

7 References

1. Barre-Sinoussi, F. *et al.* Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science (80-.)* **220**, 868–871 (1983).
2. Gallo, R. *et al.* Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science (80-.)* **224**, 500–503 (1984).
3. Levy, J. A. HIV pathogenesis: 25 years of progress and persistent challenges. *Aids* **23**, 147–160 (2009).
4. Rambaut, A., Posada, D., Crandall, K. A. & Holmes, E. C. The causes and consequences of HIV evolution. *Nat. Rev. Genet.* **5**, 52–61 (2004).
5. Sharp, P. M. & Hahn, B. H. Origins of HIV and the AIDS Pandemic. *Cold Spring Harb Perspect Med* **1**, (2011).
6. Gao, F. *et al.* Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature* **397**, 436–441 (1999).
7. Lemey, P. *et al.* Tracing the origin and history of the HIV-2 epidemic. *Proc. Natl. Acad. Sci.* **100**, 6588–6592 (2003).
8. Martin Stoltzfus, C. Chapter 1 Regulation of HIV-1 Alternative RNA Splicing and Its Role in Virus Replication. *Advances in Virus Research* **74**, 1–40 (2009).
9. Korber, B. *et al.* Timing the ancestor of the HIV-1 pandemic strains. *Science (80-.)* **288**, 1789–1796 (2000).
10. Lynch, R. M., Shen, T., Gnanakaran, S. & Derdeyn, C. A. Appreciating HIV type 1 diversity: subtype differences in Env. *AIDS Res. Hum. Retroviruses* **25**, 237–248 (2009).
11. Hemelaar, J., Gouws, E., Ghys, P. D. & Osmanov, S. Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004. *AIDS* **20**, W13–W23 (2006).
12. Gale, C. V., Myers, R., Tedder, R. S., Williams, I. G. & Kellam, P. Development of a novel human immunodeficiency virus type 1 subtyping tool, Subtype Analyzer (STAR): analysis of subtype distribution in London. *AIDS Res. Hum. Retroviruses* **20**, 457–64 (2004).
13. Faria, N. R. *et al.* HIV epidemiology. The early spread and epidemic ignition of HIV-1 in human populations. *Science (80-.)* **346**, 56–61 (2014).
14. Ariën, K. K., Vanham, G. & Arts, E. J. Is HIV-1 evolving to a less virulent form in humans? *Nat. Rev. Microbiol.* **5**, 141–151 (2007).
15. Foley, B. *et al.* HIV Sequence Compendium 2010 Editors. *Analysis* (2010).
16. Maddon, P. J. *et al.* The T4 gene encodes the AIDS virus receptor and is expressed in the immune system and the brain. *Cell* **47**, 333–348 (1986).
17. McDougal, J. S., Kennedy, J. M., Sligh, S. P., Cort, A. & Mawle, J. K. A. Binding of HTLV-III/LAV to T4 T Cells by a Complex of the 110K Viral Protein and the T4 Molecule. *Science (80-.)* **231**, 382–385 (1986).
18. Choe, H. *et al.* The B-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* **85**, 1135–1148 (1996).
19. Deng, H. *et al.* Identification of a major co-receptor for primary isolates of HIV-1. *Nature* **381**, 661–666 (1996).
20. Dragic, T. *et al.* HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* **381**, 667–673 (1996).
21. Feng, Y., Broder, C. C., Kennedy, P. E. & Berger, E. A. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* **272**, 872–877 (1996).
22. Grivel, J. C. & Margolis, L. B. CCR5- and CXCR4-tropic HIV-1 are equally cytopathic for their T-cell targets in human lymphoid tissue. *Nat. Med.* **5**, 344–346 (1999).
23. Douek, D. C., Picker, L. J. & Koup, R. A. T Cell Dynamics in HIV-1 Infection. *Annu. Rev. Immunol.* **21**, 265–304 (2003).
24. Esté, J. a *et al.* Shift of clinical human immunodeficiency virus type 1 isolates from X4 to R5 and prevention of emergence of the syncytium-inducing phenotype by blockade of CXCR4. *J. Virol.* **73**, 5577–85 (1999).
25. Caputi, M. *RNA Processing*. (InTech, 2011). doi:10.5772/832
26. Keele, B. F. *et al.* Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 7552–7 (2008).
27. Abrahams, M.-R. *et al.* Quantitating the multiplicity of infection with human

- immunodeficiency virus type 1 subtype C reveals a non-poisson distribution of transmitted variants. *J. Virol.* **83**, 3556–67 (2009).
28. McMichael, A. J., Borrow, P., Tomaras, G. D., Goonetilleke, N. & Haynes, B. F. The immune response during acute HIV-1 infection: clues for vaccine development. *Nat Rev Immunol* **10**, 11–23 (2010).
 29. Wiley, C. A., Schrier, R. D., Nelson, J. A., Lampert, P. W. & Oldstone, M. B. Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. *Proc. Natl. Acad. Sci. U. S. A.* **83**, 7089–93 (1986).
 30. Wu, L. & Kewal Ramani, V. N. Dendritic-cell interactions with HIV: infection and viral dissemination. *Nat. Rev. Immunol.* **6**, 859–68 (2006).
 31. Luciw, P. A., Pratt-Lowe, E., Shaw, K. E., Levy, J. A. & Cheng-Mayer, C. Persistent infection of rhesus macaques with T-cell-line-tropic and macrophage-tropic clones of simian/human immunodeficiency viruses (SHIV). *Proc. Natl. Acad. Sci. U. S. A.* **92**, 7490–4 (1995).
 32. Pope, M. *et al.* Conjugates of dendritic cells and memory T lymphocytes from skin facilitate productive infection with HIV-1. *Cell* **78**, 389–398 (1994).
 33. Brenchley, J. M. *et al.* CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J. Exp. Med.* **200**, 749–59 (2004).
 34. Veazey, R. S. *et al.* Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. *Science (80-)* **280**, 427–431 (1998).
 35. Wang, L. *et al.* A novel mechanism of CD4 lymphocyte depletion involves effects of HIV on resting lymphocytes: induction of lymph node homing and apoptosis upon secondary signaling through homing receptors. *J. Immunol.* **162**, 268–76 (1999).
 36. Mattapallil, J. J. *et al.* Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. *Nature* **434**, 1093–1097 (2005).
 37. Engelman, A. & Cherepanov, P. The structural biology of HIV-1: mechanistic and therapeutic insights. *Nat. Rev. Microbiol.* **10**, 279–90 (2012).
 38. Permanyer, M., Ballana, E. & Este, J. A. Endocytosis of HIV: Anything goes. *Trends Microbiol.* **18**, 543–551 (2010).
 39. Chan, D. C. & Kim, P. S. HIV entry and its inhibition. *Cell* **93**, 681–684 (1998).
 40. Gomez, C. & Hope, T. J. The ins and outs of HIV replication. *Cell. Microbiol.* **7**, 621–626 (2005).
 41. Gallay, P., Hope, T., Chin, D. & Trono, D. HIV-1 infection of nondividing cells through the recognition of integrase by the importin/karyopherin pathway. *Proc. Natl. Acad. Sci. U. S. A.* **94**, 9825–30 (1997).
 42. Bukrinsky, M. I. *et al.* A nuclear localization signal within HIV-1 matrix protein that governs infection of non-dividing cells. *Nature* **365**, 666–669 (1993).
 43. Haffar, O. K. *et al.* Two nuclear localization signals in the HIV-1 matrix protein regulate nuclear import of the HIV-1 pre-integration complex. *J. Mol. Biol.* **299**, 359–68 (2000).
 44. Jordan, A., Defechereux, P. & Verdin, E. The site of HIV-1 integration in the human genome determines basal transcriptional activity and response to Tat transactivation. *EMBO J.* **20**, 1726–1738 (2001).
 45. Schröder, a. R. W. *et al.* HIV-1 integration in the human genome favors active genes and local hotspots. *Cell* **110**, 521–529 (2002).
 46. Preston, B. D., Poiesz, B. J. & Loeb, L. A. Fidelity of HIV-1 reverse transcriptase. *Science (80-)* **242**, 1168–1171 (1988).
 47. Roberts, J. D., Bebenek, K. & Kunkel, T. a. The accuracy of reverse transcriptase from HIV-1. *Science* **242**, 1171–1173 (1988).
 48. Pollard, V. W. & Malim, M. H. The HIV-1 Rev Protein: Overview of the Retroviral Life Cycle. *Ann* **52**, 491–532 (1998).
 49. Sodroski, J. *et al.* A second post-transcriptional trans-activator gene required for HTLV-III replication. *Nature* **321**, 412–417 (1986).
 50. Malim, M. H. *et al.* HIV-1 structural gene expression requires binding of the rev trans-activator to its RNA target sequence. *Cell* **60**, 675–683 (1990).
 51. Kirchhoff, F. Is the high virulence of HIV-1 an unfortunate coincidence of primate lentiviral evolution? *Nat. Rev. Microbiol.* **7**, 467–476 (2009).
 52. Landi, A., Iannucci, V., Van Nuffel, A., Meuwissen, P. & Verhasselt, B. One Protein to Rule them All: Modulation of Cell Surface Receptors and Molecules by HIV Nef. *Curr. HIV Res.* **9**,

- 496–504 (2011).
53. Heaphy, S. *et al.* HIV-1 regulator of virion expression (Rev) protein binds to an RNA stem-loop structure located within the Rev response element region. *Cell* **60**, 685–693 (1990).
 54. Fischer, U., Huber, J., Boelens, W. C., Mattajt, L. W. & Luhrmann, R. The HIV-1 Rev Activation Domain is a nuclear export signal that accesses an export pathway used by specific cellular RNAs. *Cell* **82**, 475–483 (1995).
 55. Emerman, M. HIV-1 Regulatory/Accessory Genes: Keys to Unraveling Viral and Host Cell Biology. *Science* (80-.). **280**, 1880–1884 (1998).
 56. Peterlin, B. M. & Trono, D. Hide, shield and strike back: how HIV-infected cells avoid immune eradication. *Nat. Rev. Immunol.* **3**, 97–107 (2003).
 57. Schwartz, O., Maréchal, V., Le Gall, S., Lemonnier, F. & Heard, J. M. Endocytosis of major histocompatibility complex class I molecules is induced by the HIV-1 Nef protein. *Nat. Med.* **2**, 338–42 (1996).
 58. Bubeník, J. MHC class I down-regulation: tumour escape from immune surveillance? *Int. J. Oncol.* **25**, 487–91 (2004).
 59. Choremia-Papadopoulou, H. *et al.* Downregulation of CD28 surface antigen on CD4+ and CD8+ T lymphocytes during HIV-1 infection. *J Acquir Immune Defic Syndr* **7**, 245–253 (1994).
 60. Münch, J. *et al.* T-cell receptor:CD3 down-regulation is a selected in vivo function of simian immunodeficiency virus Nef but is not sufficient for effective viral replication in rhesus macaques. *J. Virol.* **76**, 12360–4 (2002).
 61. Mariani, R. *et al.* High frequency of defective nef alleles in a long-term survivor with nonprogressive human immunodeficiency virus type 1 infection. *J. Virol.* **70**, 7752–64 (1996).
 62. Chowers, M. Y. *et al.* Optimal infectivity in vitro of human immunodeficiency virus type 1 requires an intact nef gene. *J. Virol.* **68**, 2906–14 (1994).
 63. Daniel, M. D., Kirchhoff, F., Czajak, S. C., Sehgal, P. K. & Desrosiers, R. C. Protective effects of a live attenuated SIV vaccine with a deletion in the nef gene. *Science* **258**, 1938–1941 (1992).
 64. Kirchhoff, F., Greenough, T. C., Brettler, D. B., Sullivan, J. L. & Desrosiers, R. C. Absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection. *N. Engl. J. Med.* **332**, 228–232 (1995).
 65. Malim, M. H. & Bieniasz, P. D. HIV Restriction Factors and Mechanisms of Evasion. *Cold Spring Harb. Perspect. Med.* **2**, a006940 (2012).
 66. Doyle, T., Goujon, C. & Malim, M. H. HIV-1 and interferons: who's interfering with whom? *Nat. Rev. Microbiol.* **13**, 403–413 (2015).
 67. Freed, E. O. HIV-1 assembly, release and maturation. *Nat. Rev. Microbiol.* **13**, 484–496 (2015).
 68. Checkley, M. A., Luttge, B. G. & Freed, E. O. HIV-1 envelope glycoprotein biosynthesis, trafficking, and incorporation. *J. Mol. Biol.* **410**, 582–608 (2011).
 69. Brady, T. *et al.* HIV integration site distributions in resting and activated CD4+ T cells infected in culture. *AIDS* **23**, 1461–1471 (2010).
 70. Coiras, M., Lopez-Huertas, M. R., Perez-Olmeda, M. & Alcami, J. Understanding HIV-1 latency provides clues for the eradication of long-term reservoirs. *Nat Rev Microbiol* **7**, 798–812 (2009).
 71. Pomerantz, R. J. & Horn, D. L. Twenty years of therapy for HIV-1 infection. *Nat. Med.* **9**, 867–873 (2003).
 72. Chun, T. W. *et al.* Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature* **387**, 183–188 (1997).
 73. Bullen, C. K., Laird, G. M., Durand, C. M., Siliciano, J. D. & Siliciano, R. F. New ex vivo approaches distinguish effective and ineffective single agents for reversing HIV-1 latency in vivo. *Nat. Med.* **20**, 425–9 (2014).
 74. Chun, T. W. *et al.* Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proc. Natl. Acad. Sci. U. S. A.* **94**, 13193–7 (1997).
 75. Finzi, D. *et al.* Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat. Med.* **5**, 512–517 (1999).
 76. Siliciano, J. M. & Siliciano, R. F. The remarkable stability of the latent reservoir for HIV-1 in resting memory CD4+ T cells. *J. Infect. Dis.* **212**, 1345–1347 (2015).

77. Chomont, N. *et al.* HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. *Nat. Med.* **15**, 893–900 (2009).
78. Lorenzo-Redondo, R. *et al.* Persistent HIV-1 replication maintains the tissue reservoir during therapy. *Nature* **530**, 51–56 (2016).
79. Persaud, D. *et al.* Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J. Virol.* **78**, 968–79 (2004).
80. Ruff, C. T. *et al.* Persistence of wild-type virus and lack of temporal structure in the latent reservoir for human immunodeficiency virus type 1 in pediatric patients with extensive antiretroviral exposure. *J. Virol.* **76**, 9481–92 (2002).
81. Cohen, M. S. Preventing sexual transmission of HIV. *Clin. Infect. Dis.* **45 Suppl 4**, S287–92 (2007).
82. Quinn, T. C. *et al.* Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N. Engl. J. Med.* **342**, 921–9 (2000).
83. Ward, H. & Rönn, M. The contribution of STIs to the sexual transmission of HIV. *Curr. Opin. HIV AIDS* **5**, 305–310 (2010).
84. Auvert, B. *et al.* Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Med.* **2**, 1112–1122 (2005).
85. Curran, J. W. *et al.* Epidemiology of HIV infection and AIDS in the United States. *Science (80-.).* **239**, 610–616 (1988).
86. Cooper, E. R. *et al.* Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J. Acquir. Immune Defic. Syndr.* **29**, 484–94 (2002).
87. Semba, R. D. *et al.* Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* **343**, 1593–7 (1994).
88. Coovadia, H. M. *et al.* Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* **369**, 1107–1116 (2007).
89. Fox, J. & Fidler, S. Sexual transmission of HIV-1. *Antiviral Research* **85**, 276–285 (2010).
90. Mastro, T. D. & de Vincenzi, I. Probabilities of sexual HIV-1 transmission. *Aids* **10**, 75–82 (1996).
91. Fiebig, E. W. *et al.* Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS* **17**, 1871–1879 (2003).
92. Busch, M. P. & Satten, G. A. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. in *American Journal of Medicine* **102**, 117–124 (1997).
93. Pasternak, A. O., Lukashov, V. V & Berkhout, B. Cell-associated HIV RNA: a dynamic biomarker of viral persistence. *Retrovirology* **10**, 41 (2013).
94. Veazey, R. S. *et al.* Identifying the target cell in primary simian immunodeficiency virus (SIV) infection: highly activated memory CD4(+) T cells are rapidly eliminated in early SIV infection in vivo. *J. Virol.* **74**, 57–64 (2000).
95. Veazey, R. S. *et al.* Dynamics of CCR5 expression by CD4(+) T cells in lymphoid tissues during simian immunodeficiency virus infection. *J. Virol.* **74**, 11001–7 (2000).
96. Grossman, Z., Meier-Schellersheim, M., Paul, W. E. & Picker, L. J. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. *Nat. Med.* **12**, 289–295 (2006).
97. Deeks, S. G., Tracy, R. & Douek, D. C. Systemic Effects of Inflammation on Health during Chronic HIV Infection. *Immunity* **39**, 633–45 (2013).
98. Liao, H.-X. *et al.* Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Nature* **496**, 469–76 (2013).
99. Wu, X. *et al.* Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. *Science* **333**, 1593–602 (2011).
100. Lempicki, R. a *et al.* Impact of HIV-1 infection and highly active antiretroviral therapy on the kinetics of CD4+ and CD8+ T cell turnover in HIV-infected patients. *Proc. Natl. Acad. Sci. U. S. A.* **97**, 13778–13783 (2000).
101. Douek, D. C. Immune activation, HIV persistence, and the cure. *Top. Antivir. Med.* **21**, 128–32 (2013).

102. Lifson, A. R. *et al.* Long-term human immunodeficiency virus infection in asymptomatic homosexual and bisexual men with normal CD4+ lymphocyte counts: immunologic and virologic characteristics. *J. Infect. Dis.* **163**, 959–65 (1991).
103. Deeks, S. G. & Walker, B. D. Human Immunodeficiency Virus Controllers: Mechanisms of Durable Virus Control in the Absence of Antiretroviral Therapy. *Immunity* **27**, 406–416 (2007).
104. Pereyra, F. *et al.* Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. *J. Infect. Dis.* **197**, 563–571 (2008).
105. Migueles, S. A. *et al.* HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc. Natl. Acad. Sci. U. S. A.* **97**, 2709–14 (2000).
106. Walker, B. D. & Yu, X. G. Unravelling the mechanisms of durable control of HIV-1. *Nat. Rev. Immunol.* **13**, 487–498 (2013).
107. Okoye, A. A. & Picker, L. J. CD4(+) T-cell depletion in HIV infection: mechanisms of immunological failure. *Immunol. Rev.* **254**, 54–64 (2013).
108. Sheppard, H. W. & Ascher, M. S. The Natural History and Pathogenesis of HIV Infection. *Annu. Rev. Microbiol.* **46**, 533–64 (1992).
109. Biancotto, A. *et al.* Abnormal activation and cytokine spectra in lymph nodes of persons chronically infected with HIV-1. *J. Clin. Invest.* **109**, 1–31 (2007).
110. Schacker, T. W. *et al.* Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis Rapid Publication. *J. Clin. Invest.* **110**, 1133–1139
111. Zeng, M. *et al.* Cumulative mechanisms of lymphoid tissue fibrosis and T cell depletion in HIV-1 and SIV infections. *J. Clin. Invest.* **121**, 998–1008 (2011).
112. Colineau, L. *et al.* HIV-Infected Spleens Present Altered Follicular Helper T Cell (Tfh) Subsets and Skewed B Cell Maturation. *PLoS One* **10**, e0140978 (2015).
113. Perelson, A. S., Neumann, A. U., Markowitz, M., Leonard, J. M. & Ho, D. D. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* **271**, 1582–1586 (1996).
114. Araújo, L. A. L. & Almeida, S. E. M. HIV-1 diversity in the envelope glycoproteins: Implications for viral entry inhibition. *Viruses* **5**, 595–604 (2013).
115. Williamson, S. Adaptation in the env gene of HIV-1 and evolutionary theories of disease progression. *Mol. Biol. Evol.* **20**, 1318–25 (2003).
116. Zhuang, J. *et al.* Human immunodeficiency virus type 1 recombination: rate, fidelity, and putative hot spots. *J. Virol.* **76**, 11273–82 (2002).
117. Brenchley, J. M., Price, D. A. & Douek, D. C. HIV disease: fallout from a mucosal catastrophe? *Nat Immunol* **7**, 235–239 (2006).
118. Gonzalez, V. D., Landay, A. L. & Sandberg, J. K. Innate immunity and chronic immune activation in HCV/HIV-1 co-infection. *Clinical Immunology* **135**, 12–25 (2010).
119. Sandler, N. G. *et al.* Type I interferon responses in rhesus macaques prevent SIV infection and slow disease progression. *Nature* **511**, 601–605 (2014).
120. Mandl, J. N. *et al.* Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. *Nat Med* **14**, 1077–1087 (2008).
121. Sandler, N. G. *et al.* Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J. Infect. Dis.* **203**, 780–790 (2011).
122. Vargas-Inchaustegui, D. a, Xiao, P., Tuero, I., Patterson, L. J. & Robert-Guroff, M. NK and CD4+ T cell cooperative immune responses correlate with control of disease in a macaque simian immunodeficiency virus infection model. *J. Immunol.* **189**, 1878–85 (2012).
123. Gonzalez, V. D., Landay, A. L. & Sandberg, J. K. Innate immunity and chronic immune activation in HCV/HIV-1 co-infection. *Clin. Immunol.* **135**, 12–25 (2010).
124. Reeves, R. K. *et al.* Antigen-specific NK cell memory in rhesus macaques. *Nat. Immunol.* **16**, 927–932 (2015).
125. Sheehy, A. M., Gaddis, N. C., Choi, J. D. & Malim, M. H. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* **418**, 646–650 (2002).
126. Donahue, J. P., Vetter, M. L., Mukhtar, N. A. & D'Aquila, R. T. The HIV-1 Vif PPLP motif is necessary for human APOBEC3G binding and degradation. *Virology* **377**, 49–53 (2008).

127. Neil, S. J. D., Zang, T. & Bieniasz, P. D. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* **451**, 425–430 (2008).
128. Stremlau, M. *et al.* The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* **427**, 848–853 (2004).
129. Yap, M. W., Nisole, S., Lynch, C. & Stoye, J. P. Trim5alpha protein restricts both HIV-1 and murine leukemia virus. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 10786–91 (2004).
130. Tomaras, G. D. *et al.* Initial B-cell responses to transmitted human immunodeficiency virus type 1: virion-binding immunoglobulin M (IgM) and IgG antibodies followed by plasma anti-gp41 antibodies with ineffective control of initial viremia. *J. Virol.* **82**, 12449–12463 (2008).
131. Gray, E. S. *et al.* Neutralizing antibody responses in acute human immunodeficiency virus type 1 subtype C infection. *J. Virol.* **81**, 6187–6196 (2007).
132. Stamatatos, L., Morris, L., Burton, D. R. & Mascola, J. R. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat. Med.* **15**, 866–870 (2009).
133. Richman, D. D., Wrin, T., Little, S. J. & Petropoulos, C. J. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 4144–9 (2003).
134. Crotty, S. T Follicular Helper Cell Differentiation, Function, and Roles in Disease. *Immunity* **41**, 529–542 (2014).
135. Ma, C. S., Deenick, E. K., Batten, M. & Tangye, S. G. The origins, function, and regulation of T follicular helper cells. *J. Exp. Med.* **209**, 1241–1253 (2012).
136. Miller, J. F. A. P., De Burgh, P. M. & Grant, G. A. Thymus and the Production of Antibody-plaque-forming Cells. *Nature* **208**, 1332–1334 (1965).
137. Breitfeld, D. *et al.* Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J. Exp. Med.* **192**, 1545–52 (2000).
138. Schaerli, P. *et al.* CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. *J. Exp. Med.* **192**, 1553–62 (2000).
139. Dobner, T., Wolf, I., Emrich, T. & Lipp, M. Differentiation specific expression of a novel G protein coupled receptor from Burkitt's lymphoma. *Eur. J. Immunol.* **22**, 2795–2799 (1992).
140. Legler, D. F. *et al.* B cell-attracting chemokine 1, a human CXC chemokine expressed in lymphoid tissues, selectively attracts B lymphocytes via BLR1/CXCR5. *J. Exp. Med.* **187**, 655–60 (1998).
141. Rock, K. L. & Shen, L. Cross-presentation: underlying mechanisms and role in immune surveillance. *Immunol Rev* **207**, 166–183 (2005).
142. Hardtke, S., Ohl, L. & Förster, R. Balanced expression of CXCR5 and CCR7 on follicular T helper cells determines their transient positioning to lymph node follicles and is essential for efficient B-cell help. *Blood* **106**, 1924–1931 (2005).
143. Linterman, M. A. *et al.* IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. *J. Exp. Med.* **207**, 353–63 (2010).
144. Zotos, D. *et al.* IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism. *J. Exp. Med.* **207**, 365–378 (2010).
145. Lu, K. T. *et al.* Functional and Epigenetic Studies Reveal Multistep Differentiation and Plasticity of In Vitro-Generated and In Vivo-Derived Follicular T Helper Cells. *Immunity* **35**, 622–632 (2011).
146. Li, H. & Pauza, C. D. CD25⁺ Bcl6^{low} T follicular helper cells provide help to maturing B cells in germinal centers of human tonsil: Molecular immunology. *Eur. J. Immunol.* **45**, 298–308 (2015).
147. Rasheed, A. U., Rahn, H. P., Sallusto, F., Lipp, M. & Muller, G. Follicular B helper T cell activity is confined to CXCR5hiICOShi CD4 T cells and is independent of CD57 expression. *Eur. J. Immunol.* **36**, 1892–1903 (2006).
148. Chtanova, T. *et al.* T Follicular Helper Cells Express a Distinctive Transcriptional Profile, Reflecting Their Role as Non-Th1/Th2 Effector Cells That Provide Help for B Cells. *J. Immunol.* **173**, 68–78 (2004).
149. Onabajo, O. O., George, J., Lewis, M. G. & Mattapallil, J. J. Rhesus Macaque Lymph Node PD-1hiCD4+ T Cells Express High Levels of CXCR5 and IL-21 and Display a CCR7loICOS+Bcl6+ T-Follicular Helper (Tfh) Cell Phenotype. *PLoS One* **8**, 2–9 (2013).
150. Bryant, V. L. *et al.* Cytokine-mediated regulation of human B cell differentiation into Ig-secreting cells: predominant role of IL-21 produced by CXCR5+ T follicular helper cells. *J.*

- Immunol.* **179**, 8180–8190 (2007).
151. Chtanova, T. *et al.* T Follicular Helper Cells Express a Distinctive Transcriptional Profile, Reflecting Their Role as Non-Th1/Th2 Effector Cells That Provide Help for B Cells. *J. Immunol.* **173**, 68–78 (2004).
 152. Johnston, R. J. *et al.* Bcl6 and Blimp-1 Are Reciprocal and Antagonistic Regulators of T Follicular Helper Cell Differentiation. *Cell Differ.* **325**, 1006–1010 (2010).
 153. Kitano, M. *et al.* Bcl6 Protein Expression Shapes Pre-Germinal Center B Cell Dynamics and Follicular Helper T Cell Heterogeneity. *Immunity* **34**, 961–972 (2011).
 154. Bauquet, A. T. *et al.* The costimulatory molecule ICOS regulates the expression of c-Maf and IL-21 in the development of follicular T helper cells and TH-17 cells. *Nat. Immunol.* **10**, 167–175 (2009).
 155. Johnston, R. J., Choi, Y. S., Diamond, J. a., Yang, J. a. & Crotty, S. STAT5 is a potent negative regulator of TFH cell differentiation. *J. Exp. Med.* **209**, 243–250 (2012).
 156. Ballesteros-Tato, A. *et al.* Interleukin-2 Inhibits Germinal Center Formation by Limiting T Follicular Helper Cell Differentiation. *Immunity* **36**, 847–856 (2012).
 157. Tubo, N. J. *et al.* Single naive CD4+ T cells from a diverse repertoire produce different effector cell types during infection. *Cell* **153**, 785–796 (2013).
 158. Choi, Y. S. *et al.* ICOS Receptor Instructs T Follicular Helper Cell versus Effector Cell Differentiation via Induction of the Transcriptional Repressor Bcl6. *Immunity* **34**, 932–946 (2011).
 159. Kerfoot, S. M. *et al.* Germinal Center B Cell and T Follicular Helper Cell Development Initiates in the Interfollicular Zone. *Immunity* **34**, 947–960 (2011).
 160. Yusuf, I. *et al.* Germinal center T follicular helper cell IL-4 production is dependent on signaling lymphocytic activation molecule receptor (CD150). *J. Immunol.* **185**, 190–202 (2010).
 161. Linterman, M. A. *et al.* Follicular helper T cells are required for systemic autoimmunity. *J. Exp. Med.* **206**, 561–76 (2009).
 162. Linterman, M. A. *et al.* Foxp3+ follicular regulatory T cells control the germinal center response. *Nat. Med.* **17**, 975–82 (2011).
 163. Chung, Y. *et al.* Follicular regulatory T (Tfr) cells with dual Foxp3 and Bcl6 expression suppress germinal center reactions. *Nat. Med.* **17**, 983–988 (2011).
 164. Sage, P. T., Francisco, L. M., Carman, C. V & Sharpe, A. H. The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. *Nat. Immunol.* **14**, 152–61 (2013).
 165. Ding, Y. *et al.* Interleukin-21 promotes germinal center reaction by skewing the follicular regulatory T cell to follicular helper T cell balance in autoimmune BXD2 mice. *Arthritis Rheumatol.* **66**, 2601–2612 (2014).
 166. Wang, C. J. *et al.* CTLA-4 controls follicular helper T-cell differentiation by regulating the strength of CD28 engagement. *Proc Natl Acad Sci U S A* **112**, 524–529 (2015).
 167. Sage, P. T. & Sharpe, A. H. T follicular regulatory cells. *Immunol. Rev.* **271**, 246–259 (2016).
 168. Nutt, S. L. & Tarlinton, D. M. Germinal center B and follicular helper T cells: siblings, cousins or just good friends? *Nat. Immunol.* **131**, 472–477 (2011).
 169. Lindqvist, M. *et al.* Expansion of HIV-specific T follicular helper cells in chronic HIV infection. *J. Clin. Invest.* **122**, (2012).
 170. Petrovas, C. *et al.* CD4 T follicular helper cell dynamics during SIV infection. *J. Clin. Invest.* **122**, 3281–94 (2012).
 171. Hong, J. J., Amancha, P. K., Rogers, K., Ansari, A. A. & Villinger, F. Spatial Alterations between CD4+ T Follicular Helper, B, and CD8+ T Cells during Simian Immunodeficiency Virus Infection: T/B Cell Homeostasis, Activation, and Potential Mechanism for Viral Escape. *J. Immunol.* **188**, 3247–3256 (2012).
 172. Perreau, M. *et al.* Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. *J. Exp. Med.* **210**, 143–56 (2013).
 173. Cubas, R. a *et al.* Inadequate T follicular cell help impairs B cell immunity during HIV infection. *Nat. Med.* **19**, 494–9 (2013).
 174. Fukazawa, Y. *et al.* B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers. *Nat. Med.* **21**, 132–139 (2015).
 175. Simpson, N. *et al.* Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis*

- Rheum.* **62**, 234–44 (2010).
176. Forcade, E. *et al.* Circulating T follicular helper cells with increased function during chronic graft-versus-host-disease. *Blood* (2016). doi:10.1182/blood-2015-12-688895
 177. Boswell, K. L. *et al.* Loss of Circulating CD4 T Cells with B Cell Helper Function during Chronic HIV Infection. *PLoS Pathog.* **10**, e1003853 (2014).
 178. Morita, R. *et al.* Human Blood CXCR5+CD4+ T Cells Are Counterparts of T Follicular Cells and Contain Specific Subsets that Differentially Support Antibody Secretion. *Immunity* **34**, 108–121 (2011).
 179. Bentebibel, S. *et al.* Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. *Sci. Transl. Med.* **5**, 176ra32 (2013).
 180. Locci, M. *et al.* Human Circulating PD-1+CXCR3–CXCR5+ Memory Tfh Cells Are Highly Functional and Correlate with Broadly Neutralizing HIV Antibody Responses. *Immunity* **39**, 758–769 (2013).
 181. Schultz, B. T. *et al.* Circulating HIV-Specific Interleukin-21+CD4+ T Cells Represent Peripheral Tfh Cells with Antigen-Dependent Helper Functions. *Immunity* **44**, 167–178 (2016).
 182. Pallikkuth, S. *et al.* Peripheral T Follicular Helper Cells Are the Major HIV Reservoir Within Central Memory CD4 T Cells in Peripheral Blood from chronic HIV infected individuals on cART. *J. Virol.* **90**, JVI.02883-15 (2015).
 183. Cubas, R. *et al.* Reversible Reprogramming of Circulating Memory T Follicular Helper Cell Function during Chronic HIV Infection. *J. Immunol.* (2015). doi:10.4049/jimmunol.1501524
 184. Allen, C. D. C., Okada, T., Tang, H. L. & Cyster, J. G. Imaging of germinal center selection events during affinity maturation. *Science* **315**, 528–531 (2007).
 185. Victora, G. D. *et al.* Germinal center dynamics revealed by multiphoton microscopy with a photoactivatable fluorescent reporter. *Cell* **143**, 592–605 (2010).
 186. Gitlin, A. D., Shulman, Z. & Nussenzweig, M. C. Clonal selection in the germinal centre by regulated proliferation and hypermutation. *Nature* **509**, 637–40 (2014).
 187. Shulman, Z. *et al.* Dynamic signaling by T follicular helper cells during germinal center B cell selection. *Science* **345**, 1058–1062 (2014).
 188. Cyster, J. G. B cell follicles and antigen encounters of the third kind. *Nat. Immunol.* **11**, 989–996 (2010).
 189. El Shikh, M. E. M. & Pitzalis, C. Follicular dendritic cells in health and disease. *Frontiers in Immunology* **3**, (2012).
 190. Tarlinton, D. M. & Smith, K. G. C. Dissecting affinity maturation: A model explaining selection of antibody-forming cells and memory B cells in the germinal centre. *Immunology Today* **21**, 436–441 (2000).
 191. Jackson, K. J. L., Kidd, M. J., Wang, Y. & Collins, A. M. The Shape of the Lymphocyte Receptor Repertoire: Lessons from the B Cell Receptor. *Front. Immunol.* **4**, 1–12 (2013).
 192. Sundling, C., Phad, G., Douagi, I., Navis, M. & Karlsson Hedestam, G. B. Isolation of antibody V(D)J sequences from single cell sorted rhesus macaque B cells. *J. Immunol. Methods* **386**, 85–93 (2012).
 193. Karlsson Hedestam, G. B. *et al.* The challenges of eliciting neutralizing antibodies to HIV-1 and to influenza virus. *Nat. Rev. Microbiol.* **6**, 143–155 (2008).
 194. Georgiou, G. *et al.* The promise and challenge of high-throughput sequencing of the antibody repertoire. *Nat. Biotechnol.* **32**, (2014).
 195. Lefranc, M. P. IMGT, the international ImMunoGeneTics database. *Nucleic Acids Research* **31**, 307–310 (2003).
 196. Lefranc, M. P. in *Immunoinformatics* 1–18 (2008). doi:10.1007/978-0-387-72968-8_1
 197. Brochet, X., Lefranc, M. P. & Giudicelli, V. IMGT/V-QUEST: the highly customized and integrated system for IG and TR standardized V-J and V-D-J sequence analysis. *Nucleic Acids Res.* **36**, (2008).
 198. Schatz, D. G. & Swanson, P. C. V(D)J recombination: mechanisms of initiation. *Annu. Rev. Genet.* **45**, 167–202 (2011).
 199. Benedict, C. L., Gilfillan, S., Thai, T. H. & Kearney, J. F. Terminal deoxynucleotidyl transferase and repertoire development. *Immunol Rev* **175**, 150–157 (2000).
 200. Janeway, C. A., Travers, P., Walport, M. & Shlomchik, M. in *Immunobiology* 5 892 (2001). doi:10.1111/j.1467-2494.1995.tb00120.x
 201. Gay, D., Saunders, T., Camper, S. & Weigert, M. Receptor editing: an approach by

- autoreactive B cells to escape tolerance. *J. Exp. Med.* **177**, 999–1008 (1993).
202. Tiegs, S. L., Russell, D. M. & Nemazee, D. Receptor editing in self-reactive bone marrow B cells. *J. Exp. Med.* **177**, 1009–20 (1993).
 203. Pelanda, R. & Torres, R. M. Receptor editing for better or for worse. *Curr. Opin. Immunol.* **18**, 184–190 (2006).
 204. Kouskoff, V. & Nemazee, D. Role of receptor editing and revision in shaping the B and T lymphocyte repertoire. *Life Sciences* **69**, 1105–1113 (2001).
 205. Kabat, E. A., Wu, T. Te, Foeller, C., Perry, H. M. & Gottesman, K. S. *Sequences of Proteins of Immunological Interest*. (DIANE Publishing, 1992). at <<https://books.google.com/books?hl=en&lr=&id=3jMvZYW2ZtwC&pgis=1>>
 206. Link, J., Ivanov, I., Ippolito, G. & Schroeder, H. in *The Antibodies* 43–67 (CRC Press, 2002). doi:doi:10.1201/9780203216514.ch3
 207. Corbett, S. J., Tomlinson, I. M., Sonnhammer, E. L. , Buck, D. & Winter, G. Sequence of the human immunoglobulin diversity (D) segment locus: a systematic analysis provides no evidence for the use of DIR segments, inverted D segments, ‘minor’ D segments or D-D recombination. *J. Mol. Biol.* **270**, 587–597 (1997).
 208. Tuuillon, N. & Capra, J. D. Use of D gene segments with irregular spacers in terminal deoxynucleotidyltransferase (TdT)+/+ and TdT-/- mice carrying a human Ig heavy chain transgenic minilocus. *Proc Natl Acad Sci U S A* **95**, 1703–1708 (1998).
 209. Gu, H., Kitamura, D. & Rajewsky, K. B cell development regulated by gene rearrangement: arrest of maturation by membrane-bound D mu protein and selection of DH element reading frames. *Cell* **65**, 47–54 (1991).
 210. Benichou, J. *et al.* The restricted DH gene reading frame usage in the expressed human antibody repertoire is selected based upon its amino acid content. *J. Immunol.* **190**, 5567–77 (2013).
 211. Paul, W. E. *Fundamental Immunology*. *Fundamental Immunology* (2015).
 212. Ippolito, G. C. *et al.* Forced usage of positively charged amino acids in immunoglobulin CDR-H3 impairs B cell development and antibody production. *J. Exp. Med.* **203**, 1567–78 (2006).
 213. Xu, J. L. & Davis, M. M. Diversity in the CDR3 Region of VH Is Sufficient for Most Antibody Specificities. *Immunity* **13**, 37–45 (2000).
 214. Hardy, R. R. Chapter 7: B Lymphocyte Development and Biology. *Fundam. Immunol.* 1–66 (2010).
 215. Max, E. E. Chapter 6 Immunoglobulins : Molecular Genetics Overview of Immunoglobulin V Gene Assembly. *Genetics* 1–101 (2015).
 216. McHeyzer-Williams, L. J., Milpied, P. J., Okitsu, S. L. & McHeyzer-Williams, M. G. Class-switched memory B cells remodel BCRs within secondary germinal centers. *Nat. Immunol.* **16**, 296–305 (2015).
 217. Morbach, H., Eichhorn, E. M., Liese, J. G. & Girschick, H. J. Reference values for B cell subpopulations from infancy to adulthood. *Clin. Exp. Immunol.* **162**, 271–9 (2010).
 218. Kwong, P. D. & Mascola, J. R. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **37**, 412–425 (2012).
 219. Kwong, P. D., Mascola, J. R. & Nabel, G. J. Broadly neutralizing antibodies and the search for an HIV-1 vaccine: the end of the beginning. *Nat. Rev. Immunol.* **13**, 693–701 (2013).
 220. Buchacher, a *et al.* Generation of human monoclonal antibodies against HIV-1 proteins; electrofusion and Epstein-Barr virus transformation for peripheral blood lymphocyte immortalization. *AIDS Res. Hum. Retroviruses* **10**, 359–69 (1994).
 221. Liao, H.-X. *et al.* High-throughput isolation of immunoglobulin genes from single human B cells and expression as monoclonal antibodies. *J. Virol. Methods* **158**, 171–9 (2009).
 222. Robinson, W. H. Sequencing the functional antibody repertoire--diagnostic and therapeutic discovery. *Nat. Rev. Rheumatol.* **11**, 171–82 (2015).
 223. Montefiori, D. C. Measuring HIV neutralization in a luciferase reporter gene assay. *Methods Mol. Biol.* **485**, 395–405 (2009).
 224. Montefiori, D. C. Evaluating neutralizing antibodies against HIV, SIV, and SHIV in luciferase reporter gene assays. *Curr. Protoc. Immunol.* **Chapter 12**, Unit 12.11 (2005).
 225. Seaman, M. S. *et al.* Tiered categorization of a diverse panel of HIV-1 Env pseudoviruses for assessment of neutralizing antibodies. *J Virol* **84**, 1439–1452 (2010).
 226. Li, M. *et al.* Genetic and neutralization properties of subtype C human immunodeficiency virus

- type 1 molecular env clones from acute and early heterosexually acquired infections in Southern Africa. *J. Virol.* **80**, 11776–90 (2006).
227. deCamp, A. *et al.* Global panel of HIV-1 Env reference strains for standardized assessments of vaccine-elicited neutralizing antibodies. *J Virol* **88**, 2489–2507 (2014).
 228. Kwong, P. D. & Mascola, J. R. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **37**, 412–25 (2012).
 229. Zhu, J. *et al.* Somatic Populations of PGT135-137 HIV-1-Neutralizing Antibodies Identified by 454 Pyrosequencing and Bioinformatics. *Front Microbiol* **3**, 315 (2012).
 230. Wu, X. *et al.* Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science* **329**, 856–61 (2010).
 231. Zhou, T. *et al.* Structural Basis for Broad and Potent. *Science* (80-). **329**, 811 (2010).
 232. Larimore, K., McCormick, M. W., Robins, H. S. & Greenberg, P. D. Shaping of human germline IgH repertoires revealed by deep sequencing. *J Immunol* **189**, 3221–3230 (2012).
 233. Haynes, B. F., Kelsoe, G., Harrison, S. C. & Kepler, T. B. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. *Nat. Biotechnol.* **30**, 423–33 (2012).
 234. McLellan, J. S. *et al.* Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature* **480**, 336–43 (2011).
 235. Alam, S. M. *et al.* Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Nature* **39**, 1315–6 (2013).
 236. Alam, S. M. *et al.* Role of HIV membrane in neutralization by two broadly neutralizing antibodies. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 20234–9 (2009).
 237. Letvin, N. L. *et al.* Immune and Genetic Correlates of Vaccine Protection Against Mucosal Infection by SIV in Monkeys. *Sci. Transl. Med.* **3**, 81ra36 (2011).
 238. Moore, J. S. *et al.* Increased levels of galactose-deficient IgG in sera of HIV-1-infected individuals. *AIDS* **19**, 381–389 (2005).
 239. Ackerman, M. E. *et al.* Natural variation in Fc glycosylation of HIV-specific antibodies impacts antiviral activity. *J. Clin. Invest.* **123**, 2183–92 (2013).
 240. Banerjee, K. *et al.* IgG subclass profiles in infected HIV type 1 controllers and chronic progressors and in uninfected recipients of Env vaccines. *AIDS Res. Hum. Retroviruses* **26**, 445–58 (2010).
 241. Alter, G. & Moody, M. A. The Humoral Response to HIV-1: New Insights, Renewed Focus. *J. Infect. Dis.* **202**, S315–S322 (2010).
 242. Georgiou, G. *et al.* The promise and challenge of high-throughput sequencing of the antibody repertoire. *Nat. Biotechnol.* **32**, 158–68 (2014).
 243. DeKosky, B. J. *et al.* High-throughput sequencing of the paired human immunoglobulin heavy and light chain repertoire. *Nat. Biotechnol.* **31**, 166–169 (2013).
 244. Baum, P. D., Venturi, V. & Price, D. A. Wrestling with the repertoire: the promise and perils of next generation sequencing for antigen receptors. *Eur. J. Immunol.* **42**, 2834–9 (2012).
 245. Zhu, J. *et al.* De novo identification of VRC01 class HIV-1-neutralizing antibodies by next-generation sequencing of B-cell transcripts. *Proc. Natl. Acad. Sci. U. S. A.* **110**, E4088–97 (2013).
 246. Tan, Y. C. *et al.* High-throughput sequencing of natively paired antibody chains provides evidence for original antigenic sin shaping the antibody response to influenza vaccination. *Clin. Immunol.* **151**, (2014).
 247. Scheid, J. F. *et al.* Sequence and Structural Convergence of Broad and Potent HIV Antibodies That Mimic CD4 Binding. *Science* (80-). **333**, 1633–1637 (2011).
 248. Sanders, R. W. *et al.* Stabilization of the soluble, cleaved, trimeric form of the envelope glycoprotein complex of human immunodeficiency virus type 1. *J. Virol.* **76**, 8875–89 (2002).
 249. Sanders, R. W. *et al.* Variable-loop-deleted variants of the human immunodeficiency virus type 1 envelope glycoprotein can be stabilized by an intermolecular disulfide bond between the gp120 and gp41 subunits. *J. Virol.* **74**, 5091–5100 (2000).
 250. The rgp120 HIV Vaccine Study Group. Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV-1 Infection. *J. Infect. Dis.* **191**, 654–665 (2005).
 251. Wyatt, R. *et al.* The antigenic structure of the HIV gp120 envelope glycoprotein. *Nature* **393**, 705–11 (1998).
 252. Doria-Rose, N. A. *et al.* New Member of the V1V2-Directed CAP256-VRC26 Lineage That Shows Increased Breadth and Exceptional Potency. *J. Virol.* **90**, 76–91 (2015).

253. Stowell, R. E., Smith, E. K., Espana, C. & Nelson, V. G. Outbreak of malignant lymphoma in rhesus monkeys. *Lab. Invest.* **25**, 476–479 (1971).
254. Murphey-Corb, M. *et al.* Isolation of an HTLV-III-related retrovirus from macaques with simian AIDS and its possible origin in asymptomatic mangabeys. *Nature* **321**, 435–7 (1986).
255. Apetrei, C., Robertson, D. L. & Marx, P. a. The history of SIVS and AIDS: epidemiology, phylogeny and biology of isolates from naturally SIV infected non-human primates (NHP) in Africa. *Front. Biosci.* **9**, 225–254 (2004).
256. Lifson, J. D. & Haigwood, N. L. Lessons in nonhuman primate models for AIDS vaccine research: from minefields to milestones. *Cold Spring Harb Perspect Med* **2**, a007310 (2012).
257. Morgan, C. *et al.* The use of nonhuman primate models in HIV vaccine development. *PLoS Med.* **5**, 1200–1204 (2008).
258. Amos, J. D. *et al.* Rapid Development of gp120-Focused Neutralizing B Cell Responses during Acute Simian Immunodeficiency Virus Infection of African Green Monkeys. *J. Virol.* **89**, 9485–9498 (2015).
259. Jain, S., Trivett, M. T., Ayala, V. I., Ohlen, C. & Ott, D. E. African Green Monkey TRIM5 α Restriction in Simian Immunodeficiency Virus-Specific Rhesus Macaque Effector CD4 T Cells Enhances Their Survival and Antiviral Function. *J. Virol.* **89**, 4449–4456 (2015).
260. Jacquelin, B. *et al.* Nonpathogenic SIV infection of African green monkeys induces a strong but rapidly controlled type I IFN response. *J. Clin. Invest.* **119**, 3544–55 (2009).
261. Nath, B. M., Schumann, K. E. & Boyer, J. D. The chimpanzee and other non-human-primate models in HIV-1 vaccine research. *Trends Microbiol.* **8**, 426–431 (2000).
262. Loffredo, J. T. *et al.* Mamu-B*08-Positive Macaques Control Simian Immunodeficiency Virus Replication. *J. Virol.* **81**, 8827–8832 (2007).
263. Mothé, B. R. *et al.* Expression of the Major Histocompatibility Complex Class I Molecule Mamu-A * 01 is associated with control of Simian Immunodeficiency Virus SIV mac 239 replication. *J. Virol.* **77**, 2736 (2003).
264. Sauermann, U. *et al.* Homozygosity for a conserved Mhc class II DQ-DRB haplotype is associated with rapid disease progression in simian immunodeficiency virus-infected macaques: results from a prospective study. *J. Infect. Dis.* **182**, 716–724 (2000).
265. Yant, L. J. *et al.* The High-Frequency Major Histocompatibility Complex Class I Allele Mamu-B * 17 Is Associated with Control of Simian Immunodeficiency Virus SIVmac239 Replication. *Society* **80**, 5074–5077 (2006).
266. Zhang, Z. *et al.* Mamu-A * 01 Allele-Mediated Attenuation of Disease Progression in Simian-Human Immunodeficiency Virus Infection Mamu-A * 01 Allele-Mediated Attenuation of Disease Progression in Simian-Human Immunodeficiency Virus Infection. *76*, 12845–12854 (2002).
267. Goulder, P. J. R. & Watkins, D. I. Impact of MHC class I diversity on immune control of immunodeficiency virus replication. *Nat. Rev. Immunol.* **8**, 619–630 (2008).
268. Goulder, P. J. *et al.* Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat. Med.* **3**, 212–217 (1997).
269. Allen, T. M. *et al.* Characterization of the peptide binding motif of a rhesus MHC class I molecule (Mamu-A*01) that binds an immunodominant CTL epitope from simian immunodeficiency virus. *J. Immunol.* **160**, 6062–6071 (1998).
270. Hatzioannou, T. & Evans, D. T. Animal models for HIV/AIDS research. *Nat Rev Microbiol* **10**, 852–867 (2012).
271. Wilson, D. P. *et al.* Estimating the infectivity of CCR5-tropic simian immunodeficiency virus SIV(mac251) in the gut. *J. Virol.* **81**, 8025–8029 (2007).
272. Means, R. E., Greenough, T. & Desrosiers, R. C. Neutralization sensitivity of cell culture passaged simian immunodeficiency virus. *J. Virol.* **71**, 7895–7902 (1997).
273. Yeh, W. W. *et al.* Autologous neutralizing antibodies to the transmitted/founder viruses emerge late after simian immunodeficiency virus SIVmac251 infection of rhesus monkeys. *J. Virol.* **84**, 6018–32 (2010).
274. Sun, Y. *et al.* Antibody-Dependent Cell-Mediated Cytotoxicity in Simian Immunodeficiency Virus-Infected Rhesus Monkeys. *J. Virol.* **85**, JVI.00326-11- (2011).
275. Strickland, S. L. *et al.* Significant Genetic Heterogeneity of the SIVmac251 Viral Swarm Derived from Different Sources. *AIDS Res. Hum. Retroviruses* **27**, 1327–1332 (2011).
276. Rud, E. W. *et al.* Molecular and biological characterization of simian immunodeficiency virus

- macaque strain 32H proviral clones containing nef size variants. *J. Gen. Virol.* **75**, 529–543 (1994).
277. Lopker, M. *et al.* Heterogeneity in neutralization sensitivities of viruses comprising the simian immunodeficiency virus SIVsmE660 isolate and vaccine challenge stock. *J. Virol.* **87**, 5477–92 (2013).
 278. Wu, F. *et al.* Sequential Evolution and Escape from Neutralization of Simian Immunodeficiency Virus SIVsmE660 Clones in Rhesus Macaques. *J. Virol.* **86**, 8835–8847 (2012).
 279. Sato, S. *et al.* Potent antibody-mediated neutralization and evolution of antigenic escape variants of simian immunodeficiency virus strain SIVmac239 in vivo. *J. Virol.* **82**, 9739–9752 (2008).
 280. Johnson, W. E. *et al.* Assorted mutations in the envelope gene of simian immunodeficiency virus lead to loss of neutralization resistance against antibodies representing a broad spectrum of specificities. *J. Virol.* **77**, 9993–10003 (2003).
 281. Cranage, M. P. *et al.* Macaques infected with live attenuated SIVmac are protected against superinfection via the rectal mucosa. *Virology* **229**, 143–154 (1997).
 282. Johnson, R. P. *et al.* Induction of vigorous cytotoxic T-lymphocyte responses by live attenuated simian immunodeficiency virus. *J. Virol.* **71**, 7711–8 (1997).
 283. Nixon, D. F. *et al.* Simian immunodeficiency virus-specific cytotoxic T lymphocytes and protection against challenge in rhesus macaques immunized with a live attenuated simian immunodeficiency virus vaccine. *Virology* **266**, 203–210 (2000).
 284. Koff, W. C. *et al.* HIV vaccine design: insights from live attenuated SIV vaccines. *Nat. Immunol.* **7**, 19–23 (2006).
 285. Reynolds, M. R. *et al.* Macaques Vaccinated with Simian Immunodeficiency Virus SIVmac239 nef Delay Acquisition and Control Replication after Repeated Low-Dose Heterologous SIV Challenge. *J. Virol.* **84**, 9190–9199 (2010).
 286. Staprans, S. I. & Feinberg, M. B. The roles of nonhuman primates in the preclinical evaluation of candidate AIDS vaccines. *Expert Rev. Vaccines* **3**, S5–S2 (2004).
 287. Feinberg, M. B. & Moore, J. P. AIDS vaccine models: challenging challenge viruses. *Nat. Med.* **8**, 207–10 (2002).
 288. Girard, M. P., Osmanov, S., Assossou, O. M. & Kieny, M.-P. Human immunodeficiency virus (HIV) immunopathogenesis and vaccine development: A review. *Vaccine* **29**, 6191–6218 (2011).
 289. Gautam, R. *et al.* Pathogenicity and mucosal transmissibility of the R5-tropic simian/human immunodeficiency virus SHIV(AD8) in rhesus macaques: implications for use in vaccine studies. *J. Virol.* **86**, 8516–26 (2012).
 290. Song, R. J. *et al.* Molecularly cloned SHIV-1157ipd3N4: a highly replication- competent, mucosally transmissible R5 simian-human immunodeficiency virus encoding HIV clade C Env. *J. Virol.* **80**, 8729–8738 (2006).
 291. Ng, C. T. *et al.* Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. *Nat. Med.* **16**, 1117–1119 (2010).
 292. Hessell, A. J. *et al.* Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques. *Nat. Med.* **22**, 1–9 (2016).
 293. Barouch, D. H. *et al.* Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature* **503**, 224–228 (2013).
 294. Reimann, K. A. *et al.* A chimeric simian/human immunodeficiency virus expressing a primary patient human immunodeficiency virus type 1 isolate env causes an AIDS-like disease after in vivo passage in rhesus monkeys. *J. Virol.* **70**, 6922–8 (1996).
 295. Parker, R. A., Regan, M. M., Reimann, K. A., Parker, R. A. & Regan, M. M. Variability of Viral Load in Plasma of Rhesus Monkeys Inoculated with Simian Immunodeficiency Virus or Simian-Human Immunodeficiency Virus : Implications for Using Nonhuman Primate AIDS Models To Test Vaccines and Therapeutics Variability of Viral Load in. *J. Virol.* **75**, 11234–11238 (2001).
 296. Yamamoto, T. *et al.* Quality and quantity of T FH cells are critical for broad antibody development in SHIV AD8 infection. *Sci. Transl. Med.* **7**, 1–12 (2015).
 297. Nishimura, Y. *et al.* Generation of the pathogenic R5-tropic simian/human immunodeficiency virus SHIVAD8 by serial passaging in rhesus macaques. *J. Virol.* **84**, 4769–81 (2010).

298. Shingai, M. *et al.* Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. *Nature* **503**, 277–80 (2013).
299. Jia, M., Lu, H., Markowitz, M., Cheng-Mayer, C. & Wu, X. Development of broadly neutralizing antibodies and their mapping by monomeric gp120 in HIV-1 infected humans and SHIV_{SF162P3N} infected macaques. *J. Virol.* JVI.02898-15 (2016). doi:10.1128/JVI.02898-15
300. Fouts, T. *et al.* Crosslinked HIV-1 envelope-CD4 receptor complexes elicit broadly cross-reactive neutralizing antibodies in rhesus macaques. *Proc. Natl. Acad. Sci.* **99**, 11842–11847 (2002).
301. Namikawa, R., Kaneshima, H., Lieberman, M., Weissman, I. L. & McCune, J. M. Infection of the SCID-hu mouse by HIV-1. *Science* **242**, 1684–1686 (1988).
302. Goldman, J. P. *et al.* Enhanced human cell engraftment in mice deficient in RAG2 and the common cytokine receptor γ chain. *Br. J. Haematol.* **103**, 335–342 (1998).
303. Melkus, M. W. *et al.* Humanized mice mount specific adaptive and innate immune responses to EBV and TSST-1. *Nat. Med.* **12**, 1316–1322 (2006).
304. M Barry, S. Trial, Error, and Breakthrough: A Review of HIV Vaccine Development. *J. AIDS Clin. Res.* **5**, (2014).
305. Leslie, A. J. *et al.* HIV evolution: CTL escape mutation and reversion after transmission. *Nat. Med.* **10**, 282–9 (2004).
306. Boutwell, C. L., Rolland, M. M., Herbeck, J. T., Mullins, J. I. & Allen, T. M. Viral evolution and escape during acute HIV-1 infection. *J. Infect. Dis.* **202 Suppl**, (2010).
307. Duerr, A., Wasserheit, J. N. & Corey, L. HIV vaccines: new frontiers in vaccine development. *Clin. Infect. Dis.* **43**, 500–11 (2006).
308. Hüttner, G. *et al.* Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* **360**, 692–8 (2009).
309. Whitney, J. B. *et al.* Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys. *Nature* **512**, 74–7 (2014).
310. Berry, N. *et al.* Early potent protection against heterologous SIVsmE660 challenge following live attenuated SIV vaccination in mauritian cynomolgus macaques. *PLoS One* **6**, (2011).
311. Baba, T. W. *et al.* Live attenuated, multiply deleted simian immunodeficiency virus causes AIDS in infant and adult macaques. *Nat. Med.* **5**, 194–203 (1999).
312. Angel, J. B., Routy, J.-P., Graziani, G. M. & Tremblay, C. L. The Effect of Therapeutic HIV Vaccination With ALVAC-HIV With or Without Remune on the Size of the Viral Reservoir (A CTN 173 Substudy). *J. Acquir. Immune Defic. Syndr.* **70**, 122–8 (2015).
313. Moore, J. P. *et al.* Primary isolates of human immunodeficiency virus type 1 are relatively resistant to neutralization by monoclonal antibodies to gp120, and their neutralization is not predicted by studies with monomeric gp120. *J. Virol.* **69**, 101–9 (1995).
314. Mascola, J. R. *et al.* Immunization with envelope subunit vaccine products elicits neutralizing antibodies against laboratory-adapted but not primary isolates of human immunodeficiency virus type 1. The National Institute of Allergy and Infectious Diseases AIDS Vaccine Evaluation. *J. Infect. Dis.* **173**, 340–8 (1996).
315. Graham, B. S. *et al.* Phase 1 safety and immunogenicity evaluation of a multiclade HIV-1 DNA candidate vaccine. *J. Infect. Dis.* **194**, 1650–60 (2006).
316. Cooney, E. L. *et al.* Safety of and immunological response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein. *Lancet (London, England)* **337**, 567–72 (1991).
317. Hu, S. L., Kosowski, S. G. & Dalrymple, J. M. Expression of AIDS virus envelope gene in recombinant vaccinia viruses. *Nature* **320**, 537–40
318. Hu, S. L. *et al.* Effect of immunization with a vaccinia-HIV env recombinant on HIV infection of chimpanzees. *Nature* **328**, 721–3
319. Mothe, B. *et al.* Safety and immunogenicity of a modified vaccinia Ankara-based HIV-1 vaccine (MVA-B) in HIV-1-infected patients alone or in combination with a drug to reactivate latent HIV-1. *J. Antimicrob. Chemother.* **70**, 1833–42 (2015).
320. Bonsignori, M. *et al.* Maturation Pathway from Germline to Broad HIV-1 Neutralizer of a CD4-Mimic Antibody. *Cell* **165**, 449–463 (2016).
321. Hansen, S. G. *et al.* Immune clearance of highly pathogenic SIV infection. *Nature* **502**, 100–4 (2013).
322. Hansen, S. G. *et al.* Cytomegalovirus Vectors Violate CD8+ T Cell Epitope Recognition Paradigms. *Science (80-.).* **340**, 1237874–1237874 (2013).

323. Excler, J.-L., Ake, J., Robb, M. L., Kim, J. H. & Plotkin, S. A. Nonneutralizing functional antibodies: a new ‘old’ paradigm for HIV vaccines. *Clin. Vaccine Immunol.* **21**, 1023–36 (2014).
324. Douek, D. C. *et al.* Assessment of thymic output in adults after haematopoietic stemcell transplantation and prediction of T-cell reconstitution. *Lancet* **355**, 1875–1881 (2000).
325. Palmer, S. *et al.* New Real-Time Reverse Transcriptase-Initiated PCR Assay with Single-Copy Sensitivity for Human Immunodeficiency Virus Type 1 RNA in Plasma. *J. Clin. Microbiol.* **41**, 4531–4536 (2003).
326. Lifson, J. D. *et al.* Role of CD8(+) lymphocytes in control of simian immunodeficiency virus infection and resistance to rechallenge after transient early antiretroviral treatment. *J. Virol.* **75**, 10187–99 (2001).
327. Gall, A. *et al.* Universal amplification, next-generation sequencing, and assembly of HIV-1 genomes. *J. Clin. Microbiol.* **50**, 3838–44 (2012).
328. Mason, R. D. *et al.* Targeted Isolation of Antibodies Directed against Major Sites of SIV Env Vulnerability. *PLoS Pathog.* **12**, e1005537 (2016).
329. Tiller, T. *et al.* Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. *J. Immunol. Methods* **329**, 112–124 (2008).
330. Watson, S. J. *et al.* Viral population analysis and minority-variant detection using short read next-generation sequencing. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **368**, 20120205 (2013).
331. Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. Basic local alignment search tool. *J. Mol. Biol.* **215**, 403–10 (1990).
332. Bashford-Rogers, R. J. *et al.* Network properties derived from deep sequencing of human B-cell receptor repertoires delineate B-cell populations. *Genome Res.* (2013). doi:10.1101/gr.154815.113
333. Hunt, M. *et al.* IVA: Accurate de novo assembly of RNA virus genomes. *Bioinformatics* **31**, 2374–2376 (2015).
334. Rose, P. P. & Korber, B. T. Detecting hypermutations in viral sequences with an emphasis on G --> A hypermutation. *Bioinformatics* **16**, 400–1 (2000).
335. Katoh, K. & Standley, D. M. MAFFT multiple sequence alignment software version 7: Improvements in performance and usability. *Mol. Biol. Evol.* **30**, 772–780 (2013).
336. Koichiro, T. *et al.* MEGA5: Molecular Evolutionary Genetics Analysis. *Mol. Biol. Evol.* **28**, 2731–2739 (2011).
337. Price, M. N., Dehal, P. S. & Arkin, A. P. FastTree 2 - Approximately maximum-likelihood trees for large alignments. *PLoS One* **5**, (2010).
338. Zhu, J. *et al.* Mining the antibodyome for HIV-1-neutralizing antibodies with next-generation sequencing and phylogenetic pairing of heavy/light chains. *Proc Natl Acad Sci U S A* **110**, 6470–6475 (2013).
339. Lifson, J. D. *et al.* The extent of early viral replication is a critical determinant of the natural history of simian immunodeficiency virus infection. *J. Virol.* **71**, 9508–9514 (1997).
340. Kilgore, K. M. *et al.* Characterization and Implementation of a Diverse Simian Immunodeficiency Virus SIVsm Envelope Panel in the Assessment of Neutralizing Antibody Breadth Elicited in Rhesus Macaques by Multimodal Vaccines Expressing the SIVmac239 Envelope. *J Virol* **89**, 8130–8151 (2015).
341. Francica, J. R. *et al.* Analysis of immunoglobulin transcripts and hypermutation following SHIVAD8 infection and protein-plus-adjuvant immunization. *Nat. Commun.* **6**, 6565 (2015).
342. Galson, J. D. *et al.* BCR repertoire sequencing: different patterns of B cell activation after two Meningococcal vaccines. *Immunol. Cell Biol.* 1–11 (2015). doi:10.1038/icb.2015.57
343. Yu, L. & Guan, Y. Immunologic Basis for Long HCDR3s in Broadly Neutralizing Antibodies Against HIV-1. *Front. Immunol.* **5**, 250 (2014).
344. Sundling, C. *et al.* High-resolution definition of vaccine-elicited B cell responses against the HIV primary receptor binding site. *Sci. Transl. Med.* **4**, 142ra96 (2012).
345. Euler, Z. & Schuitemaker, H. Cross-reactive broadly neutralizing antibodies: timing is everything. *Front. Immunol.* **3**, 215 (2012).
346. Volpe, J. M. & Kepler, T. B. Large-scale analysis of human heavy chain V(D)J recombination patterns. *Immunome Res.* **4**, 1–10 (2008).
347. Sundling, C. *et al.* Single-Cell and Deep Sequencing of IgG-Switched Macaque B Cells Reveal a Diverse Ig Repertoire following Immunization. *J. Immunol.* **192**, 3637–44 (2014).

348. Phad, G. E. *et al.* Diverse Antibody Genetic and Recognition Properties Revealed following HIV-1 Envelope Glycoprotein Immunization. *J. Immunol.* **150**, 0122 (2015). doi:10.4049/jimmunol.1500122
349. Moir, S. & Fauci, A. S. B cells in HIV infection and disease. *Nat. Rev. Immunol.* **9**, 235–45 (2009).
350. Li, W., Jaroszewski, L. & Godzik, A. Clustering of highly homologous sequences to reduce the size of large protein databases. *Bioinformatics* **17**, 282–3 (2001).
351. Hoi, K. H. & Ippolito, G. C. Intrinsic bias and public rearrangements in the human immunoglobulin V λ light chain repertoire. *Genes Immun.* **14**, 1–6 (2013).
352. Galson, J. D. *et al.* In-depth assessment of within-individual and inter-individual variation in the B cell receptor repertoire. *Front. Immunol.* **6**, 1–13 (2015).
353. Quigley, M. F. *et al.* Convergent recombination shapes the clonotypic landscape of the naive T-cell repertoire. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 19414–9 (2010).
354. Venturi, V., Price, D. A., Douek, D. C. & Davenport, M. P. The molecular basis for public T-cell responses? *Nat. Rev. Immunol.* **8**, 231–8 (2008).
355. Kedzierska, K. *et al.* Quantification of Repertoire Diversity of Influenza-Specific Epitopes with Predominant Public or Private TCR Usage. *J. Immunol.* **177**, 6705–6712 (2006).
356. Price, D. A. *et al.* Public clonotype usage identifies protective Gag-specific CD8+ T cell responses in SIV infection. *J. Exp. Med.* **206**, 923–36 (2009).
357. Parameswaran, P. *et al.* Convergent antibody signatures in human dengue. *Cell Host Microbe* **13**, 691–700 (2013).
358. Wu, Y.-C. C. *et al.* High-throughput immunoglobulin repertoire analysis distinguishes between human IgM memory and switched memory B-cell populations. *Blood* **116**, 1070–1078 (2010).
359. Kidera, A., Konishi, Y., Oka, M., Ooi, T. & Scheraga, H. a. *Statistical Analysis of the Physical Properties of the 20 Naturally Occurring Amino Acids*. *Journal of Protein Chemistry* **4**, (1985).
360. Moore, D. S. Amino acid and peptide net charges: A simple calculational procedure. *Biochem. Educ.* **13**, 10–11 (1985).
361. Ikai, A. Thermostability and Aliphatic Index of Globular Proteins. *J. Biochem.* **88**, 1895–1898 (1980).
362. Wang, Y. *et al.* High-Resolution Longitudinal Study of HIV-1 Env Vaccine-Elicited B Cell Responses to the Virus Primary Receptor Binding Site Reveals Affinity Maturation and Clonal Persistence. *J. Immunol.* (2016). doi:10.4049/jimmunol.1502543
363. Schnittman, S. M. *et al.* Preferential infection of CD4+ memory T cells by human immunodeficiency virus type 1: evidence for a role in the selective T-cell functional defects observed in infected individuals. *Proc. Natl. Acad. Sci. U. S. A.* **87**, 6058–62 (1990).
364. Brenchley, J. M. *et al.* T-cell subsets that harbor human immunodeficiency virus (HIV) in vivo: implications for HIV pathogenesis. *J. Virol.* **78**, 1160–8 (2004).
365. Stieh, D. J. *et al.* Th17 Cells Are Preferentially Infected Very Early after Vaginal Transmission of SIV in Macaques. *Cell Host Microbe* **19**, 529–40 (2016).
366. Gosselin, A. *et al.* Peripheral blood CCR4+CCR6+ and CXCR3+CCR6+CD4+ T cells are highly permissive to HIV-1 infection. *J. Immunol.* **184**, 1604–16 (2010).
367. Yamamoto, T. *et al.* Quality and quantity of T FH cells are critical for broad antibody development in SHIV AD8 infection. *7*, 1–12 (2015).
368. Ma, A., Koka, R. & Burkett, P. Diverse functions of IL-2, IL-15, and IL-7 in lymphoid homeostasis. *Annu. Rev. Immunol.* **24**, 657–79 (2006).
369. Zhang, S.-Y. *et al.* Progressive CD127 down-regulation correlates with increased apoptosis of CD8 T cells during chronic HIV-1 infection. *Eur. J. Immunol.* **39**, 1425–34 (2009).
370. Hutloff, A. *et al.* ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* **397**, 263–6 (1999).
371. Jin, H.-T., Ahmed, R. & Okazaki, T. Role of PD-1 in regulating T-cell immunity. *Curr. Top. Microbiol. Immunol.* **350**, 17–37 (2011).
372. Charles A Janeway, J., Travers, P., Walport, M. & Shlomchik, M. J. Appendix II. CD Antigens. (2001). at <<http://www.ncbi.nlm.nih.gov/books/NBK10772/>>
373. Yamazaki, T. *et al.* CCR6 regulates the migration of inflammatory and regulatory T cells. *J. Immunol.* **181**, 8391–8401 (2008).
374. Panzer, U. *et al.* Chemokine receptor CXCR3 mediates T cell recruitment and tissue injury in nephrotoxic nephritis in mice. *J. Am. Soc. Nephrol.* **18**, 2071–84 (2007).

375. Faustino, L. *et al.* Regulatory T cells migrate to airways via CCR4 and attenuate the severity of airway allergic inflammation. *J. Immunol.* **190**, 2614–21 (2013).
376. Dunham, R. M. *et al.* CD127 and CD25 expression defines CD4+ T cell subsets that are differentially depleted during HIV infection. *J. Immunol.* **180**, 5582–5592 (2008).
377. Porichis, F. *et al.* High-throughput detection of miRNAs and gene-specific mRNA at the single-cell level by flow cytometry. *Nat. Commun.* **5**, 5641 (2014).
378. Wang, F. *et al.* RNAscope: a novel in situ RNA analysis platform for formalin-fixed, paraffin-embedded tissues. *J. Mol. Diagn.* **14**, 22–9 (2012).
379. Pantaleo, G. *et al.* HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature* **362**, 355–8 (1993).
380. Connors, M. *et al.* HIV infection induces changes in CD4+ T-cell phenotype and depletions within the CD4+ T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. *Nat. Med.* **3**, 533–540 (1997).
381. Haase, A. T. Population biology of HIV-1 infection: viral and CD4+ T cell demographics and dynamics in lymphatic tissues. *Annu. Rev. Immunol.* **17**, 625–56 (1999).
382. Josefsson, L. *et al.* Majority of CD4 + T cells from peripheral blood of HIV-1-infected individuals contain only one HIV DNA molecule. doi:10.1073/pnas.1107729108
383. Batorsky, R. *et al.* Estimate of effective recombination rate and average selection coefficient for HIV in chronic infection. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 5661–6 (2011).
384. Perelson, A. S. *et al.* Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature* **387**, 188–91 (1997).
385. Besson, G. J. *et al.* HIV-1 DNA decay dynamics in blood during more than a decade of suppressive antiretroviral therapy. *Clin. Infect. Dis.* **59**, 1312–21 (2014).
386. Pruss, D., Bushman, F. D. & Wolffe, A. P. Human immunodeficiency virus integrase directs integration to sites of severe DNA distortion within the nucleosome core. *Proc. Natl. Acad. Sci. U. S. A.* **91**, 5913–7 (1994).
387. Wang, G. P., Ciuffi, A., Leipzig, J., Berry, C. C. & Bushman, F. D. HIV integration site selection: analysis by massively parallel pyrosequencing reveals association with epigenetic modifications. *Genome Res.* **17**, 1186–94 (2007).
388. Del Prete, G. Q. *et al.* Comparative Characterization of Transfection- and Infection-Derived Simian Immunodeficiency Virus Challenge Stocks for In Vivo Nonhuman Primate Studies. *J. Virol.* **87**, 4584–4595 (2013).
389. Chen, H. Y., Di Mascio, M., Perelson, A. S., Ho, D. D. & Zhang, L. Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 19079–84 (2007).