Published in final edited form as:

J Acquir Immune Defic Syndr. 2012 May 1; 60(1): 68–71. doi:10.1097/QAI.0b013e31824bed3f.

Equal HIV-1 Decay Kinetics in HSV-2-Infected and -Uninfected Clinical Trial Participants Treated with Antiretroviral Therapy

Jeffrey Thomas Schouten, M.D., J.D. and
Fred Hutchinson Cancer Research Center

Joshua T Schiffer, M.D.
Fred Hutchinson Cancer Research Center

Abstract

Herpes simplex virus-2 (HSV-2) increases HIV-1 viral load and may augment HIV-1 transmission probability. To test the hypothesis that lower HIV-1 clearance rates in HSV-2 infected persons may account for this higher HIV-1 viral load, we studied 149 participants from three ACTG viral dynamic studies (A315, A5160s and A5166s). Though HIV-1 viral load was 0.19 logs higher in HSV-2 positive versus HSV-2 negative persons, first and second phase clearance rates during ART were equal between participants in these two groups.

Keywords

HIV; HSV-2; viral kinetics; viral dynamics

Introduction

The chronic phase of HIV-1 infection is notable for extremely high rates of production and clearance of virus, as well as rapid turnover of infected cells.^{1–4} A viral load steady state that is predictive of time to progression of AIDS and death, is achieved several months after acute infection, and is defined by equal rates of viral production and elimination.⁵ Antiretroviral therapy (ART) regimens perturb this highly dynamic equilibrium by preventing ongoing infection of CD4⁺ lymphocytes and monocytes.⁶ Plasma viremia decreases in a multi-phase process with clearance rates in each phase defined by the death rates of different populations of infected cells.^{1–3, 7}

Herpes simplex virus-2 (HSV-2) co-infection alters HIV-1 kinetics during chronic infection.⁸ Median HIV-1 viral loads are higher in HSV-2 infected persons, and antiviral therapy for HSV-2 infection reduces levels of HIV-1 RNA in plasma and genital compartments by roughly 50%.^{9, 10} These factors were the impetus for a large trial, which revealed that acyclovir therapy for HSV-2 / HIV-1-positive members of HIV-1

Corresponding Author: Jeffrey Thomas Schouten, M.D., J.D. Fred Hutchinson Cancer Research Center, Seattle, WA.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest: Jeffrey Schouten is principle investigator on a research grant from Abbott Labs but receives no salary support. No other conflicts exist.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

serodiscordant couples did not decrease HIV-1 transmission to the HIV-1-negative partner.¹¹ To better understand interactions between these two viruses, we used data from prior HIV viral dynamic studies to compare viral clearance rates in ART-treated HSV-2-positive and -negative persons. We hypothesized that viral decay would differ by 10% between HSV-2 infected and uninfected groups, while patients on prophylactic HSV-2 antiviral medicines would have decay rates that are the same as HSV-2 uninfected persons.

Methods

Study design

We utilized data from 149 total clinical trial enrollees who were previously enrolled in viral dynamic studies in which samples for quantitative HIV-1 RNA were obtained at entry, days 2, 7, and 10, and weeks 2, 4 and 8 after initiating antiretroviral therapy. Subjects were instructed to time their medications and scheduled blood draws precisely to ensure accurate kinetic measures. All subjects signed informed consent to participate in the primary studies as well as viral dynamic sub-studies, which required more frequent sampling. The current study was also reviewed by our local IRB.

Forty-eight participants were from ACTG 315, an open-label study to evaluate the effects of highly active antiretroviral therapy consisting of 10 days of ritonavir escalation, followed by triple therapy with ritonavir, zidovudine and lamivudine (RTV→3TC/ZDV/RTV). Therefore, most first-phase decay samples occurred during low-dose RTV dosing.¹² Sixty-seven participants were from ACTG 5160s, a viral dynamics sub-study of ACTG 5142 which assessed the relative antiretroviral potency of the three treatment arms:¹³ while all participants received two nucleoside reverse transcriptase inhibitors (NRTIs) including either tenofovir, zidovudine or stavudine plus lamivudine (2 NRTIs), 22, 25 and 20 participants received lopinavir (2NRTIs + LPV/r), efavirenz (2NRTIs + EFV) and 2NRTIs + LPV/r/EFV respectively. Thirty-four participants were from ACTG 5166s, a viral dynamics sub-study of ACTG 5095 which compared three protease inhibitor-sparing treatment options for the initial treatment of HIV-1 infection: 16 and 18 participants received 3TC/ZDV/EFV and 3TC/ZDV/EFV plus abacavir (ABC), respectively.¹⁴

Statistical analysis

As previously described, a parametric non-linear mixed-effects model with a bi-exponential form was used to fit to log converted measures of viral load, and to derive estimates of first and second phase viral clearance rates.¹⁴ Due to non-normal distributions of outcomes, Wilcoxon rank-sum tests were used to compare clearance rates, as well as pre-treatment log₁₀ HIV-1 viral load between HSV-2-infected and -uninfected persons, as well between other exposure variables (HSV-1 status, and Hepatitis C serostatus). We used Kruskal-Wallis tests to compare clearance rates between the six different treatment regimens.

Laboratory methods

HSV-2 and HSV-1 serostatus was evaluated with Western blot on stored samples gathered during the three trials as previously described¹⁵. The nucleic acid sequence-based amplification assay (NASBA HIV-1 RNA QT; Organon Teknika, Durham, NC) was used to measure plasma HIV-1 RNA in ACTG 315. The Roche HIV-1 Monitor Assay was used to measure HIV-1 viral load in ACTG 5160s and 5166s.

¹Ritonavir 200 mg orally twice daily for 2 days, 300 mg twice daily for 2 days, 400 mg twice daily for 2 days, 500 mg twice daily for 2 days, and 600 mg twice daily thereafter. Beginning on day 10, zidovudine (200 mg thrice daily) and lamivudine 150 mg (twice daily) was added.

Results

Pre-therapy HIV-1 viral load in HSV-2 infected versus uninfected persons

Four participants had equivocal HSV-2 Western blots, while 64% of subjects were HSV-2 positive. HSV-2 infected and uninfected persons were well matched according to most demographic features, though a higher proportion of infected than uninfected persons were women (Table 1). Only three of 93 participants with HSV-2 infection were taking suppressive doses of famciclovir, valacyclovir or acyclovir. HSV-1 seropositivity was found in 82% and 92% of HSV-2 positive and negative persons, respectively.

Baseline HIV-1 viral load was lower in HSV-2 uninfected versus infected persons: median 4.77 log₁₀ HIV-1 RNA / mL, (IQR 4.41, 5.13) vs. 4.96 log₁₀ HIV-1 RNA / mL, (IQR 4.59, 5.26), $p < 0.05$. There were no statistically significant differences between baseline HIV-1 viral load based on gender, HIV-1 regimen, hepatitis C serostatus or HSV-1 infection. CD4+ lymphocyte count did not significantly differ between HSV-2 infected (median=190, IQR: 82, 278 per mm³) and uninfected (median = 208, IQR: 118, 298 per mm³) persons, or between men and women, at the time of ART initiation.

HIV-1 clearance kinetics

HIV-1 primary phase clearance rate was not statistically different between HSV-2 infected (median= 0.57/day, IQR 0.43–0.67) and uninfected (median= 0.59/day, IQR 0.48–0.70) persons (Figure 1). During primary decay phase, median plasma viral half-life was 1.22 days and 1.17 days in HSV-2 infected and uninfected persons, respectively. HIV-1 primary phase clearance rate was significantly higher in HSV-1 infected (median=0.59/day, IQR 0.49–0.67) and uninfected (median= 0.45/day, IQR 0.34–0.59) persons ($p=0.02$). There were no differences between primary clearance rates according to gender or hepatitis C serostatus.

HIV-1 secondary phase clearance rate was equivalent between HSV-2 infected (median=0.044/day, IQR: 0.034–0.052) and uninfected (median= 0.038/day, IQR 0.023–0.051) persons. During the second clearance phase, plasma viral half-life was 15.8 days and 18.2 days in HSV-2 infected and uninfected persons, respectively. There were also no statistically significant differences between second phase clearance rates according to gender, hepatitis C, or HSV-1 infection.

First and second phase clearance rates differed according to HIV-1 regimen with RTV→3TC/ZDV/RTV leading to slower clearance than other regimens. Median first phase decay rates were 0.49/day, 0.56/day, 0.58/day, 0.6/day, 0.67/day, and 0.67/day for RTV→3TC/ZDV/RTV, 2NRTIs/LPV/r, ABC/3TC/ZDV/EFV, 2NRTIs/LPV/r/EFV, 2NRTIs/EFV, and 3TC/ZDV/EFV respectively ($p=0.0002$). Median second phase decay rates were 0.038/day, 0.038/day, 0.045/day, 0.046/day, 0.048/day, and 0.054/day for RTV→3TC/ZDV/RTV, 2NRTIs/EFV, 2NRTIs/LPV/r/EFV, 2NRTIs/LPV/r, ABC/3TC/ZDV/EFV, and 3TC/ZDV/EFV respectively ($p < 0.01$).

If only the 99/146 total subjects not on RTV→3TC/ZDV/RTV were included in the analysis, then there were no significant differences in first phase or second phase clearance rates between HSV-1 infected and uninfected persons, as HSV-1 positive persons were relatively underrepresented in the RTV→3TC/ZDV/RTV cohort. If only the 99/146 total subjects not on RTV→3TC/ZDV/RTV were analyzed, then there were no significant differences in first phase or second phase clearance rates between HSV-2 infected and uninfected persons, suggesting no effect modification of regimen on HIV-1 clearance rates between HSV-2 positive and negative persons.

Discussion

Our results confirm the finding that HSV-2 co-infection leads to an increase in baseline in HIV-1 viral load.¹¹ We also identified that HSV-2 co-infection had no impact on either first or second phase clearance rates of HIV-1 during chronic therapy. First phase clearance rates of HIV-1 are determined by the half-life of actively infected CD4+ T-cells, which in turn is a function of viral lysis, and perhaps density dependent immune effects against actively infected cells.⁷ The etiology of second phase decay is not completely understood,⁶ but may relate to a longer-lived subset of CD4+ lymphocytes or other infected macrophages which do not experience lytic infection with HIV-1.¹⁶ HSV-2 co-infections appear to have no impact on either of these processes *in vivo*. HSV-1 infection correlated with increased clearance rates of HIV-1 during ART therapy, though this finding probably occurred because there was a lower percentage of HSV-1 infected persons who received what is now understood to be the least effective regimen (RTV monotherapy with dose escalation followed by ZDV/3TC/RTV) included in this study. Few patients were on HSV-2 therapy at the time of ART initiation making it impossible to assess the effect of these therapies on HIV-1 clearance rate.

The synergistic interactions between HSV-2 and HIV-1 are numerous. HIV-1 acquisition,^{17–19} and transmission,²⁰ are increased in the presence of HSV-2 infection, and endemic HSV-2 infection has had a dramatic effect on the prevalence of HIV-1 at the population level.^{19, 21–24} The biology underpinning enhanced HIV-1 acquisition may be related to frequent sub-clinical HSV-2 reactivations in the genital mucosa.^{25–27} HSV-2 infection in keratinocytes leads to frequent recruitment of dense infiltrates of CCR5+ CD4 T-cells in genital mucosa, and these cells serve as optimal targets for HIV-1 entry and replication.²⁸ The dynamic interplay between viral shedding and activated T cell response determines the extent of HSV-2 disease expression.^{29, 30}

During chronic HIV-1 infection, activated T cells are also critical reservoirs for maintenance of HIV-1's dynamic replicating state.^{31, 32} Immune activation may therefore explain why chronic HSV-2 infection up regulates mucosal HIV-1 levels in the genital tract,^{33, 34} correlates with higher HIV-1 plasma viral loads,³⁵ and in turn leads to increased HIV-1 transmission. Viral load steady state in HIV-1-infected patients is determined by total body viral production rate, free viral decay rate and infected cell decay rate.³ Because our results imply that HSV-2 co-infection does not impact clearance rate of actively HIV-1 infected cells, and because there is no obvious hypothesis for why HSV-2 co-infection would slow free viral HIV-1 decay rate in serum, the higher average HIV-1 plasma viral load in co-infected persons is likely to be due to enhanced HIV-1 production during the co-infected state: cell culture experiments demonstrate an increased replication rate of HIV-1 in co-infected cells,³⁶ while another explanation may be that a higher proportion of CD4+ T-cells are activated and thereby HIV-1 infected during HSV-2 co-infection.

Unfortunately, at standard prophylactic doses, acyclovir does not appear to decrease HIV-1 acquisition or transmission rate,^{11, 37} perhaps because it does completely eliminate the HSV-2-associated immune response. A more detailed understanding of the synergistic kinetics of these two viruses may allow for HSV-2-directed therapies that impact the HIV-1 epidemic.

Acknowledgments

The authors would like to acknowledge the contributions of Heather Ribaud (data provision from the viral dynamic studies A315, A5160s and A5166s) and Rhoda Morrow and Anne Cent (Corey Herpes Lab).

Funding: The project described was supported by Award Numbers U01 AI068636, U01 AI68634 and AI069434, and K23 AI087206 from the National Institute of Allergy and Infectious Diseases (NIAID).

References

1. Ho D, Neumann A, Perelson A, Chen W, Leonard J, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995 Jan; 373(6510):123–126. 1995. [PubMed: 7816094]
2. Wei X, Ghosh S, Taylor M, et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*. 1995 Jan; 373(6510):117–122. 1995. [PubMed: 7529365]
3. Perelson A, Neumann A, Markowitz M, Leonard J, Ho D. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science*. 1996 Mar; 271(5255):1582–1586. 1996. [PubMed: 8599114]
4. Markowitz M, Louie M, Hurley A, et al. A novel antiviral intervention results in more accurate assessment of human immunodeficiency virus type 1 replication dynamics and T-cell decay in vivo. *J Virol*. 2003 Apr; 77(8):5037–5038. 2003. [PubMed: 12663814]
5. Mellors J, Muñoz A, Giorgi J, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997 Jun; 126(12):946–954. 1997. [PubMed: 9182471]
6. Spivak AM, Rabi SA, McMahon MA, et al. Dynamic Constraints on the Second Phase Compartment of HIV-Infected Cells. *AIDS Res Hum Retroviruses*. 2011 Jan 15; 27(7):759–761. [PubMed: 21105850]
7. Perelson A, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature*. 1997 May; 387(6629):188–191. 1997. [PubMed: 9144290]
8. Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis*. 2002 Dec 15; 186(12):1718–1725. [PubMed: 12447756]
9. Nagot N, Ouédraogo A, Foulongne V, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med*. 2007 Feb; 356(8):790–799. 2007. [PubMed: 17314338]
10. Zuckerman R, Lucchetti A, Whittington W, et al. Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis*. 2007 Nov; 196(10):1500–1508. 2007. [PubMed: 18008230]
11. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010 Feb 4; 362(5):427–439. [PubMed: 20089951]
12. Wu H, Kuritzkes DR, McCleron DR, et al. Characterization of viral dynamics in human immunodeficiency virus type 1-infected patients treated with combination antiretroviral therapy: relationships to host factors, cellular restoration, and virologic end points. *J Infect Dis*. 1999 Apr; 179(4):799–807. [PubMed: 10068574]
13. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008 May 15; 358(20):2095–2106. [PubMed: 18480202]
14. Kuritzkes D, Ribaud H, Squires K, et al. Plasma HIV-1 RNA dynamics in antiretroviral-naïve subjects receiving either triple-nucleoside or efavirenz-containing regimens: ACTG A5166s. *J Infect Dis*. 2007 Apr; 195(8):1169–1176. 2007. [PubMed: 17357053]
15. Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. *J Clin Microbiol*. 1988 Apr; 26(4):662–667. [PubMed: 2835389]
16. Arfi V, Riviere L, Jarrosson-Wuilleme L, et al. Characterization of the early steps of infection of primary blood monocytes by human immunodeficiency virus type 1. *J Virol*. 2008 Jul; 82(13):6557–6565. [PubMed: 18417568]
17. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis*. 2002 Jan; 185(1):45–52. 2002. [PubMed: 11756980]

18. Freeman E, Weiss H, Glynn J, Cross P, Whitworth J, Hayes R. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*. 2006 Jan; 20(1):73–83. 2006. [PubMed: 16327322]
19. Corey L, Wald A, Celum C, Quinn T. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr*. 2004 Apr; 35(5):435–445. 2004. [PubMed: 15021308]
20. Gray R, Wawer M, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet*. 2001 Apr; 357(9263):1149–1153. 2001. [PubMed: 11323041]
21. Weiss H, Buvé A, Robinson N, et al. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. *AIDS*. 2001 Aug; 15(Suppl 4):S97–S108. 2001. [PubMed: 11686471]
22. Brown E, Wald A, Hughes J, et al. High risk of human immunodeficiency virus in men who have sex with men with herpes simplex virus type 2 in the EXPLORE study. *Am J Epidemiol*. 2006 Oct; 164(8):733–741. 2006. [PubMed: 16896053]
23. Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. *Herpes*. 2004 Apr; 11(Suppl 1):24A–35A. 2004.
24. Freeman E, Orroth K, White R, et al. Proportion of new HIV infections attributable to herpes simplex 2 increases over time: simulations of the changing role of sexually transmitted infections in sub-Saharan African HIV epidemics. *Sex Transm Infect*. 2007 Aug; 83(Suppl 1):i17–i24. 2007. [PubMed: 17405782]
25. Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis*. 2008 Oct 15; 198(8):1141–1149. [PubMed: 18783315]
26. Schiffer JT, Abu-Raddad L, Mark KE, et al. Frequent release of low amounts of herpes simplex virus from neurons: results of a mathematical model. *Sci Transl Med*. 2009 Nov 18; 1(7):7ra16.
27. Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. *J Clin Invest*. 1997 Mar 1; 99(5):1092–1097. [PubMed: 9062368]
28. Zhu J, Hladik F, Woodward A, et al. Persistence of HIV-1 receptor-positive cells after HSV-2 reactivation is a potential mechanism for increased HIV-1 acquisition. *Nat Med*. 2009 Aug; 15(8):886–892. [PubMed: 19648930]
29. Zhu J, Koelle D, Cao J, et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. *J Exp Med*. 2007 Mar; 204(3):595–603. 2007. [PubMed: 17325200]
30. Schiffer JT, Abu-Raddad L, Mark KE, et al. Mucosal host immune response predicts the severity and duration of herpes simplex virus-2 genital tract shedding episodes. *Proc Natl Acad Sci U S A*. 2010 Nov 2; 107(44):18973–18978. [PubMed: 20956313]
31. Giorgi J, Hultin L, McKeating J, 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 Apr; 179(4):859–870. 1999. [PubMed: 10068581]
32. Schindler M, Münch J, Kutsch O, et al. Nef-mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1. *Cell*. 2006 Jun; 125(6):1055–1067. 2006. [PubMed: 16777597]
33. Augenbraun M, Feldman J, Chirgwin K, et al. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med*. 1995 Dec; 123(11):845–847. 1995. [PubMed: 7486467]
34. Schacker T, Ryncarz A, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA*. 1998 Jul; 280(1):61–66. 1998. [PubMed: 9660365]
35. Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis*. 2002 Dec; 186(12):1718–1725. 2002. [PubMed: 12447756]

36. Kucera LS, Leake E, Iyer N, Raben D, Myrvik QN. Human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 2 (HSV-2) can coinfect and simultaneously replicate in the same human CD4+ cell: effect of coinfection on infectious HSV-2 and HIV-1 replication. *AIDS Res Hum Retroviruses*. 1990 May; 6(5):641–647. [PubMed: 1972888]
37. Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008 Jun; 371(9630):2109–2119. [PubMed: 18572080]

Figure 1.
Boxplots of first phase HIV-1 clearance rates in HSV-2 positive and negative persons.

Table 1

Characteristics of trial participants (percentages in parentheses unless otherwise noted).

	HSV-2 (+), 93 (64)	HSV-2 (-), 52 (36)
Sex		
Male	50 (54)	48 (92)
Female	43 (46)	4 (8)
Regimen		
RTV->3TC/ZDV/RTV	28 (30)	20 (38)
2NRTIs/LPV/r	17 (18)	5 (10)
2NRTIs/EFV	15 (16)	9 (17)
2NRTIs/LPV/r/EFV	11 (12)	8 (15)
3TC/ZDV/EFV	11 (12)	4 (8)
ABC/3TC/ZDV/EFV	11 (12)	6 (12)
Median age (Q1, Q3)	41 (34, 47)	37 (32, 45)
HSV-1 seropositive	76/93 (82)	46/50 (92)
Hepatitis C seropositive	11/63 (17)	6/31 (19)
Median log₁₀ HIV-1 viral load (Q1, Q3)^I	4.96 (4.59, 5.26)	4.77 (4.41, 5.13)
Median CD4+ count/mm³ (Q1, Q3)	190 (82, 278)	208 (118, 298)

^I
p<0.05