Minocycline Attenuates HIV Infection and Reactivation by Suppressing Cellular Activation in Human CD4+ T Cells

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(See the editorial commentary by Copeland and Brooks, on pages 1115–1117.)

Treatment of human immunodeficiency virus (HIV) infection with highly active antiretroviral therapy (HAART) is effective but can be associated with toxic effects and is expensive. Other options may be useful for long-term therapy. The immunomodulatory antibiotic minocycline could be an effective, low-cost adjunctive treatment to HAART. Minocycline mediated a dose-dependent decrease in single-cycle CXCR4-tropic HIV infection and decreased viral RNA after infection of CD4+ T cells with HIV NL4–3. Reactivation from latency was also decreased in a primary CD4+ T cell–derived model and in resting CD4+ T cells from HIV-infected patients. Minocycline treatment resulted in significant changes in activation marker expression and inhibited proliferation and cytokine secretion of CD4+ T cells in response to activation. This study demonstrates that minocycline reduces HIV replication and reactivation and decreases CD4+ T cell activation. The anti-HIV effects of minocycline are mediated by altering the cellular environment rather than directly targeting virus, placing minocycline in the class of anticellular anti-HIV drugs.

Human immunodeficiency virus (HIV)–infected patients must remain on a lifelong regimen of highly active antiretroviral therapy (HAART). The presence of a latent viral reservoir in resting CD4+ T cells necessitates long-term treatment to prevent HIV reactivation and spread from perpetuating disease. Latent reservoirs are therefore the main barrier to eradication of HIV infection. The challenges of long-term HAART treatment include limited penetration to tissues that harbor latent virus (such as the brain), prohibitive cost, and both short- and long-term toxic effects [1–4]. Minocycline, a second-generation tetracycline derivative, has a number of properties that address these concerns (enhanced penetration to tissues, low incidence of toxicity with long-term administration, low cost). Because of these properties, along with its immunomodulatory abilities, it may prove to be an effective complement to HAART [5, 6].

We have shown elsewhere that minocycline has multiple beneficial effects in our simian immunodeficiency virus (SIV) macaque model of HIV-associated neurological disease [7]. In the central nervous system (CNS), treatment with minocycline significantly decreased virus load in the cerebrospinal fluid, viral RNA in the brain, and the severity of CNS disease. In the periphery, plasma viral load was decreased in minocycline-treated animals with encephalitis compared with those without encephalitis. Minocycline also decreased p38 activation and HIV replication in primary human lymphocytes, which suggests that it acts through its effects on CD4+ T cells, the primary host cell for HIV infection. Minocycline has also been shown to affect T cell activation...
and proliferation. Synovial T cell clones derived from arthritic patients treated with minocycline in vitro possess an impaired proliferative response to anti-CD3 and decreased production of activation-induced cytokines [8]. The effect of minocycline was also found to be signal dependent, resulting in decreased levels of tumor necrosis factor (TNF)–α messenger RNA in response to stimulation with phorbol 12–myristate 13–acetate or anti-CD28 [9].

These in vitro observations, along with our in vivo findings in the SIV primate model, represent evidence that minocycline can modulate cellular activation and proliferation by altering cell signaling. Owing to the tightly coupled regulation of the HIV long terminal repeat (LTR) by many T cell regulatory signals and the dependence of productive HIV replication on the activation state of the host cell [10–12], in this study, we demonstrate that minocycline decreases single-cycle HIV replication, intracellular viral RNA levels after in vitro infection of primary human CD4+ T cells, reactivation of HIV from a primary CD4+ T cell–derived model of HIV latency, and reactivation of HIV from resting CD4+ T cell reservoirs from patients who have clinically undetectable viremia during HAART. Furthermore, we demonstrate that minocycline alters T cell activation, blunting changes in expression of T cell activation/proliferation markers and cytokine secretion, many of which are critical for activation pathways that regulate HIV replication.

**METHODS**

**Isolation of CD4+ cells.** Whole blood specimens were obtained from HIV-negative healthy donors or HIV-positive donors receiving HAART with suppressed viremia. Peripheral blood mononuclear cells were isolated by Ficoll-Paque density gradient centrifugation (GE Healthcare). From healthy donors, CD4+ T cells (routinely >95% purity) were isolated using positive selection by anti-CD4 conjugated magnetic beads (Miltenyi Biotec or Invitrogen/Dynal). From HIV-positive donors, highly purified (>99% purity) resting CD4+ HLA-DR− T cells were isolated as described elsewhere [13]. All protocols were approved by the Johns Hopkins Institutional Review Board, and informed consent obtained from donors.

**Cell culture and activation.** Purified CD4+ T cells were cultured in R10 (Roswell Park Memorial Institute 1640 medium, 10% fetal bovine serum, l-glutamine, HEPES, gentamicin) and maintained at 37°C and 5% CO2. For some HIV-positive cells, antiretroviral drugs were maintained in culture where appropriate. Cells were transferred and incubated in anti-CD3 coated plates for up to 7 days. Supernatants from HIV-positive donor cell cultures were frozen at −80°C. Virus was pelleted and RNA prepared with a Qiagen QiaAmp Viral RNA Mini Kit.

**Single-cycle replication assay.** Purified CD4+ T cells at a density of 1×10⁶ cells/mL in R10 were activated for 24 h with soluble antibodies to CD3 and CD28 (2.5 μg/mL) or phytohemagglutinin (10 ng/mL) (Sigma). Minocycline was subsequently added, and cells were treated for 18–24 h. Cells were then seeded into a 96-well plate at a density of 1×10³ cells/well in 100 μL of R10. CXCR4-pseudotyped HIV (a kind gift from R.F.S. and M. A. McMahon) was then added at a multiplicity of infection of 0.1, and cells were spinoculated for 2 h at 1200g and 30°C. Cells were collected after 3 days and fixed with formaldehyde, and green fluorescent protein (GFP) expression was analyzed by fluorescence-activated cell sorting (FACS) analysis.

**Primary CD4+ T cell–derived model of HIV latency.** Cells from a primary CD4+ T cell model of HIV latency [14] were seeded at a density of 1×10⁶ cells/well in 100 μL R10 and pretreated with minocycline overnight. Anti-CD3/CD28 were then added (2 μg/mL each). After 72 h, cells were washed 3 times with phosphate-buffered saline. GFP expression was analyzed by FACS.

**In vitro infection.** Purified CD4+ T cells were isolated, plated at a density of 1.25×10⁵ cells/mL in 2 mL R10, and pretreated overnight, with or without minocycline. The next day, cells were activated with anti-CD3/CD28, as described above. After 48 h, cells were infected with HIV NL4–3 at a multiplicity of infection of 0.01 in 0.5 mL R10 and minocycline, where appropriate. After 24 h, cell pellets were isolated and frozen at −80°C until lysed to isolate RNA and DNA (Qiagen AllPrep DNA/RNA Mini Kit).

**FACS analysis.** Cells were collected and surface stained (CD25–phycoerythrin, CD69–peridinin–chlorophyll protein, CD95–fluorescein isothiocyanate (FITC), CD195–FITC, HLA-DR–FITC, CD28–phycoerythrin, CD11a–FITC; BD Biosciences) for 15 min at room temperature. Some samples were then permeabilized using a BD Perm/Fix kit and stained with Ki-67 FITC (BD Biosciences). Analysis was conducted on ≥10,000 gated viable lymphocytes by forward and side scatter. This gating was validated by CD3−, annexin V−, and 7AAD-stained controls. The mean fluorescence intensity (MFI) was calculated for the positive-stained population.

**Real-time reverse-transcription (RT) polymerase chain reaction (PCR)/PCR.** HIV RNA/DNA was quantified using RT PCR/PCR (developed by Michael Piatak and Thomas Parks,
to characterize the effect of minocycline on HIV-1 replication, primary CD4+ T cells were activated, pre-treated with minocycline, and then infected with a recombinant CXCR4-tropic HIV-1 pseudovirus that expresses the reporter gene GFP in place of a portion of the envelope gene [15]. Minocycline treatment mediated a significant, dose-dependent decrease in the percentage of cells expressing GFP 3 days after infection, with a median inhibitory concentration of ~30 μg/mL (Figure 1). It had no significant effect on the MFI of GFP in infected cells (data not shown). These results demonstrate that minocycline decreases the level of productive HIV infection in a dose-dependent manner and suggests that it acts before translation of HIV proteins.

Effect of minocycline on intracellular HIV RNA and HIV DNA levels in de novo infected CD4+ T cells. To further characterize the effect of minocycline on HIV-1 replication, CD4+ T cells were activated with or without minocycline pretreatment and then infected with replication-competent HIV NL4–3. Minocycline treatment at 20 μg/mL had no significant effect on intracellular HIV DNA levels 24 h after infection (Figure 2A). Intracellular HIV RNA levels were significantly decreased (P = .0131) >2-fold at 24 h relative to infection in untreated, activated controls (Figure 2B). That HIV DNA levels were not significantly affected by treatment indicates that minocycline must inhibit HIV replication after entry and RT steps. The inhibition of HIV RNA production by minocycline was associated with CD4+ T cell activation; HIV RNA levels in minocycline-treated, activated cells were not significantly different from those in untreated, unactivated controls. This observation strongly suggests that minocycline’s anti-HIV effect is dependent on inhibiting an activation-associated event necessary for a post–RT step in the viral life cycle, including viral DNA integration or transcription.

Effect of minocycline on HIV-1 expression in a primary CD4+ T cell–derived model of HIV-1 latency. Latency is the major barrier to eradicating HIV infection with current HAART regimens. Expression from integrated provirus in the latent reservoir of resting CD4+ T cells is dependent on activation of infected cells from a resting state and viral gene expression driven by the HIV LTR [16, 17]. The data presented above show that minocycline decreased HIV RNA production after infection. Minocycline has been shown elsewhere to attenuate T cell activation signals, most of which have downstream effectors that are also important regulators of the HIV LTR. On the basis of these observations, we hypothesized that minocycline would decrease gene expression from latent, integrated virus.

We used a novel primary CD4+ T cell model of HIV postintegration latency developed by Yang et al to determine the effects of minocycline on reactivation [14]. These cells retain a quiescent, resting phenotype with a 1%–2% frequency of latently infected cells, much higher than reported in CD4+ T cells isolated from peripheral blood of patients who have suppression of viremia during HAART (~1–10 cells/10^6 CD4+ T cells). Other in vitro HIV latency models use cell lines, which present a more activated cellular phenotype. The advantages of this model are that (1) it exhibits a higher frequency of latent infection and
Minocycline Attenuates HIV Infection in CD4+ T Cells

Figure 2. Intracellular human immunodeficiency virus (HIV) DNA and RNA levels after in vitro HIV NL4–3 infection of CD4+ T cells. CD4+ T cells were pretreated with minocycline (diamonds) or not pretreated (squares), followed by activation with anti-CD3/CD28 antibodies with minocycline maintenance. Cells were subsequently infected with HIV NL4–3 (multiplicity of infection, 0.01). Total cellular DNA and RNA were isolated 24 h after infection. A, HIV DNA levels normalized to interferon β DNA (n = 5). B, HIV gag RNA levels normalized to 18S ribosomal RNA (n = 5). Lines represent means. *Significant difference compared with untreated control (paired t test).

(2) the parental cells are primary CD4+ T cells, not cell lines, resulting in a quiescent state that recapitulates the characteristics of resting CD4+ cells in vivo. Cells were pretreated with or without minocycline, followed by activation with soluble anti-CD3/CD28 antibody costimulation. Minocycline treatment reduced the intensity of GFP expression in reactivating cells by 60% at doses of 20 and 40 μg/mL (Figure 3A). These results demonstrate that minocycline decreases the efficiency of HIV reactivation. Interestingly, the frequency of reactivation events is decreased by ~20% at a dose of 40 μg/mL but appeared unchanged at 20 μg/mL (Figure 3B). This suggests that minocycline treatment may not present a complete block to reactivation but rather decreases its magnitude by decreasing either proviral transcription or the translation of viral RNAs.

Effect of minocycline on activation and HIV production ex vivo by resting CD4+ T cells from HIV-infected patients with suppression of viremia during HAART. Current treatment paradigms aim to stably suppress HIV infection to create a manageable, chronic condition that necessitates life-long drug therapy. We demonstrated that minocycline decreased gene expression from reactivation of latent provirus in a primary cell model and reduced the efficiency of single-cycle replication and decreased HIV RNA expression in CD4+ T cells. Accordingly, we hypothesized that the effects of minocycline on reactivation and replication would prevent recovery of virus from the resting CD4+ T cell reservoir of HIV-positive patients.

Resting CD4+ T cells were isolated from HIV-infected patients treated with HAART who had an undetectable viral load for >6 months. Cells were pretreated with or without minocycline and subsequently activated by CD3/CD28 antibody costimulation. Some cultures included antiretrovirals. Minocycline treatment of resting CD4+ T cells from HIV-infected patients significantly reduced HIV RNA levels in pooled supernatants after 7 days of activation when compared with untreated, activated controls (P = .0087) (Figure 4A). Minocycline treatment also reduced viral RNA levels in supernatants below levels for cells cultured in the presence of antiretrovirals, providing further evidence that minocycline can decrease reactivation of HIV from primary resting CD4+ cells. Frequently, viral RNA levels in supernatants from minocycline-treated cells were at or below the limit of detection for the quantitative RT-PCR assay (sensitivity, 10 copy equivalents of HIV RNA). These results demonstrate for the first time that minocycline can decrease virus expression from the resting CD4+ T cell viral reservoir ex vivo and that the anti-HIV effects of minocycline apply to both laboratory strains (demonstrated above and in [7]) and clinical strains of HIV. The various antiviral activities of minocycline appear to produce a cumulative effect. The drug’s reduction of gene expression after reactivation of latent provirus could synergize with the decreased efficiency of single-cycle replication, creating a barrier to reinitiation of virus replication from latency. The antiviral effects of minocycline are linked to its ability to decrease activation of CD4+ T cells, resulting in decreased permissiveness of CD4+ T cells to HIV infection and decreased reactivation of integrated, latent proviruses. Minocycline-treated cells from HIV-infected individuals had significantly decreased expression of both CD25 and Ki-67, demonstrating minocycline’s suppressive effect on T cell activation and proliferation, respectively (Figure 4B). Interestingly, surface expression of the early activation marker CD69 was not significantly changed by minocycline treatment and visually trended higher. These data demonstrate that minocycline attenuates T cell activation in the context of HIV infection; the fact that CD69 was successfully up-regulated to normal levels indicates
that minocycline does not completely suppress T cell activation, suggesting that the drug target may be downstream of early events in T cell activation.

**Effect of minocycline on activation-induced marker changes and cytokine secretion in CD4+ T cells.** The activation-induced phenotype of minocycline-treated CD4+ T cells was further characterized in CD4+ T cells from healthy, uninfected donors. Cells were pretreated overnight with minocycline, and expression of multiple activation and proliferation markers was evaluated: CD45RA (naive lymphocytes), CD69 (early activation), CD25 (intermediate or late activation), HLA-DR (late activation), chemokine (C-C motif) receptor 5 (CCR5) (activation, HIV coreceptor), Ki-67 (proliferation), and CD71 (early activation). By 2 days after activation, CD25 showed significantly decreased expression in the presence of 10 or 20 µg/mL minocycline, with ∼70% decrease in MFI (Figure 5A). CD71 expression was significantly decreased (by nearly 90%) at all doses of minocycline (Figure 5A). By day 5 after activation, samples treated with 10 or 20 µg/mL minocycline had significantly more CD45RA+ cells than untreated, activated controls and significantly reduced proliferation at all doses, shown by fewer Ki-67+ cells (Figure 5A and 5B). Minocycline treatment also resulted in significantly fewer HLA-DR+ cells at all doses and significantly fewer CCR5+ and CD11a+ cells for 20 µg/mL minocycline (Figure 5A and 5B). Minocycline-treated samples tended to have more CD69+ cells after 5 days of activation, but this difference was significant only at 10 µg/mL (Figure 5A). The up-regulation of CD69 requires both de novo RNA and protein synthesis; its up-regulation in the presence of minocycline indicates that the drug effect is not a global, nonspecific suppression of RNA or protein synthesis [18].

In addition to exhibiting a dramatically altered expression profile as determined by FACS, minocycline-treated CD4+ T cells secreted reduced levels of cytokines, similar to findings reported elsewhere [8, 9]. Minocycline-treated cells activated by anti-CD3/CD28 antibody costimulation secreted much lower amounts of cytokines than untreated, activated controls. Supernatants from minocycline-treated cells 24 h after activation showed significant decreases in interleukin (IL)–2, IFN-γ, and TNF-α secretion (Figure 5C). IL-2 inhibition was consistent with reports by Kloppenburg et al [8, 9]. Minocycline treatment also consistently attenuated activation-induced increases in T cell size in a dose-dependent manner (data not shown).

**DISCUSSION**

The results presented demonstrate that minocycline has significant anti-HIV effects in primary human CD4+ T cells; minocycline treatment reduced single-cycle replication, reactivation from a primary CD4+ T cell–derived model of HIV latency, and viral RNA expression after de novo infection with reference strain HIV NL4–3. These effects acted cumulatively to prevent ex vivo expansion of latent virus from isolated resting CD4+ reservoirs of HIV-infected individuals during HAART. Further phenotyping demonstrated that minocycline has effects on immune activation in primary human CD4+ T cells of healthy and HIV-infected individuals during HAART. These were consistent with previous studies in synovial rheumatoid arthritis–derived T cell clones and healthy peripheral blood mononuclear cells [8, 9, 19]. These observations suggest that minocycline may have its anti-HIV effect by decreasing the impact of multiple pathways involved in HIV infection and immunopathogenesis.

HIV requires T cell activation for efficient replication and reactivation of latent virus. In CD4+ T cells, major transcription factors important in activation (nuclear factor [NF] κB, NF of activated T cells) have been shown to regulate HIV LTR activity [17, 20]. Our data are consistent with the minocycline-mediated attenuation of multiple events downstream of activation...
Minocycline Attenuates HIV Infection in CD4+ T Cells

A

B

Figure 4. Ex vivo reactivation of latent human immunodeficiency virus (HIV) in resting CD4+ T cells from HIV-infected patients with suppressed viremia during highly active antiretroviral therapy. Highly purified resting (>99%) CD4-DR- T cells were pretreated with minocycline (filled diamonds) or not pretreated (open squares). Two replicates were maintained with antiretrovirals in culture (shaded squares and shaded diamonds). Cells were then activated for 7 days with anti-CD3/CD28 antibodies and cultured with minocycline and antiretrovirals. A, Viral RNA isolated from pooled supernatants was quantified using real-time reverse-transcription polymerase chain reaction targeting HIV-1 gag RNA (n = 6) (P values calculated by Wilcoxon matched-pairs test). B, Cells at day 7 after activation were stained with antibodies to CD25 (n = 6), CD69 (n = 4), and Ki-67 (n = 6), and marker expression was analyzed by fluorescence-activated cell sorting. Viability in minocycline-treated cultures remained >80% until day 5. By day 7, viability was typically 60%–80% (relative to untreated control, as shown by Trypan blue staining). Lines represent means (P values calculated by paired t tests).

through CD3 and CD28: decreased cytokine production, decreased changes in expression of multiple surface markers (CD25, CD45RA, CD71, HLA-DR), suppression of proliferation (Ki-67), and cell cycle arrest in G0/G1 (unpublished data). The cytokine IL-2 and its cognate receptor CD25 are critical factors in T cell activation. Minocycline-mediated decreases in CD25 expression could result in IL-2–hyporesponsive cells. This is supported by our data showing that minocycline treatment decreased expression of CD71, an IL-2–dependent marker [21]. Minocycline potentially reduces IL-2 signaling through decreased surface CD25 as well as decreased IL-2 production; this would be beneficial in HIV infection, because IL-2 signaling has been shown elsewhere to directly reactivate latent HIV infection and enhance productive HIV replication through NF-κB. Other cytokines down-regulated by minocycline treatment (TNF-α, IL-1β) also directly enhance NF-κB–mediated HIV expression in CD4+ T cells [22]. These barriers to reactivation could reduce residual viremia in patients receiving HAART, preventing reactivation of latent HIV in CD4+ T cells. Taken together, these observations suggest that minocycline treatment could reduce multiple factors that promote HIV infection and reactivation from latency, stabilizing and enhancing existing HAART regimens.

T cell activation also mobilizes markers to facilitate trafficking of lymphocytes, which ultimately contributes to immunopathogenesis in tissues of HIV-infected patients. Minocycline treatment reduced the expression of many of these surface markers after activation. Decreased expression of CD11a and cytokine receptors CCR5 and CD25 on minocycline-treated cells suggests diminished sensitivity of these cells to interactions with other cells and the immune environment. Cells treated with minocycline also secrete a relative paucity of proinflammatory cytokines (TNF-α and IFN-γ). In HIV infection, this could reduce hyperactivation, slowing the immune exhaustion that is thought to underlie disease progression. Treated cells show decreased proliferation, suggesting that minocycline may be able to reduce T cell turnover (a factor in T cell depletion) and help preserve naive pools of cells, indicated by the retention of CD45RA [23]. A dose-dependent decrease in CCR5+-activated CD4+ T cells suggests that minocycline could reduce the potential for spread of R5-tropic viruses. Studies in sooty mangabeys show that these animals, in which SIV establishes a nonpathogenic infection, have diminished CCR5 expression in CD4+ T cells, compared with pathogenic hosts [24]. In addition to being an HIV coreceptor, CCR5 has been implicated in promoting leukocyte trafficking to the brain and other tissues. Thus, minocycline-mediated reduction in CCR5 expression on CD4+ T cells may shift patients toward a less pathogenic infection. Minocycline-mediated decreases in CD11a would probably impair the formation of the immunological synapse as well as extravasation processes, lessening inflammation and the entry of virus infected-cells into the CNS and other tissues. A study by Giuliani et al [25] showed that minocycline-treated T cells are less efficient in cell-to-cell contact with microglia through decreased CD40/CD40-L interaction. This axis plays a role in many neuroinflammatory diseases and has been shown in vivo to induce HIV gene expression in a transgenic mouse model [26]. These immunomodulatory effects could reduce the damaging immunopathogenesis arising from HIV infection, particularly in tissues such as the brain. In the context of HAART,
Figure 5. Phenotypes of minocycline-treated CD4+ T cells after CD3/CD28 costimulation. CD4+ T cells were pretreated with minocycline or not pretreated, followed by activation with anti-CD3/CD28 antibodies. Fluorescence-activated cell sorting was used to analyze longitudinal expression of CD25, CD71, CD69, and CD11a (mean fluorescence intensity) (A) and Ki-67, CD45RA, HLA-DR, and chemokine (C-C motif) receptor 5 (CCR5) (percentage of positive cells) (B) up to day 5 after activation; values represent means ± standard deviations (SDs) (n ≥ 3 where error bars are shown). C, Cytokines were quantified in cell culture supernatants by multiplex enzyme-linked immunosorbent assay. Secretion of interleukin (IL)–2, interferon (IFN)–γ, and tumor necrosis factor (TNF)–α from minocycline-treated cells is shown, relative to that in untreated, activated controls; values represent means ± SDs (n = 4). P values for comparisons with controls were calculated by paired (A and B) or 1-sample (C) t test; *20 μg/mL, †10 and 20 μg/mL, ‡all doses.
where de novo infection is suppressed, minocycline could provide a beneficial immunomodulatory effect to alleviate the negative effects of hyperactivation and inflammatory processes.

What is the relevance of our findings to clinical applications? The effective dose of minocycline used in our latent virus studies (20 μg/mL) is higher than the range of serum concentrations reported in low-dose minocycline regimens (100 mg/day). However, we observed that minocycline had significant effects on multiple markers of T cell activation at doses of 5–10 μg/mL, levels within the range of reported serum concentrations (<6 μg/mL) [27]. Because of its lipophilicity, minocycline has significant tissue penetration and accumulates in leukocytes, suggesting even higher concentrations in these areas and cells. Most importantly, minocycline treatment was found to be effective in clinical trials for multiple sclerosis, rheumatoid arthritis, and asthma, in which beneficial effects have been linked to minocycline’s capacity as an immunomodulatory agent for T cells [28–30]. These observations, and other findings by our group, strongly suggest that the therapeutic effects of minocycline we observed in vitro should be achievable in vivo [7].

Minocycline has many effects on CD4+ T cells after activation that impair HIV by reducing permissiveness and reactivation from latency. The result is a cumulative effect that prevents viral replication in CD4+ T cells. Minocycline decreases the response of CD4+ T cells to costimulation, blunts secretion of cytokines, and alters surface marker expression. The immunomodulatory and anti-HIV effects of minocycline strongly suggest that it would be effective as a novel maintenance therapy for use with HAART. Minocycline could prevent reseeding of infection from the CD4+ T cell latent reservoir and provide therapeutic immunomodulation by dampening chronic activation and inflammatory processes that contribute to pathogenesis. Owing to the widespread usage of minocycline as both a new therapeutic and a traditional antibiotic, these results have immediate relevance to medical professionals and strongly suggest that minocycline should be further investigated for use as a novel anti-HIV agent.

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References


