National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

Purple Paper

Innate Immunity to HIV

Aida Sivro,[1] Derek Stein,[1] Lyle McKinnon[2,3]
[1] Department of Medical Microbiology, University of Manitoba, Winnipeg, MB Canada; [2] Department of Medicine, University of Toronto, Toronto, ON Canada; [3] Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya

Overview of HIV

During the span of three decades, the human immunodeficiency virus (HIV) has infected over 50 million people, and despite large international prevention efforts, more than 2 million new infections occur every year[1]. However, there have been some successes in prevention (male circumcision[2-4], prevention of mother-to-child transmission) and declines in HIV prevalence have been observed in some countries[5-7]. There are also promising results not yet ready for widespread clinical use from the Thai vaccine trial[8] and a female microbicide trial in South Africa[9]. At the same time, antiretroviral treatment (ART) is highly effective and continually improving in its ability to extend the life of HIV-infected individuals. Moreover, there is evidence that ART might decrease HIV transmission from an infected person on ART[10]. However, treatment has yet to reach all who need it[11], and the idea of combining prevention modalities is taking shape. It is for these reasons that many believe that the realization of an effective HIV vaccine remains a part of the best long-term strategy to limit or stop the HIV pandemic.

Vaccines represent one of the most successful public health interventions of the last century. But despite many attempts, only one HIV vaccine efficacy trial has shown a mildly positive result (called the Thai trial)[8]. While there are many reasons to explain the difficulties of realizing an effective HIV vaccine, the most obvious explanation relates to the biology of HIV infection. In contrast to other viruses for which successful vaccines are available, HIV establishes chronic, latent infection that cannot be cleared (aside from an extreme case in Germany[12]). In addition, while neutralizing antibodies are a main correlate of protection against other viral infections [13], these are rarely elicited in HIV, and when they are, escape tends to occur rapidly[14]. The evolutionary capacity of HIV represents another major challenge, allowing HIV to mutate and avoid immune recognition[15]. Furthermore, HIV attacks the immune system (CD4+ T cells), such that by eliciting an immune response

Key Points

- HIV infects the cells of the immune system such as T cells, monocytes and macrophages. Whereas adaptive immune responses during HIV infection have been extensively studied, knowledge regarding the innate immune response to HIV is still scarce.
- Very early (days) into HIV infection, innate responses can play an important role in preventing mucosal transmission before HIV infection is established.
- Intracellular restriction of retroviruses has evolved in primates, and HIV has also evolved mechanisms to overcome this restriction and use the host cellular machinery to its advantage.
- Innate immune responses restrict the viral replication and activate adaptive immunity to fight the virus; however the same responses also increase the target cell availability and thereby facilitate further viral replication and contribute to disease progression. Dendritic cell, NK cell, and cytokine responses are prominent in acute HIV infection.
- Chronic innate immune activation is a major contributor of HIV immunopathogenesis and progression to AIDS.
- The failure of previous HIV-1 vaccine trials to induce B and T cell immunity emphasizes the need to look beyond adaptive immunity in order to gain control of HIV infection. It is becoming evident that both innate and adaptive arms of the immune system need to be harnessed in order to develop a successful HIV vaccine.

against HIV, the number of cells for HIV to potentially infect increases, particularly in mucosal tissues[16,17]. Finally, immunity to HIV is rare in nature, confined to small groups of long-term non-progressors (survive >10 years with HIV in the absence of disease), elite controllers (undetectable levels of virus)[18], and HIV-exposed seronegative individuals[19]. Further research on these groups may provide important clues that could inform HIV vaccine design.

Innate Immunity

The immune system can be divided into two main arms: innate and adaptive. These arms of the immune system have evolved to combat pathogens, in some cases with a high degree of specificity (adaptive), while in other cases a "less" specific response is directed at portions of HIV common to other microbes (innate). The adaptive immune system has long been the focus of vaccinologists, since its B and T cells exhibit classical immunological memory and specificity. In contrast, the innate immune system comprises cells and tissues that respond immediately to foreign invaders through the detection of danger signals. Natural killer (NK) cells and phagocytes (neutrophils, monocytes and macrophages) are examples of innate cellular immune effectors. The field of innate immunity has expanded rapidly in the past decade, including studies of innate responses to successful vaccines such as yellow fever[20,21]. This review focuses on innate immune responses to HIV, and how these might assist with development of biomedical prevention modalities.

Initial Events of HIV Infection

The best chance for the innate immune system to control HIV occurs at the time of exposure, before infection is established. For most of the world, this occurs across a mucosal surface, whether it is the penis, rectum or female genital tract. In fact, based on rates of HIV transmission observed in discordant couples[22], one can surmise that mucosal surfaces are generally quite effective (>99%) at thwarting HIV infection[23]. The most basic innate defenses against HIV include the epithelial layer, vaginal pH, and mucous. In the presence of co-factors that increase the rate of HIV transmission, such as other sexually transmitted infections[24,25], the effectiveness of these defenses can be diminished. Even without pre-existing inflammation due to other infections, semen may also facilitate HIV transmission. Exposure of cervical vaginal epithelium to semen results in production of pro-inflammatory cytokines that recruit dendritic cells, macrophages and lymphocytes into the area, thereby providing target cells for the virus[26].

The epithelium itself is more than just a physical barrier that protects against viral invasion. Epithelial cells respond to viruses via Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns (evolutionarily conserved structures on pathogens). This recognition leads to secretion of molecules called cytokines and chemokines that result in inflammation and recruitment of immune cells such as dendritic cells (DCs). In response, DCs produce interferons, important for initiating antiviral immunity[23,27]. Release of interferon from virus-infected cells represents an important part of the innate immune response. When a virus invades a cell, the presence of viral nucleic acids triggers the cell to produce interferon. Once released, interferon binds receptors on healthy cells and triggers them to prepare for the potential viral attack by producing host proteins that block the production of the virus.

However this response also leads to influx of susceptible immune cells to the mucosa, providing new targets for HIV and creating conditions for effective cell-to-cell spread[28]. There are a number of innate mucosal factors that are secreted into the lumen of the female genital tract, many of which have demonstrated anti-HIV activity *in vitro*[29]. These include α-defensins, SLP-1, Trappin2, and serpin proteases. While the latter two have been associated with HIV-resistance in a Nairobi-based cohort[30,31], other molecules with anti-HIV activity can cause inflammation and therefore may increase HIV susceptibility[32], and perhaps should be avoided. This hypothesis was recently tested by a microbicide that blocked a chemokine associated with inflammation called CCL20, which prevented cellular recruitment and protected non-human primates from a low-dose simian immunodeficiency virus (SIV) challenge[33].

The exact details of how HIV crosses the mucosal barrier remain poorly elucidated[34]. However, once

HIV enters the submucosa, it comes into contact with other components of the immune system. It is in these first 4-5 days of infection, referred to as the eclipse period, where in order to survive, HIV must infect enough target cells to establish small foci of infection[23]. Since this is prior to the appearance of the adaptive immune response, any chance of ablating HIV infection at this stage is the task of the innate immune system. Preventing HIV spread at this stage is critical; once HIV infects enough target cells in the submucosa, these cells drain through the lymphatic system (where CD4+ T cells are abundant), irreversibly establishing lifelong HIV infection.

Intracellular Restriction of HIV

All viruses require host machinery to replicate, and several of the host factors that HIV requires have been identified [35]. In addition, humans are equipped with genes called restriction factors that have evolved to inhibit HIV and other retroviruses, and therefore form an important part of the innate response. To date three major antiviral restriction factors have been identified: APOBEC[36], TRIM5α[37], and tetherin[38,39]. These genes can target a number of HIV-1 replication steps inside the cell, including uncoating, reverse transcription and virus release. APOBEC proteins can be incorporated into newly formed virions and carried to the next cell HIV infects where they induce mutations in the viral genome, preventing further viral replication. TRIM5α binds to retroviruses and targets them for degradation by the cell machinery before they can replicate. Tetherin causes the retention of viral particles on the cell surface, preventing them from being released and infecting neighboring cells. To counteract these host restriction factors, HIV encodes a number of accessory genes. One of these, called Vif, neutralizes the activity of APOBEC by preventing its packaging into viral particles. Another HIV gene called Vpu mediates the release of viral particles from the cell surface by reducing the expression of tetherin[40]. These examples demonstrate the innate struggle between host and virus, and represent possible therapeutic avenues for treating HIV.

Early Innate Immunity to HIV

Once HIV gains entry into the systemic circulation, the innate response induces adaptive (T and B cell) immune responses. Monocytes, DCs and macrophages are professional antigen presenting cells (APCs) that play an important role in host immune responses by linking innate and adaptive immunity. Since HIV can productively infect macrophages and DCs[41], these cells also serve as viral reservoirs, aiding in viral spread. This is supported by the finding that DC numbers are reduced in HIV infection[42]. Rapid decline of DCs in the blood occurs through both activation and migration of DCs into lymphoid tissues, and by depletion of DCs due to apoptosis and cytopathic effects of HIV. DCs can also transmit the virus without being productively infected[43], a process known as *trans*-infection. In this way, DCs act as "Trojan horses", capturing the virus in the peripheral tissues then migrating into the lymph nodes where HIV can be transferred to CD4+ T cells. This is just one example of how HIV is able to use the immune responses against it to its advantage.

The DC response also leads to activation and recruitment of another important innate cell, natural killer (NK) cells, to the site of infection and lymph nodes[44,45]. NK cells are elevated in acute HIV infection, but their function decreases as chronic infection is established[46]. NK cells play an important role in HIV immunity due to their ability to kill virally infected cells, particularly those that try to avoid T cell recognition. In addition they produce large amounts of chemokines that block the cellular receptors HIV uses for entry. NK cells express a complex network of receptors on their surface that can either be inhibitory or activating in nature. One major class of receptors is the killer immunoglobulin receptors (KIR). Polymorphisms in the KIR locus have been associated with differential outcomes in various cancers and infectious diseases including HIV[47]. Even though not yet used for viral infections, therapeutic strategies targeting NK cells have been successfully used in cancer and transplantation therapy[44,48].

Another important feature of the acute innate response to HIV is the "cytokine storm," characterized by dramatic increases in the production of cytokines and chemokines by innate

immune cells, including interleukin 15 (IL-15), type I interferons, and others[49]. While some of these cytokines play important roles in antiviral immune response, they also seem to promote viral replication and contribute to immune activation and disease progression[50]. Resolution of this acute inflammation might be one mechanism associated with non-pathogenic SIV infection in sooty mangabeys (monkeys who get SIV infection but rarely develop AIDS)[51].

Chronic Stage Innate Immunity – Immune Activation and Disease Progression

Chronic immune activation is one of the hallmarks of HIV infection, as continued viremia leads to manifestations of immune exhaustion, deregulation, and altered homeostasis. In fact, immune activation is an independent predictor of HIV disease progression[52]. It has been suggested that chronic innate immune activation is an important contributor to impaired adaptive immunity and immune deficiency[53]. The same immune responses that play a protective role in the initial stages of the HIV infection can prove to be detrimental during chronic infection. Interferon secretion by DCs may contribute to pathogenesis and disease progression by inducing apoptosis of both infected and uninfected CD4+ T cells[54]. The nature of the interferon response has been suggested to account for differences in disease progression between men and women, with women tending to have higher IFNα production and lower viral load initially, but increased T cell activation and disease progression as infection progresses[55]. Decreased immune activation is also associated with non-pathogenic SIV infection, and has been linked to innate immune signaling[56].

Microbial translocation, or leakage of microbial products from the gut lumen into blood, has been hypothesized as one of the causes of immune activation during HIV infection[57]. Increased plasma levels of lipopolysaccharide (LPS), a common bacterial structure and inducer of innate immunity, have been observed in chronic HIV infection. Levels of LPS and IFNα correlate and may contribute to the hyperactivation of the innate immune system. Many bacterial products signal through pattern recognition molecules, which are elevated in HIV infection and associated with HIV viral load[58]. Stimulation of intracellular TLRs (TLR7/8/9) results in a strong pro-inflammatory/antimicrobial response. Chronic activation of these receptors in the late stages of HIV infection has been shown to account for functionally impaired virus-specific T cells and T cell exhaustion. Overall, innate immunity in chronic infection is often “too late”, and likely is an important contributor to immune activation and progression to AIDS.

Vaccine and Innate Immunity

Like all immune responses, innate immunity to HIV can have a range of positive and negative effects. For example, depending on the context, innate immunity can both limit and induce HIV replication. Although required to limit viral replication in the initial stages of infection and initiate adaptive immunity, continuous activation of the innate immune system for prolonged periods can result in dysregulated T and B cell responses[59], contributing to the immune deficiency of chronic HIV infection. The fine balance between protection and harm was shown in a recent study that administered IL-15 during acute SIV infection in rhesus macaques. During this study, NK cell and SIV-specific CD8+T cell numbers were increased, but so was activation and proliferation of CD4+ T cells, with the end result of higher viral loads and accelerated disease progression[60]. However, given the difficulty in inducing protective B and T cell immunity in previous HIV-1 vaccine trials, the need to look beyond adaptive immunity to HIV cannot be ignored. The roles innate immunity plays, particularly at the time of exposure and during the eclipse phase, are critical areas in need of further research and could represent a window in which an effective vaccine could protect. Ideally, a vaccine should induce immune mechanisms that will clear the founder virus before infection is established. Furthermore, the innate immune system can play a key role, in conjunction with the adaptive arm, in clearing HIV infected cells[61]. One of the proposed mechanisms of protection of the Thai vaccine, which remains to be confirmed, was through antibody binding and induction of NK cells that killed cells expressing the HIV envelope[62]. Another avenue where innate immunity can contribute to HIV vaccinology is the use of TLR adjuvants. Adjuvants

are compounds that stimulate the innate immune system, leading to enhanced vaccine responses. Currently, BCG is one of the only commercially available vaccines that has been proven to signal through TLRs[63]. HIV vaccine strategies that stimulate the TLR9 pathway are being developed[64]. Therapeutic vaccines, which during the early stages of infection, adoptively transfer autologous DCs pulsed with inactivated HIV-1, have shown exciting results in primate models and in clinical trials[65,66]. Unfortunately, such treatments are unlikely to be feasible in developing countries, where HIV vaccines are needed most, since they would need to be made differently for every vaccinated individual. It is also important to reflect on the very definitions of innate and adaptive immunity, since some have suggested there is a bigger overlap between the two arms than was previously appreciated[67,68]. Of course there is no precedent for vaccines that rely on innate immunity, so the development of one for HIV, if possible, would likely be a long-term venture. A more comprehensive understanding of the immune system seems to be in reach – whether and when this will translate into better rational vaccine design remains to be seen.

References

1. UNAIDS. AIDS Epidemic Update 2009, 2009.
2. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007;**369**(9562)**:**657-66.
3. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007;**369**(9562)**:**643-56.
4. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005;**2**(11)**:**e298.
5. Gregson S, Garnett GP, Nyamukapa CA, et al. HIV decline associated with behavior change in eastern Zimbabwe. *Science* 2006;**311**(5761)**:**664-6.
6. Hallett TB, Aberle-Grasse J, Bello G, et al. Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti. *Sex Transm Infect* 2006;**82 Suppl 1:**i1-8.
7. Kimani J, Kaul R, Nagelkerke NJ, et al. Reduced rates of HIV acquisition during unprotected sex by Kenyan female sex workers predating population declines in HIV prevalence. *Aids* 2008;**22**(1)**:**131-7.
8. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009;**361**(23)**:**2209-20.
9. Karim QA, Karim SS, Frohlich JA, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science*.
10. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*;**375**(9731)**:**2092-8.
11. Stover J, Bertozzi S, Gutierrez JP, et al. The global impact of scaling up HIV/AIDS prevention programs in low- and middle-income countries. *Science* 2006;**311**(5766)**:**1474-6.
12. Hutter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* 2009;**360**(7)**:**692-8.
13. Amanna IJ, Messaoudi I, Slifka MK. Protective immunity following vaccination: how is it defined? *Hum Vaccin* 2008;**4**(4)**:**316-9.
14. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat Med* 2009;**15**(8)**:**866-70.
15. Goulder PJ, Watkins DI. HIV and SIV CTL escape: implications for vaccine design. *Nat Rev Immunol* 2004;**4**(8)**:**630-40.
16. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004;**200**(6)**:**749-59.
17. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004;**200**(6)**:**761-70.
18. Deeks SG, Walker BD. Human immunodeficiency virus controllers: mechanisms of durable virus control in the absence of antiretroviral therapy. *Immunity* 2007;**27**(3)**:**406-16.

19. Fowke KR, Nagelkerke NJ, Kimani J, et al. Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. *Lancet* 1996;**348**(9038)**:**1347-51.

20. Querec TD, Akondy RS, Lee EK, et al. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nat Immunol* 2009;**10**(1)**:**116-25.

21. Gaucher D, Therrien R, Kettaf N, et al. Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses. *J Exp Med* 2008;**205**(13)**:**3119-31.

22. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001;**357**(9263)**:**1149-53.

23. Haase AT. Perils at mucosal front lines for HIV and SIV and their hosts. *Nat Rev Immunol* 2005;**5**(10)**:**783-92.

24. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol* 2004;**2**(1)**:**33-42.

25. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *Aids* 2006;**20**(1)**:**73-83.

26. Berlier W, Cremel M, Hamzeh H, et al. Seminal plasma promotes the attraction of Langerhans cells via the secretion of CCL20 by vaginal epithelial cells: involvement in the sexual transmission of HIV. *Hum Reprod* 2006;**21**(5)**:**1135-42.

27. Wira CR, Fahey JV, Sentman CL, Pioli PA, Shen L. Innate and adaptive immunity in female genital tract: cellular responses and interactions. *Immunol Rev* 2005;**206:**306-35.

28. Haase AT. Targeting early infection to prevent HIV-1 mucosal transmission. *Nature*;**464**(7286)**:**217-23.

29. Iqbal SM, Kaul R. Mucosal innate immunity as a determinant of HIV susceptibility. *Am J Reprod Immunol* 2008;**59**(1)**:**44-54.

30. Iqbal SM, Ball TB, Levinson P, et al. Elevated elafin/trappin-2 in the female genital tract is associated with protection against HIV acquisition. *Aids* 2009;**23**(13)**:**1669-77.

31. Burgener A, Boutilier J, Wachihi C, et al. Identification of Differentially Expressed Proteins in the Cervical Mucosa of HIV-1-Resistant Sex Workers. *J Proteome Res* 2008.

32. Kaul R, Rebbapragada A, Hirbod T, et al. Genital levels of soluble immune factors with anti-HIV activity may correlate with increased HIV susceptibility. *Aids* 2008;**22**(15)**:**2049-51.

33. Li Q, Estes JD, Schlievert PM, et al. Glycerol monolaurate prevents mucosal SIV transmission. *Nature* 2009;**458**(7241)**:**1034-8.

34. Hirbod T, Broliden K. Mucosal immune responses in the genital tract of HIV-1-exposed uninfected women. *J Intern Med* 2007;**262**(1)**:**44-58.

35. Brass AL, Dykxhoorn DM, Benita Y, et al. Identification of host proteins required for HIV infection through a functional genomic screen. *Science* 2008;**319**(5865)**:**921-6.

36. Sheehy AM, Gaddis NC, Choi JD, Malim MH. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* 2002;**418**(6898)**:**646-50.

37. Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J. The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* 2004;**427**(6977)**:**848-53.

38. Neil SJ, Zang T, Bieniasz PD. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* 2008;**451**(7177)**:**425-30.

39. Kirchhoff F. Immune evasion and counteraction of restriction factors by HIV-1 and other primate lentiviruses. *Cell Host Microbe*;**8**(1)**:**55-67.

40. Strebel K, Luban J, Jeang KT. Human cellular restriction factors that target HIV-1 replication. *BMC Med* 2009;**7:**48.

41. Lore K, Smed-Sorensen A, Vasudevan J, Mascola JR, Koup RA. Myeloid and plasmacytoid dendritic cells transfer HIV-1 preferentially to antigen-specific CD4+ T cells. *J Exp Med* 2005;**201**(12)**:**2023-33.

42. Killian MS, Fujimura SH, Hecht FM, Levy JA. Similar changes in plasmacytoid dendritic cell and CD4 T-cell counts during primary HIV-1 infection and treatment. *Aids* 2006;**20**(9)**:**1247-52.

43. Geijtenbeek TB, Kwon DS, Torensma R, et al. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell* 2000;**100**(5)**:**587-97.

44. Megjugorac NJ, Young HA, Amrute SB, Olshalsky SL, Fitzgerald-Bocarsly P. Virally stimulated plasmacytoid dendritic cells produce chemokines and induce migration of T and NK cells. *J Leukoc Biol* 2004;**75**(3)**:**504-14.

45. Gerosa F, Baldani-Guerra B, Nisii C, Marchesini V, Carra G, Trinchieri G. Reciprocal activating interaction between natural killer cells and dendritic cells. *J Exp Med* 2002;**195**(3)**:**327-33.

46. Alter G, Teigen N, Davis BT, et al. Sequential deregulation of NK cell subset distribution and function starting in acute HIV-1 infection. *Blood* 2005;**106**(10)**:**3366-9.

47. Alter G, Altfeld M. NK cells in HIV-1 infection: evidence for their role in the control of HIV-1 infection. *J Intern Med* 2009;**265**(1)**:**29-42.

48. Terme M, Ullrich E, Delahaye NF, Chaput N, Zitvogel L. Natural killer cell-directed therapies: moving from unexpected results to successful strategies. *Nat Immunol* 2008;**9**(5)**:**486-94.

49. Stacey AR, Norris PJ, Qin L, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. *J Virol* 2009;**83**(8)**:**3719-33.

50. McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. *Nat Rev Immunol*;**10**(1)**:**11-23.

51. Bosinger SE, Li Q, Gordon SN, et al. Global genomic analysis reveals rapid control of a robust innate response in SIV-infected sooty mangabeys. *J Clin Invest* 2009;**119**(12)**:**3556-72.

52. Giorgi JV, Hultin LE, McKeating JA, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis* 1999;**179**(4)**:**859-70.

53. Boasso A, Shearer GM. Chronic innate immune activation as a cause of HIV-1 immunopathogenesis. *Clin Immunol* 2008;**126**(3)**:**235-42.

54. Gonzalez VD, Landay AL, Sandberg JK. Innate immunity and chronic immune activation in HCV/HIV-1 co-infection. *Clin Immunol*;**135**(1)**:**12-25.

55. Meier A, Chang JJ, Chan ES, et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med* 2009;**15**(8)**:**955-9.

56. Mandl JN, Barry AP, Vanderford TH, et al. Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. *Nat Med* 2008;**14**(10)**:**1077-87.

57. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006;**12**(12)**:**1365-71.

58. Lester RT, Yao XD, Ball TB, et al. Toll-like receptor expression and responsiveness are increased in viraemic HIV-1 infection. *Aids* 2008;**22**(6)**:**685-94.

59. Moir S, Fauci AS. B cells in HIV infection and disease. *Nat Rev Immunol* 2009;**9**(4)**:**235-45.

60. Mueller YM, Do DH, Altork SR, et al. IL-15 treatment during acute simian immunodeficiency virus (SIV) infection increases viral set point and accelerates disease progression despite the induction of stronger SIV-specific CD8+ T cell responses. *J Immunol* 2008;**180**(1)**:**350-60.

61. Huber M, Trkola A. Humoral immunity to HIV-1: neutralization and beyond. *J Intern Med* 2007;**262**(1)**:**5-25.

62. Forthal DN, Gilbert PB, Landucci G, Phan T. Recombinant gp120 vaccine-induced antibodies inhibit clinical strains of HIV-1 in the presence of Fc receptor-bearing effector cells and correlate inversely with HIV infection rate. *J Immunol* 2007;**178**(10)**:**6596-603.

63. Tsuji S, Matsumoto M, Takeuchi O, et al. Maturation of human dendritic cells by cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guerin: involvement of toll-like receptors. *Infect Immun* 2000;**68**(12)**:**6883-90.

64. Becker Y. CpG ODNs treatments of HIV-1 infected patients may cause the decline of transmission in high risk populations - a review, hypothesis and implications. *Virus Genes* 2005;**30**(2)**:**251-66.

65. Lu W, Arraes LC, Ferreira WT, Andrieu JM. Therapeutic dendritic-cell vaccine for chronic HIV-1 infection. *Nat Med* 2004;**10**(12)**:**1359-65.

66. Lu W, Wu X, Lu Y, Guo W, Andrieu JM. Therapeutic dendritic-cell vaccine for simian AIDS. *Nat Med* 2003;**9**(1)**:**27-32.

67. Sun JC, Lanier LL. Natural killer cells remember: an evolutionary bridge between innate and adaptive immunity? *Eur J Immunol* 2009;**39**(8)**:**2059-64.

68. Lanier LL, Sun JC. Do the terms innate and adaptive immunity create conceptual barriers? *Nat Rev Immunol* 2009;**9**(5)**:**302-3.