Scientists and Health Care Workers Committed to HIV/AIDS

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NON-INFECTIOUS X4 BUT NOT R5 HIV-1 VIRIONS INHIBIT HUMORAL IMMUNE RESPONSES IN HUMAN LYMPHOID TISSUE *EX VIVO*

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INTRODUCTION: *Ex vivo* HIV-1 infection of human lymphoid tissue recapitulates some aspects of *in vivo* infection, including a severe depletion of CD4+ T cells and suppression of humoral immune responses to recall antigens or to polyclonal stimuli. To isolate the mechanisms of suppression of immune responses from T cell depletion, we used inactivated virions that do not deplete CD4+ T cells in human lymphoid tissues *ex vivo.*

METHODS: Humoral immune response of the tissue was evaluated by antigen-specific and total immunoglobulin productions after *ex vivo* challenge with Tetanus toxoid and pokeweed mitogen. Immunoglobulin production of these tissues was compared with that following exposure to AT-2 inactivated HIV-1.

RESULTS: AT-2 inactivated X4, but not R5 HIV-1 virions, even with only a brief exposure, inhibited antibody responses in human lymphoid tissue *ex vivo.* The efficiency of this inhibition was comparable to that mediated by infectious virus. The inhibition is dependent on the maintenance of native X4 virion structure since neither baculovirus-expressed gp120, nor heat-denatured AT-2-inactivated X4 virus inhibited immune responses of *ex vivo* human lymphoid tissue. Moreover, the virus itself is only required to trigger suppression of B cell responses; the suppressive activity is maintained without the continuous presence of virions and can be transferred by conditioned medium.

CONCLUSIONS: Thus, neither productive viral infection, nor CD4+ T cell depletion are necessary to mediate HIV-induced inhibition of antibody production in human

lymphoid tissue in *ex vivo*. This phenomenon is mediated by soluble immunosuppressive factor(s) (ISF) secreted by lymphoid tissue exposed to viral particles.

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