# Differences in time of virus appearance in the blood and virus-specific immune responses in intravenous and intrarectal primary SIVmac251 infection of rhesus macaques; a pilot study


## ABSTRACT

These data may suggest that the natural mucosal barrier may delay viral spreading. The consequences of this observation, if confirmed in studies with a larger number of animals, may have implications in vaccine development.


## INTRODUCTION

Background Infection with human immunodeficiency vims (HIV) elicits an acute retroviral syndrome characterized by fever, pharyngitis, lymphadenopathy, myalgia, rash, and headache. Sexual transmission of HIV infection occurs mostly via the intestinal or vaginal mucosa but HIV-I is also effectively transmitted by the intravenous route. Recent studies have shown that the HIV-I or SIV virus rapidly penetrates vaginal, rectal, or oral mucosa attaching to and infecting primarily CD4+ T-cells where it replicates and consequently spreads to lymphoid tissue and systemic organs. Accumulating evidence has implicated virus-specific CTL in containing primary HIV/SIV infection and HIV-I/SIV-specific CD8+ CTL have been documented during the early weeks following infection, before a neutralizing Ab response is demonstrable. Despite the rapid dissemination of HIV-I by mucosal routes, productive mucosal transmission appears to be relatively inefficient and is estimated to occur once in 300 or more high-risk exposures. Cell-mediated immunity and direct killing by cytotoxic lymphocytes from the vagina and colon lamina propria may be an important factor in containing viral infection at the site of primary infection. Mucosal T lymphocytes appear to be functionally distinct from those present in the peripheral circulation. While activated T-cells reenter lymphoid tissues and preferentially accumulate at the site of the initial activation, memory T-cells migrate continuously and randomly, similar to naive T-cells. The implication in terms of HIV infection is that, in the initial phase of an immune response, once primed, Ag-specific memory T-cells randomly enter and leave various lymphoid compartments but preferentially are retained in the lymphoid compartment where the antigen was presented at first. In humans, it is unfeasible to evaluate the immunological events that occur shortly after infection in the mucosal compartments. However, in the SIVmac251 macaque model, some of these issues can be addressed. SIVmac251 establishes persistent infection in rhesus macaques and causes an immunodeficiency syndrome closely resembling human AIDS. As in humans, the clinical course of SIVmac251 infection varies considerably among macaques. Recent evidence from our lab suggests that macaques that express the major histocompatibility class I Mamu-A*01 molecule restrict SIVmac251 replication following intrarectal exposure, as reported for HIV-I-infected individuals that express the HLA B*5701, further validating this animal model of HIV-I infection. In this model, virus strain, dose, and especially route of infection can be defined and host-virus interactions under different conditions can be assessed. Here we used genetically defined Mamu-A*01 rhesus macaques to study the extent of virus-specific CD8+ T-cell response and the trafficking of lymphocytes to the gut during the first 12 days of intrarectal or intravenous transmission of the same stock of SIVmac251.

## CONCLUSION

Conclusions In conclusion, this study, within the limitation of the small number of animals used, appears to suggest that exposure by the mucosal site, a natural barrier to pathogens, delays viral appearance in the blood. The differences in the relative percentage of homing markers may not necessarily reflect a true qualitative difference in the overall lymphocyte trafficking related to the mode of viral encounter and may depend on the time of analysis, since the kinetic of viral replication was delayed in the macaque exposed intrarectally. Nevertheless, these data demonstrate that a short window of opportunity to contain viral infection following mucosal exposure exists and that potentiating the effectiveness of the mucosal natural barrier by local immunization may further limit or halt viral replication. In fact, in a previous study, we have observed that it appears to be easier to protect vaccinated macaques by intrarectal exposure than intravenous exposure to SIV251. In particular, since a CD8+ T-cell response to Tat appears to be the earliest, this protein may be a key component of a preventive vaccine, as suggested by other .