Coagulation and Inflammation Biomarkers Correlate with Disease Progression in SIV Infections

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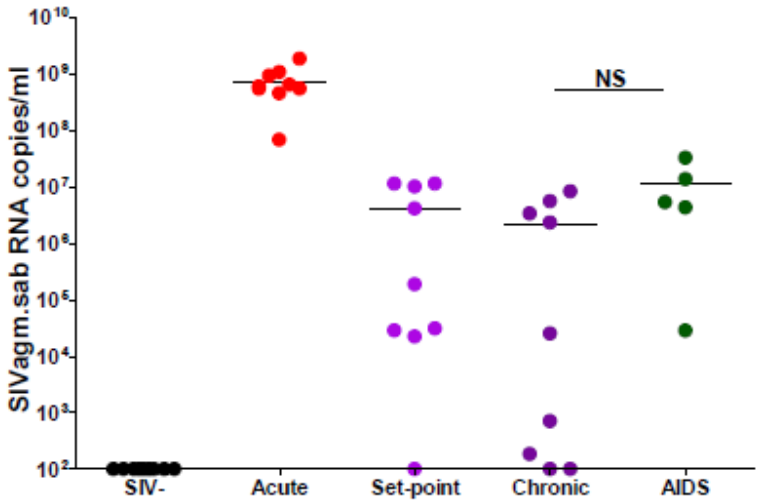
Non-human primate models for AIDS

Progressive

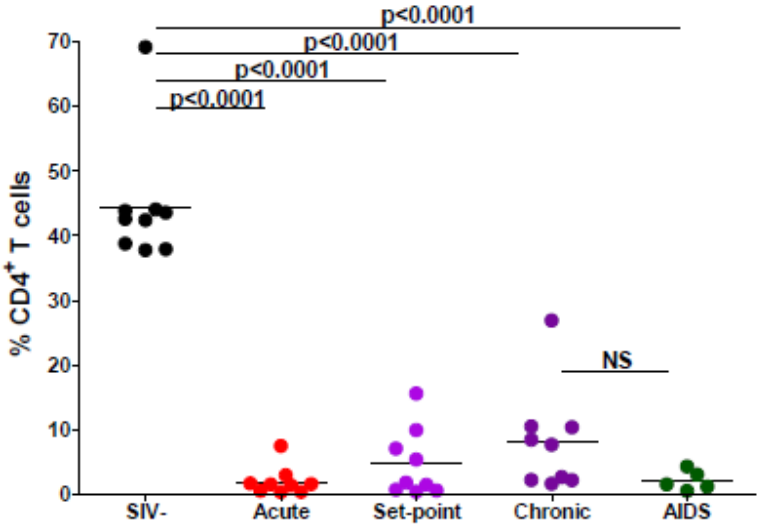
Non-progressive

Pathogenic SIVagm.sab infection of PTMs

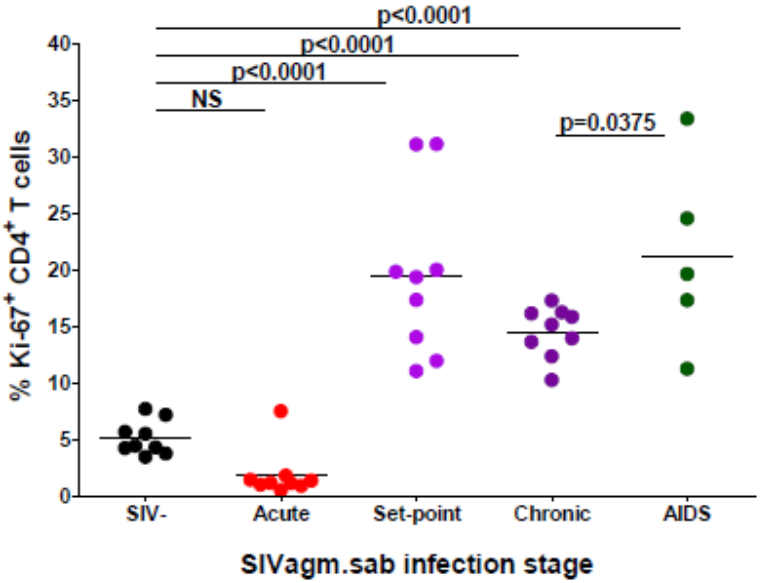
Plasma Viral Loads



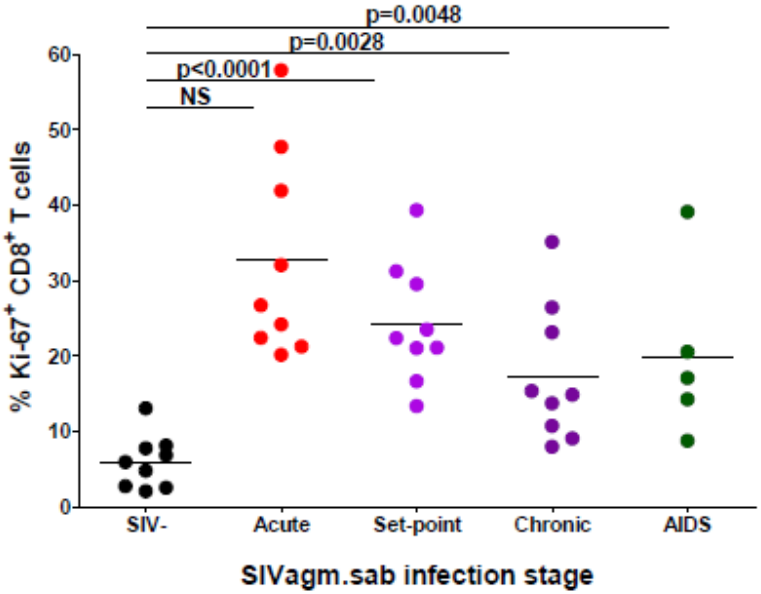
Changes in Mucosal CD4⁺ T Cells



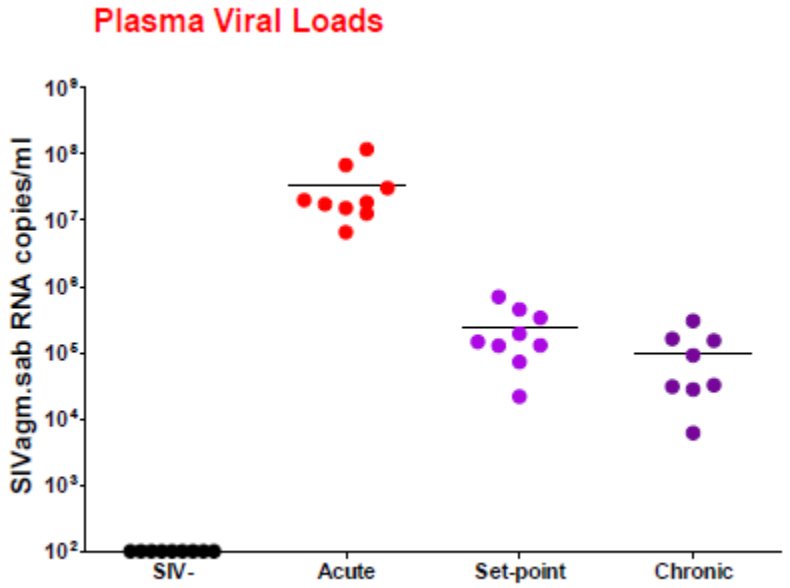
Changes in CD4⁺ T Cell Immune Activation (Ki-67)

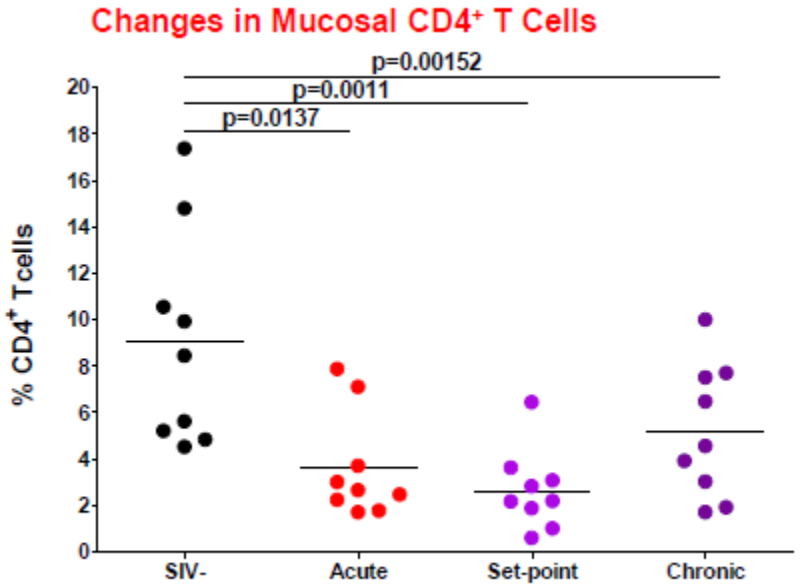


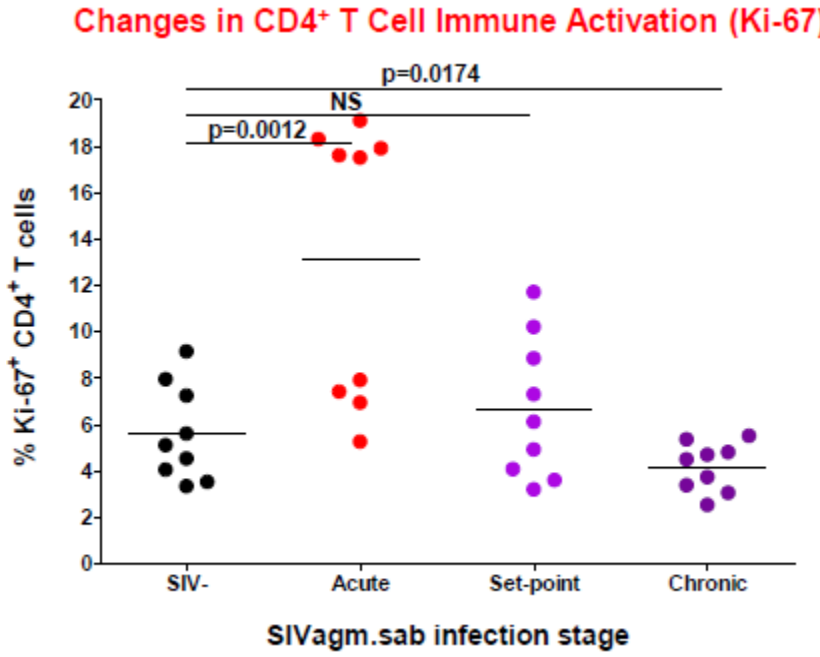
Changes in CD8⁺ T Cell Immune Activation (Ki-67)

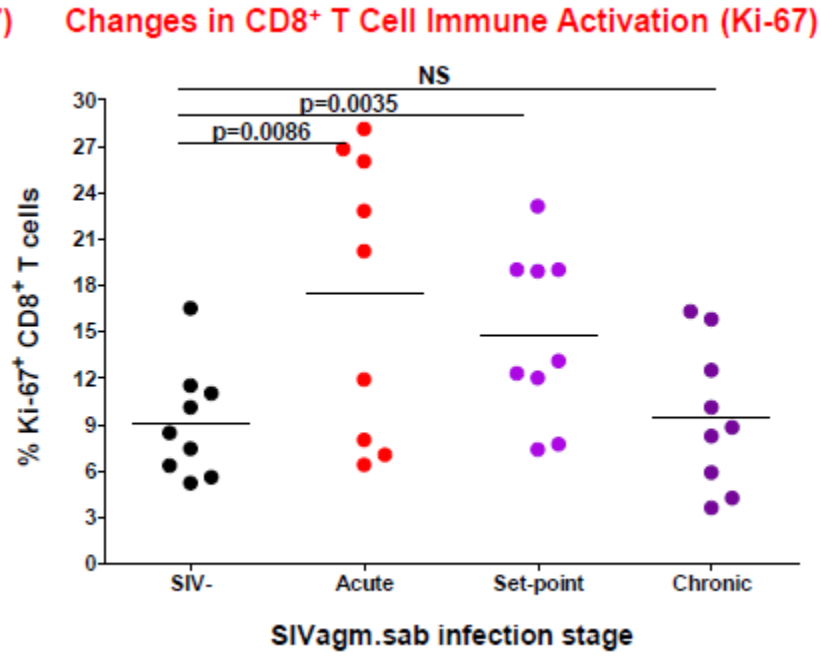


Nonpathogenic SIVagm.sab infection of AGMs









Hypothesis

The cross-cutting correlations between the CV biomarkers and inflammatory biomarkers on one hand and between inflammatory biomarkers and bacterial translocation biomarkers on the other hand prompted us to elaborate the hypothesis that the "microsepsis" associated with HIV/SIV infection activates inflammatory mediators that may play a role in hypercoagulation.

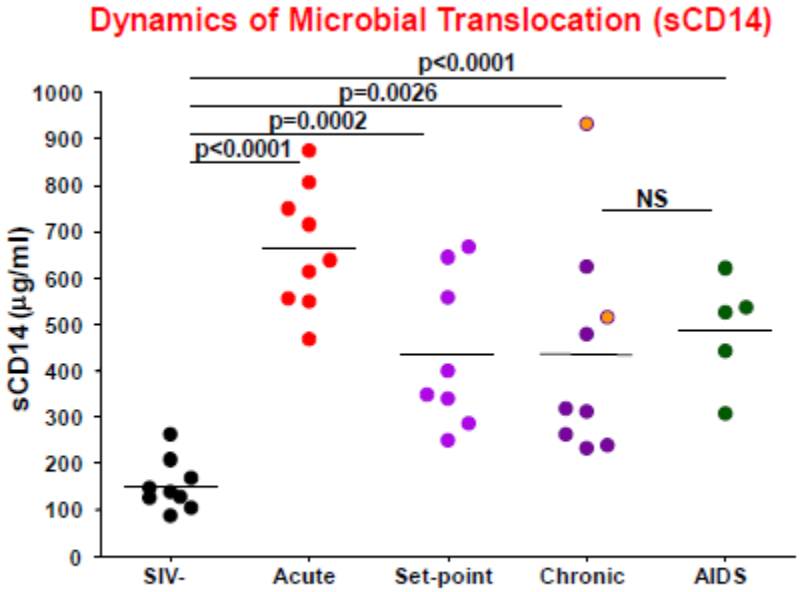
Aims

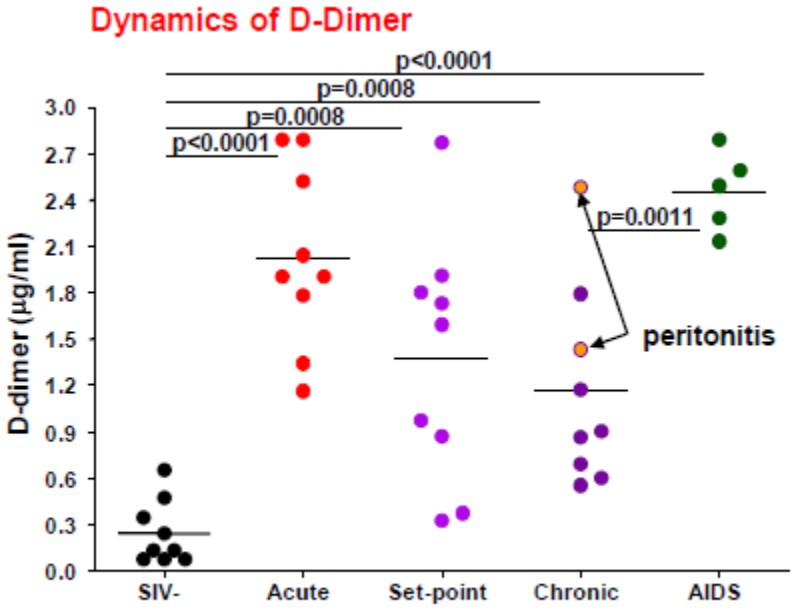
- **To validate the usefulness of AIDS animal models for the study of the role of vascular events in disease progression and death in HIV-infected patients.**
- **To determine the correlations between the DD expression with levels of plasma viremia, degree of mucosal CD4 T cell depletion in the gut, levels of immune activation (defined by Ki-67 expression and levels of pro-inflammatory IL-6) and levels of microbial translocation (defined by sCD14).**

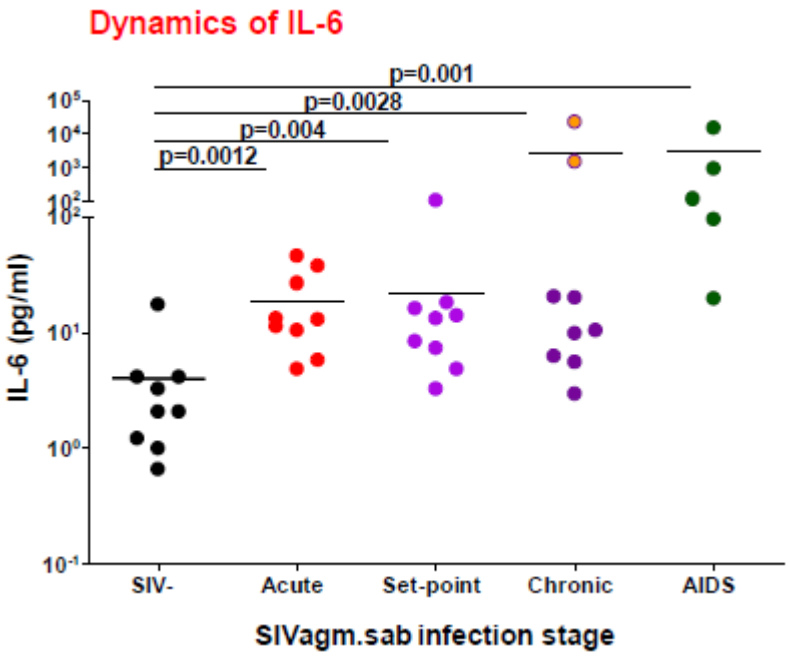
Animals and methods

- **A cross-sectional study involved measurements of sCD14 and DD in two NHP species that are natural hosts of SIV and do not progress to AIDS upon SIV infection: African green monkeys (AGMs) (uninfected, n=12; SIV-infected, n=27), sooty mangabeys (SMs) (uninfected, n=5; SIV-infected, n=28) and in macaques that normally progress to AIDS upon SIV infection (uninfected, n=17 and SIV-infected, n=17).**
- **Prospective studies involved 9 AGMs experimentally infected with SIVagm.sab, 8 rhesus macaques (RMs) experimentally infected with SIVmac239 and 9 pigtailed macaques (PTMs) experimentally infected with SIVagm.sab.**
- **Samples (blood, lymph nodes and intestinal biopsies) were collected from experimentally infected animals prior to SIV inoculation, during acute infection [days 9-11 post-inoculation (pi)], at the set-point (day 42 pi, which marks the beginning of chronic infection), throughout chronic infection and at the time of AIDS.**
- **Methods involved serological testing of sCD14 (as a marker of microbial translocation), DD (as a CV biomarker) and IL-6 (a proinflammatory cytokine); viral load quantification in plasma; flow cytometric measurements of the major lymphocyte populations, as well as of immune activation (Ki-67) marker.**

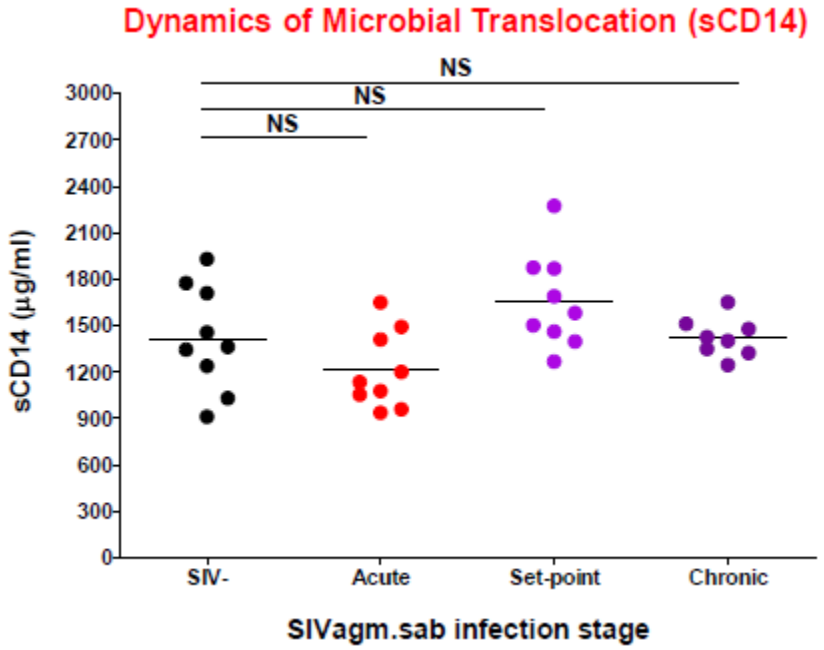
Pathogenic SIVagm.sab infection of PTMs

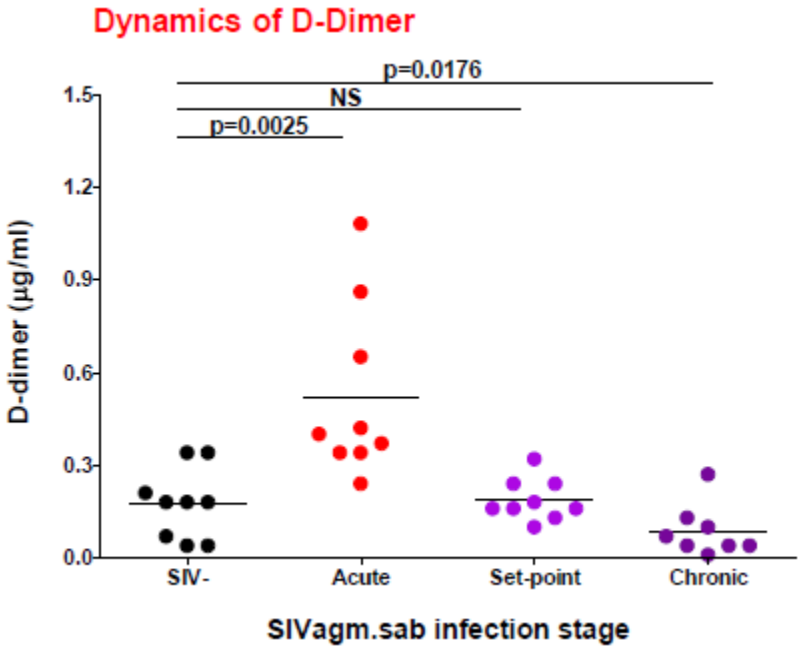


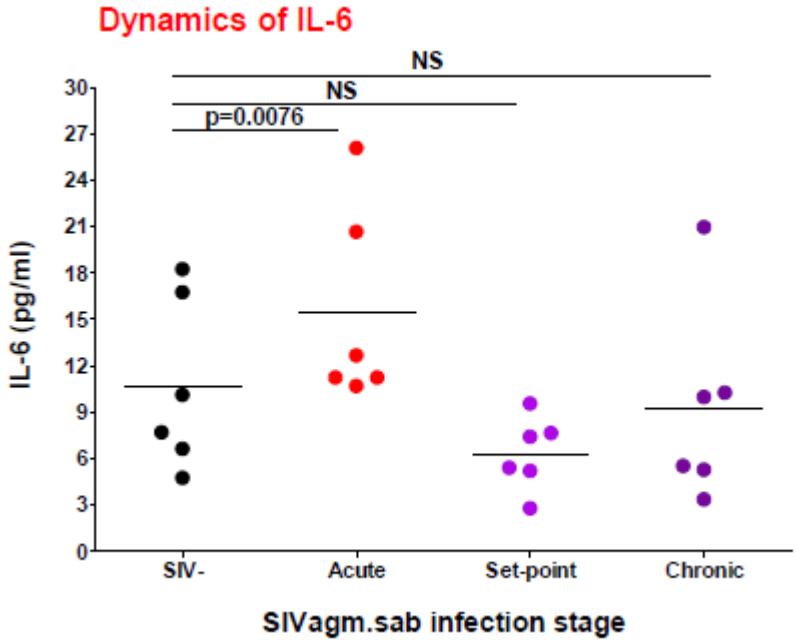




Nonpathogenic SIVagm.sab infection of AGMs

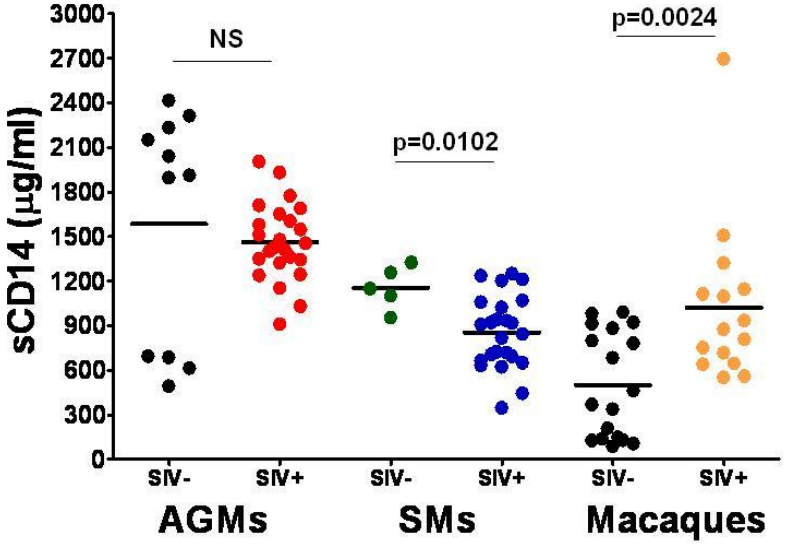


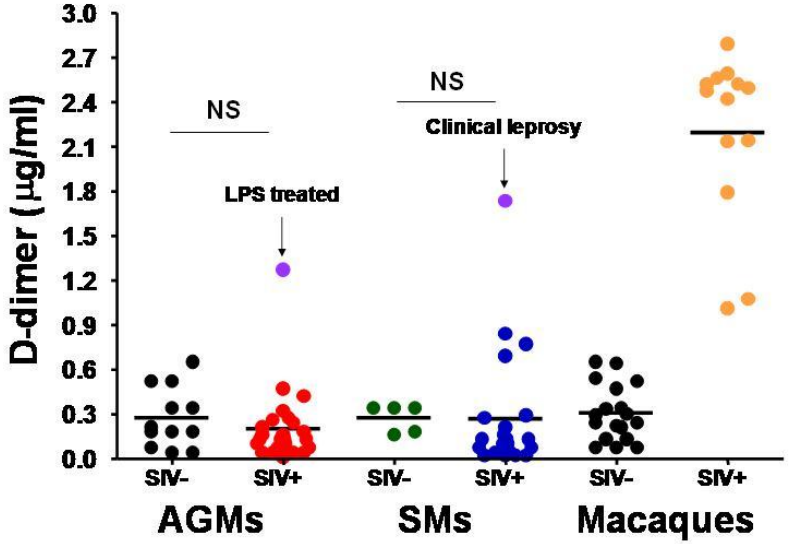




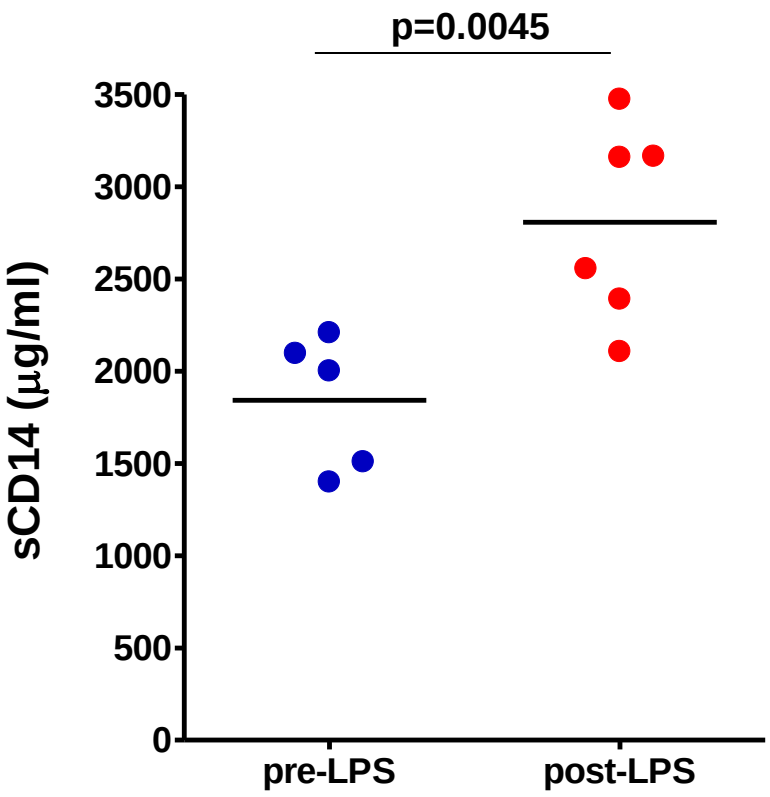
Cross-sectional data

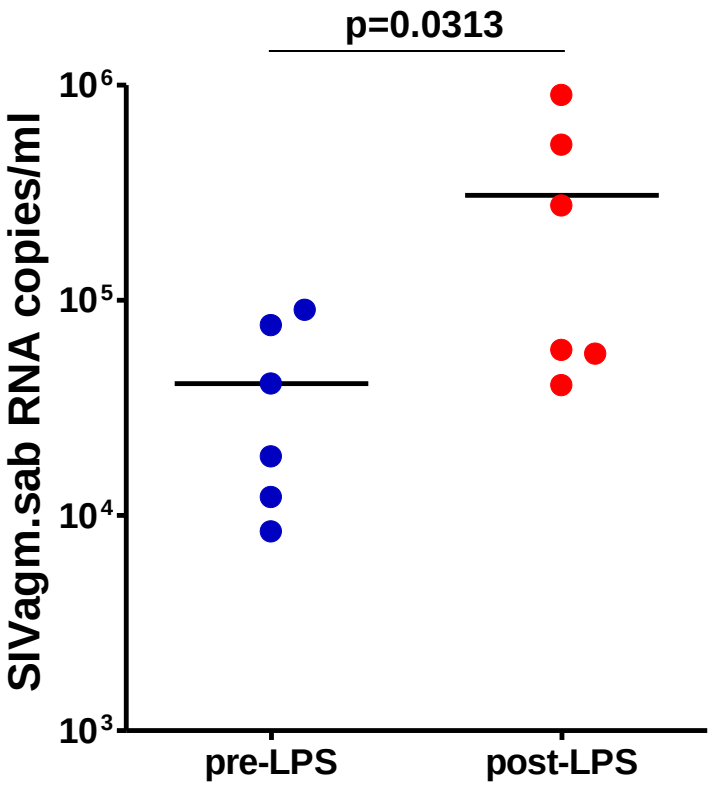
Pathogenic SIV infections associate significant increases in both microbial translocation (assessed by measurement of the levels of sCD14) and hypercoagulopathy (as assessed by measurement of D-dimer). Nonpathogenic SIV infections of African green monkeys and sooty mangabeys do not associate such changes.





Experimental administration of LPS to Chronically SIVagm.sab-Infected AGMs Results in Significant Increase in Viral Replication





Conclusions

1. **DD and IL-6 are increased in pathogenic SIV infections, which also associate increased MT and IA. Conversely, DD and IL-6 do not significantly increase in nonpathogenic infections, in which there is no MT and excessive IA is controlled.**
2. **VLs did not always correlate with DD levels, suggesting that viral replication alone may not fully account for HIV-associated CV complications.**
3. **D-dimer is independently strongly correlated with immune activation and SIV disease progression.**
4. **Furthermore, strong direct correlations exist between the levels of sCD14 (microbial translocation) and the levels of DD.**
5. **Animals with peritonitis or receiving LPS treatment, two conditions that mimic MT, had significant increases in DD levels.**
6. **Therefore, our results confirm our hypothesis that the "microsepsis" associated with HIV/SIV infection activates inflammatory mediators that may play a role in hypercoagulation.**
7. **Experimental administration of LPS to AGMs, a natural host of SIV that controls MT and disease progression, resulted in increased viral replication, thus providing direct proof for the hypothesis that MT drives immune activation and disease progression.**
8. **Development of AIDS animal model that faithfully reproduces the cardiovascular complications described in humans will allow studies that cannot be performed in AIDS patients, which are aimed at: (i) identifying the timing of the onset of CV abnormalities during the HIV infection, (ii) establishing correlation between serologic biomarkers of CV disease and tissue lesions and (iii) testing new therapies. Such experiments will contribute to determine the mechanism of CV disease in HIV patients and the role of CV conditions in HIV disease progression and death.**