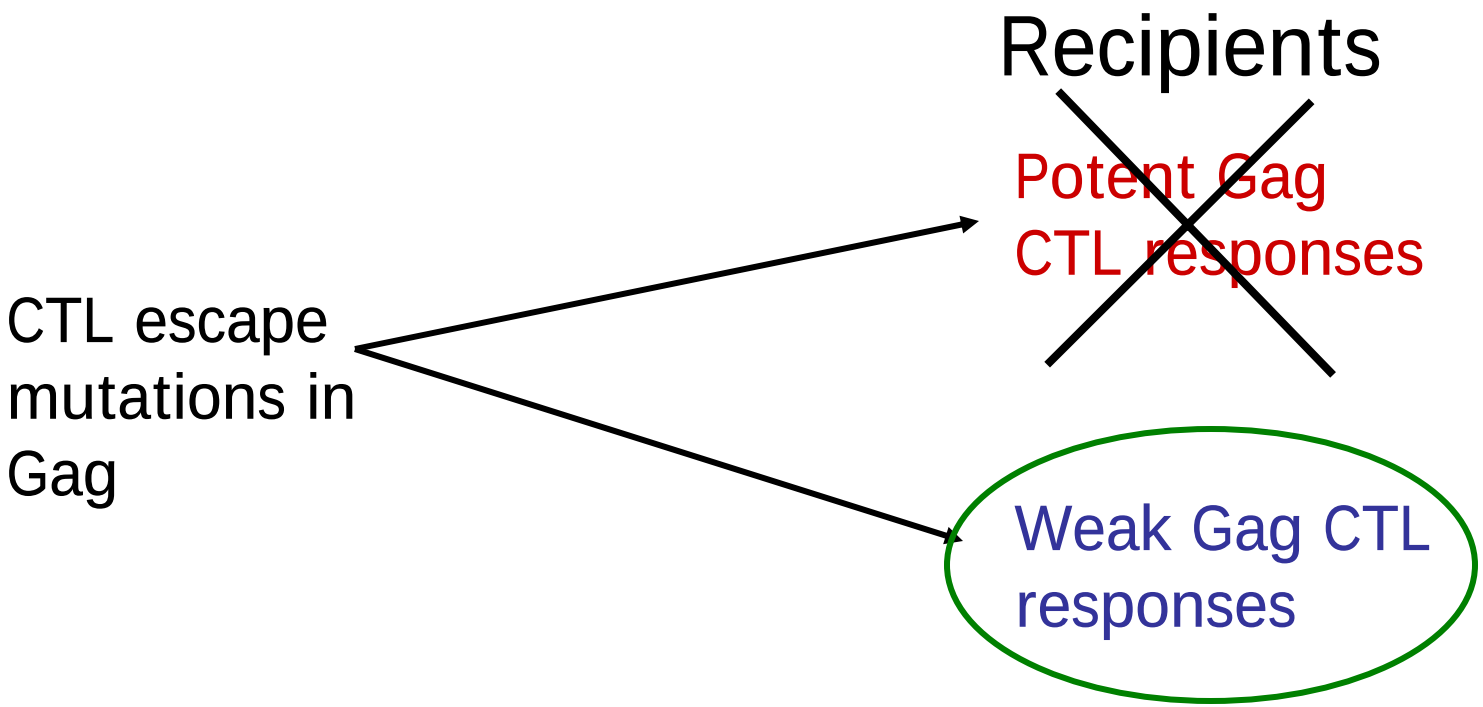
Studying CTL Escape in Linked Transmission Pairs



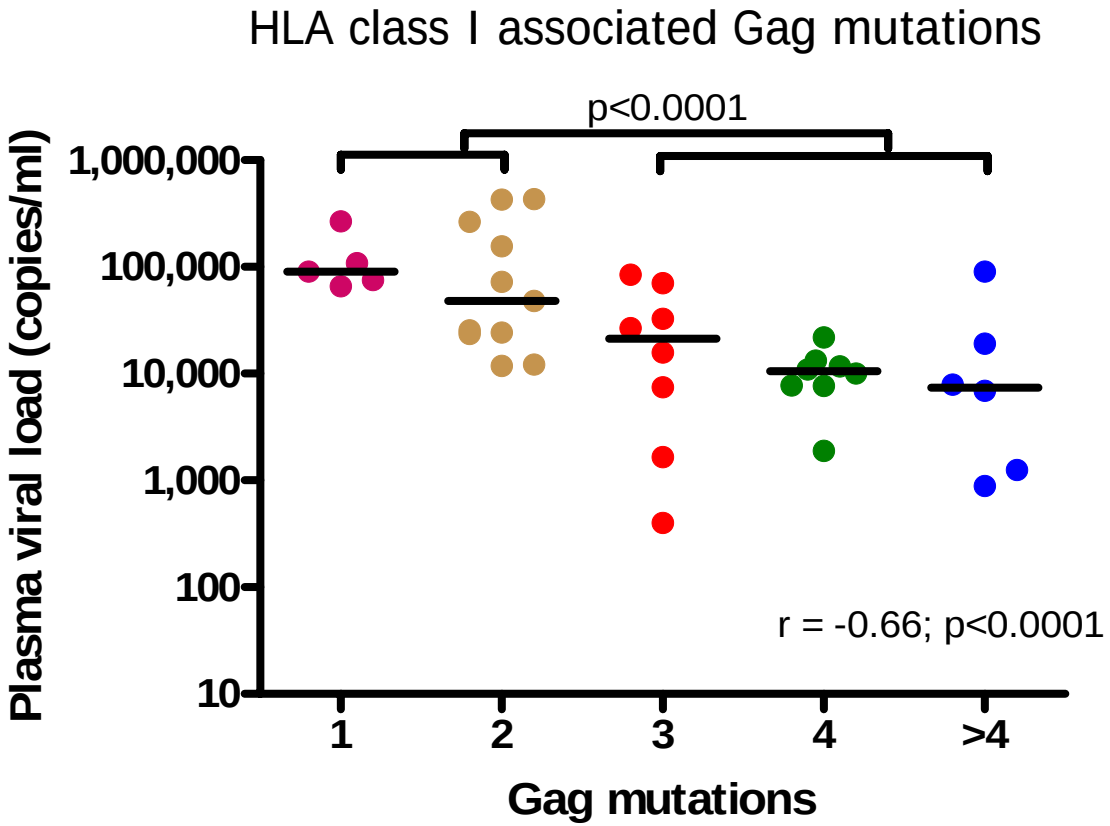
Exclusion of matched HLA recipients infected with CTL escape mutations in Gag



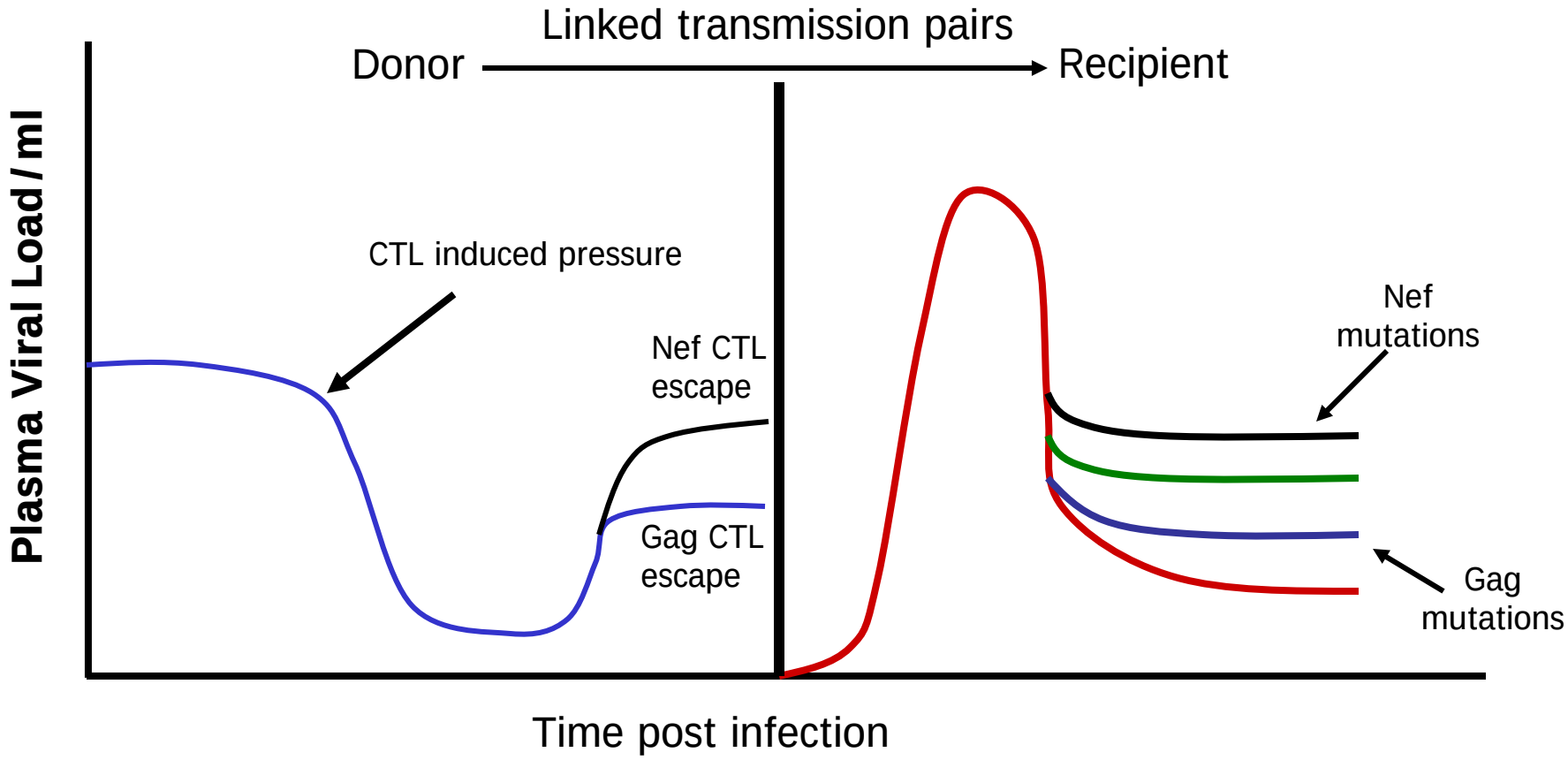
Which recipients benefit the most?



Recipients without effective Gag CD8 T cells



Determination of *in vivo* viral fitness: Proposed model



Conclusions

- CTL escape mutations in Gag are associated with *in vivo* fitness costs
- Nef CTL escapes are not associated with obvious viral load differences even those induced by favorable alleles
- Recipients who most benefit are those not able to target Gag efficiently themselves
- Gag based CTL vaccine may benefit both the vaccinee and potential recipients

Acknowledgements

T cell Laboratory

Anju Bansal
Sonya Heath
Steffanie Sabbaj
Simi Akinsiku
Latonya Williams

UAB

Richard Kaslow
James Tang

Emory

Eric Hunter
Susan Allen
Cindy Derdeyn
Paul Farmer
Wendy Lumm

Zambia

Joseph Mulenga

Oxford

Philip Goulder
Philippa Matthews
Andrew Prendergast

LANL

Bette Korber
Karina Yusim

Microsoft

David Heckerman
Jonathan Carlson

South African and ZEHRP Patient Cohorts

All HLA-B associated HIV polymorphisms