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Author manuscript

HIV Clin Trials. Author manuscript; available in PMC 2017 August 29.

Published in final edited form as:

HIV Clin Trials. 2013 ; 14(4): 149–159. doi:10.1310/hct1404-149.

Baseline CD4+ T-Cell Counts Predict HBV Viral Kinetics to Adefovir Treatment in Lamivudine-Resistant HBV-Infected Patients with or without HIV Infection

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Abstract

Background—Coinfection with HIV and hepatitis B virus (HBV) substantially alters the course of HBV. Directly acting anti-HBV agents suppress HBV viral levels; however, the kinetics of HBV decline in mono- and coinfecting persons have not been evaluated. We investigated the role of baseline CD4+ T-cell counts as a predictor of HBV response to adefovir (ADV) therapy in chronic HBV with and without HIV coinfection.

Methods—We conducted a double-blind, randomized, placebo-controlled study of HIV-infected (n = 12) and uninfected (n = 5) chronic HBV patients treated with ADV. Five HIV uninfected patients received ADV; the HIV+ patients received ADV or placebo for a total of 48 weeks. At the end of 48 weeks, all patients received open-label ADV for an additional 48 weeks. HBV, HIV viral loads, CD4+ T-cell counts, and safety labs were performed on days 0, 1, 3, 5, 7, 10, 14, and 28 and then every 4 weeks.

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Conflict of interest: None of the authors have any conflicts of interest to report.

Results—Lower HBV slopes were observed among coinfecting compared to monoinfected patients ($P = .027$ at 4 weeks, $P = .019$ at 24 weeks, and $P = .045$ at 48 weeks). Using a mixed model analysis, we found a significant difference between the slopes of the 2 groups at 48 weeks ($P = .045$). Baseline CD4+ T-cell count was the only independent predictor of HBV decline in all patients.

Conclusion—HIV coinfection is associated with slower HBV response to ADV. Baseline CD4+ T-cell count and not IL28B genotype is an independent predictor of HBV decline in all patients, emphasizing the role of immune status on clearance of HBV.

Keywords

CD4; HBV; HIV; viral kinetics

Globally, about 350 million people are living with chronic hepatitis B (CHB), which remains the leading cause of hepatocellular carcinoma and cirrhosis.¹ The population of persons with CHB overlaps significantly with persons infected with human immunodeficiency virus-1 (HIV) due to shared routes of transmission, with an estimate of 2 to 4 million coinfecting people.² Furthermore, although use of antiretroviral therapy (ART) is effective in slowing the progression of HIV, prolonged survival increases the risk of liver-related mortality in persons coinfecting with HIV-1 and HBV.³ Studies have also demonstrated that individuals with HIV-1 who are exposed to HBV have a greater risk of developing chronicity, a lower rate of spontaneous HBsAg and HBeAg seroconversion, a higher level of HBV DNA, and only modest responses to antiviral treatment.⁴ Although nucleoside analogs have been shown to suppress HBV replication in vivo to below the level of detection,⁵ only interferon-alpha (IFN- α) has been associated with the development of HBV-specific protective immunity.^{6,7} The differential treatment responses observed between immunomodulatory (IFN) and directly acting (nucleoside analogs) HBV drugs suggest that an immune-mediated mechanism directed toward HBV antigens is essential for the clearance of HBV and the development of protective immunity. Presently, IFN is the only immune-based therapeutic agent available to treat HBV; however, it is associated with significant adverse events and poor tolerance.⁵ Treatment with nucleoside analogs is well tolerated, but often results in treatment failure, incomplete suppression, and rebound of HBV DNA associated with emergence of resistance. Therefore, determination of the influence of baseline factors on HBV viral decline is an important step toward the development of better management strategies for HBV infection. In this study, we examined the effect of baseline host factors, CD4+ and CD8+ T cell counts, on HBV viral load (VL) decline with treatment with adefovir dipivoxil (ADV) for lamivudine-resistant HBV-infected patients.

METHODS

Patients

Patients who were enrolled in a prospective double-blind randomized control trial were also invited to participate in this substudy. All participants signed informed consent approved by the National Institute of Allergy and Infectious Disease Institutional Review Board, and the Clinical Trial was registered as NCT00023153 at ClinicalTrials.gov. Most participants were

referred from outside clinics and were on lamivudine for more than 3 years. All individuals with HBV infection (mono- or coinfecting with HIV) had documented YMDD mutations upon entry to the study. HBV and HIV VL levels were checked on days 0, 1, 3, 5, 7, 10, 14, and 28 and every 4 weeks thereafter by Bayer bDNA 3.0 assays. T-cell counts (CD4+, CD8+), and safety labs were performed at baseline and every month after initiation of treatment. Trough and peak concentration of ADV (Gilead Sciences) in 15 patients (2 HBV +/HIV+ receiving placebo, 5 HBV+/HIV- receiving ADV, and 8 HBV+/HIV+ receiving ADV) were determined longitudinally in a blinded fashion as previously described.⁸

HBV Genotyping

Serum specimens from each individual patient were used for DNA extraction using a commercially available QIAamp DNA blood mini kit (Qiagen GmbH, Hilden, Germany). HBV DNA was amplified and hybridized with INNO-LiPA HBV DR v2/v3 primers according to the manufacturer's instructions (Innogenetics).

Sequencing

The sequence and mutational analysis was performed using an AB377 sequencer and a BigDye Terminator V3.1 kit (Applied Biosystems, Foster City, CA, USA).

IL28 Genotyping

IL28B genotyping was conducted in a blinded fashion on DNA specimens collected from each individual, using the 5' nuclease assay with allele-specific TaqMan probes (ABI TaqMan allelic discrimination kit and the ABI7900HT Sequence Detection System; Applied Biosystems, Carlsbad, CA, USA) according to the manufacturer's instructions.

Statistical Analysis

This pilot study was carried out to evaluate the kinetics of viral decline (slopes) between the 2 main groups of patients (HBV monoinfected and HIV/HBV coinfecting) with chronic hepatitis B, summarizing each patient's viral decline by a slope over time using the Wilcoxon rank sum test as the primary analysis and a mixed model for supporting analysis. To show that CD4+ T-cell count appears to be most significantly associated with HBV VL decline, we initially fit single line relating slopes to baseline CD4+ T-cell count among coinfecting and monoinfected patients followed by computation of residuals. Finally, Wilcoxon rank sum test was used to determine differences between coinfecting and monoinfected patients in CD4+ T-cell count-adjusted slopes. This nonparametric approach was used as the primary analysis, because it does not require the assumption of a normal distribution for the data, which would have been impossible to verify with such small sample sizes. Nonetheless, parametric methods such as mixed models have greater power than nonparametric methods if their underlying assumptions are correct, and hence they were used as supportive analyses. A Wilcoxon test was used to analyze whether IL28B haplotypes were associated with HBV VL decline at weeks 4, 24, and 48 of treatment with ADV. We also analyzed the early and delayed HBV decay kinetics on ADV as previously described and their relationship with baseline CD4+ T-cell counts.⁹

RESULTS

Baseline Characteristics

Demographic characteristics and baseline laboratory profiles of all patients who participated in this study are shown in Tables 1 and 2. The 2 groups of patients were statistically similar on most baseline characteristics such as age, gender, HBV VL, ALT and AST levels, and liver fibrosis stage, but differed on baseline CD4+ T-cell counts (Table 2). At baseline, all patients were HBeAg positive and HBeAb negative with one exception. All patients had been receiving lamivudine for at least 3 years at the time of enrollment, with confirmed mutations in the YMDD motif of HBV DNA polymerase. All patients continued to receive lamivudine throughout the study. Most patients had HBV genotype A.

HBV monoinfected patients have a faster early HBV VL decline than HIV/HBV coinfecting patients—Although HIV+ individuals were well controlled (HIV-1 RNA levels <50 copies or lower than the limit of detection of commercially available assays), the HBV viral decay was clearly faster in the monoinfected individuals than in the HIV/HBV coinfecting individuals (Figures 1 and 2, respectively). Statistical analyses confirmed that the slope of viral decay was steeper among HBV monoinfected patients when compared to that of coinfecting patients (Figures 1 and 2) over 4 weeks and over 24 weeks ($P = .027$ and $.019$, respectively, by Wilcoxon rank sum test). The comparison of slopes over 48 weeks did not reach statistical significance ($P = .082$). A mixed model that allowed every single patient to have his/her own slope and intercept was used to test whether the monoinfected patients had a different mean slope from the coinfecting patients (Figure 3). This more sophisticated supportive statistical analysis weights people who have fewer data points less than people with more data points. This mixed model analysis revealed a significant difference between the slopes of mono- and coinfecting patients over 48 weeks ($P = .045$). We then augmented the model by allowing quadratic in addition to linear terms, which allows a curve instead of just a line to be fit to the log VL data over time (Figure 3). The results demonstrate that the pattern of HBV decline over time of the coinfecting patients was different than that of the monoinfected patients ($P = .001$, for comparing these 2 patterns using an approximate chi-square test) (Figure 3). Plasma trough and peak concentration of ADV in mono- and coinfecting patients did not differ significantly (Figure 4).

HBV VL decline is dependent on baseline immune status as determined by the CD4+ T-cell counts—Our earlier analysis demonstrated that the rate of viral decay of HBV was different in HBV monoinfected than in HIV/HBV coinfecting individuals, and this difference might be mediated by factors such as baseline CD4+ T-cell count. Baseline CD4+ T-cell count was noted to be higher among HBV monoinfected patients to a significant degree ($P < .05$) by the Mann-Whitney U test. CD4+ T-cell count seems to be an independent predictor of HBV decay in plasma. Baseline CD4+ T-cell count was lower in those patients who had a slower HBV viral decay with ADV therapy, which was independent of ADV plasma levels (Figure 4). Figures 5A–C show individual patient slopes of viral decline by baseline CD4+ T-cell count. The fact that a single line appears to fit data from both groups suggests that the difference in viral decline between monoinfected and coinfecting patients may be caused by differences in baseline CD4+ T-cell count. Supporting

this conclusion is the fact that, although there was a statistically significant difference in HBV VL decline between monoinfected and coinfecting patients (Figure 6A), this difference disappeared once we adjusted for baseline CD4+ T-cell count (Figure 6B). When we investigated whether IL28B genotype influenced HBV viral decline, we observed that there were no statistically significant differences in HBV VL declines at every time point we examined in an univariate analysis (Wilcoxon test, $P = .09$, for week 4). Baseline CD4+ T-cell counts correlated positively with the decline of HBV in all patients ($r = 0.8$, $P < .001$), particularly in coinfecting patients ($r = .65$, $P < .05$) (Figure A1).

DISCUSSION

Our results demonstrate that immunodeficiency associated with HIV, as defined by baseline CD4+ T-cell counts, significantly affects HBV viral response to ADV therapy. The underlying mechanisms responsible for lower HBV viral kinetic responses observed in HIV coinfecting patients are not due to delayed pharmacokinetic responses, but are due to lower baseline CD4+ T-cell counts. The role of baseline CD4+ T-cell count status on HBV viral response to ADV was apparent even among HBV monoinfected patients, where those with higher CD4+ T-cell counts had a better HBV viro-logic response. These data suggest that baseline CD4+ T-cell count is a major determinant in clearance of HBV with non-immune-mediated therapy using nucleoside analogs.

Several studies have shown that the first phase of HBV decline (1–2 weeks) after initiation of therapy (clearance of circulating HBV DNA) and the second phase of decline of HBV DNA (clearance of HBV from infected hepatocytes) have been correlated to long-term viral suppression.¹⁰ In this study, we have demonstrated that high baseline CD4+ T-cell counts are associated with faster HBV decline and lower HBV DNA levels at the end of treatment. More clinically relevant correlations of early HBV viral kinetics would be those with clear end-points, such as HBsAg or HBeAg seroconversion. However, those studies have not yet been performed due to the low rates of seroconversion. Our study demonstrates that early viral kinetics are clinically relevant in predicting long-term HBV DNA suppression in both HBV monoinfected and HIV/HBV coinfecting patients. Indeed, HBV treatment responses to ADV were significantly lower among HIV/HBV coinfecting patients when compared to those observed with HBV monoinfected patients treated with the same dose and duration of ADV during the first 24 weeks. The exact mechanism for this phenomenon is not understood. An impaired immune status may result in increased HBV replication and mutagenesis influencing therapeutic responses to nucleotide analogs. However, in our study, HBV monoinfected patients had higher baseline HBV VL, suggesting that enhanced HBV replication and mutagenesis are unlikely reasons. The higher VL among HBV monoinfected individuals may have been a direct result of selection bias due to the small sample size. However, this has not influenced the study results, which clearly demonstrate that baseline CD4+ T-cell count and not baseline HBV VL is a better predictor of HBV VL decline in response to ADV in this patient population. These results are consistent with recent studies that have shown that HBV clearance rates of HBsAg-positive and HBeAg-positive HIV-infected patients are decreased compared with persons without HIV infection¹¹ and may be related to the degree of immunosuppression. Furthermore, a recent study demonstrated that HIV-infected men had worse responses to long-term suppressive therapy with nucleos(t)ide

analogs, including HBeAg loss in 5 years, compared to the HIV-seronegative men.¹² Our study did not show a statistically significant difference in the liver fibrosis staging or peak and trough concentrations of ADV in plasma between HIV/HBV coinfecting and HBV mono-infected patients, suggesting that these characteristics do not explain the differences in therapeutic responses observed between the 2 groups.

Conceivably, baseline CD4+ T-cell count may represent overall immune status or could more specifically reflect one's ability to mount specific immune responses against HBV. Several studies have suggested that long-term suppression of HBV has resulted in reconstitution of HBV-specific immunity in HBV mono-infected but not coinfecting patients.¹³ In this regard, our observations of a clear association between baseline immune status and response to ADV may also explain the lower rates of HBeAg and HBsAg seroconversion observed in HIV/HBV coinfecting patients. By comparison in this study, IL28B C/C haplotype, which has been identified as a biomarker for response to treatment in HCV-infected patients, was not associated with ADV treatment response in patients with HBV infection. Likewise genotype of HBV (predominantly of A in this study) and preexisting mutations (2 or more in every subject) did not influence the outcome. Future studies are required to address the influence of baseline immune status on reconstitution of HBV immunity and HBeAg and HBsAg seroconversion rates. Our study provides another line of evidence that host immune factors are vital in the clearance of HBV and the development of protective immunity. These results provide yet another rationale for treating HIV/HBV coinfecting patients with ART earlier than those without HBV to ensure better rates of control for HBV.^{14,15}

We confronted several problems caused by small sample sizes in this study. First, it is challenging to verify assumptions used in parametric analyses, which led us to rely primarily on nonparametric methods. Second, the power to detect differences is low (though this issue would have been more relevant had differences not been found). Nonetheless, alternative statistical analyses led to the same conclusion. In addition, it is difficult to say whether differences between mono-infected and coinfecting patients might be explained by other factors, some of which may not have been measured. Although randomized clinical trial data were used, the comparison of interest, mono-infected versus coinfecting, was not randomized. Finally, further evaluation of other immunological parameters as well as the results presented here need to be corroborated in a study with larger sample sizes with clinical endpoints such as HBsAg seroconversion. A recent study reported similar HBV viral dynamics in HIV/HBV coinfecting individuals in response to treatment with either lamivudine or tenofovir or a combination of both.¹⁶ However, there has not been a study that directly compared HBV viral dynamics in HIV/HBV and HBV mono-infected patients simultaneously, which is a major strength of our study.

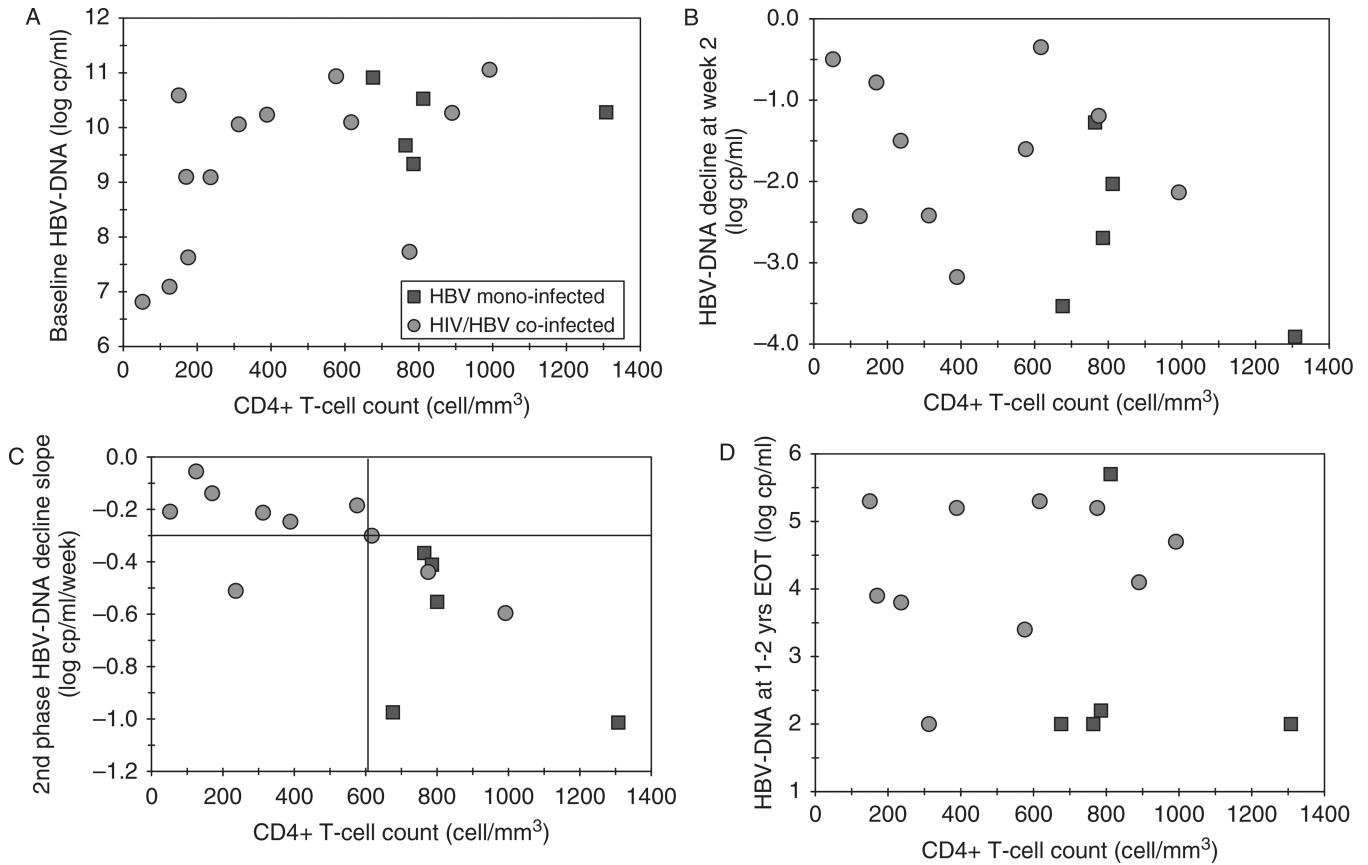
Acknowledgments

Financial support: This research was supported in part by the Intramural Research Program of the NIH (National Institute of Allergy and Infectious Diseases).

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APPENDIX

**Figure A1.**

Correlation between baseline CD4+ T-cell counts and hepatitis B virus (HBV) DNA decline after initiation of ADV treatment. Data from HIV/HBV coinfecting subjects are indicated as *circles* and data from HBV mono-infected subjects are indicated as *squares*. (Panel A) Relationship between baseline HBV DNA levels and baseline CD4 T-cell counts. (Panel B) Relationship between HBV DNA decline (0–2 weeks) after initiation of ADV therapy. The early phase of HBV viral decay (0–2 weeks) was faster in the 5 mono-infected individuals (–1.5 to –4.0 log copies/mL), whereas it was variable among the HIV/HBV co-infected (–0.5 to –3.5 log copies/mL). (Panel C) Relationship between HBV DNA decline (after week 2 to week 4) after initiation of ADV therapy. Baseline CD4+ T cell counts correlated positively with slope decline of HBV in all patients ($r = 0.8$, $P < .001$), particularly in co-infected patients ($r = 0.65$, $P < .05$). Co-infected patients with CD4+ T-cell counts less than 600 cells/mm³ had a much lower HBV viral load decline than those with CD4+ T-cell counts >600 cells/mm³ ($P < .04$). (Panel D) Relationship between baseline CD4 T-cell counts and HBV DNA levels at 96 weeks. HBV DNA levels at 96 weeks after initiation of therapy were lower in the HBV mono-infected subjects. Subjects with higher baseline CD4 T-cell counts had lower HBV DNA levels regardless of HIV serostatus.

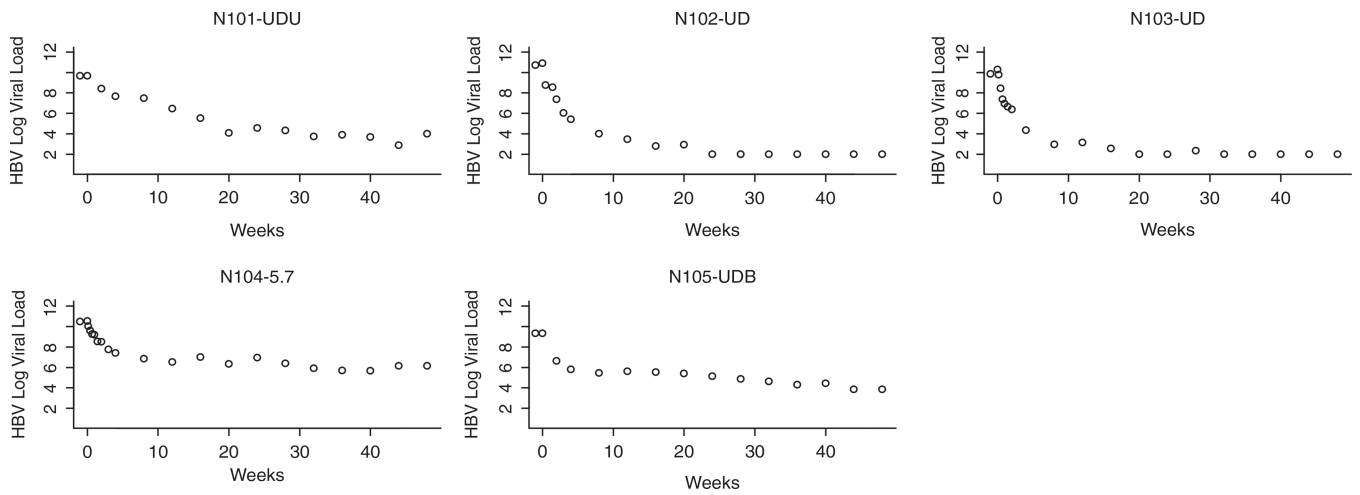


Figure 1. Hepatitis B virus (HBV) viral decay in 5 HIV-/HBV+ individuals. The figure displays HBV viral load versus time in weeks of treatment. Although there is variation in the slope of the decay, most of it occurs in the first 12 weeks of treatment. With exception of subject 5, a step slope can be clearly seen. The numbers above each graph represent the number at randomization.

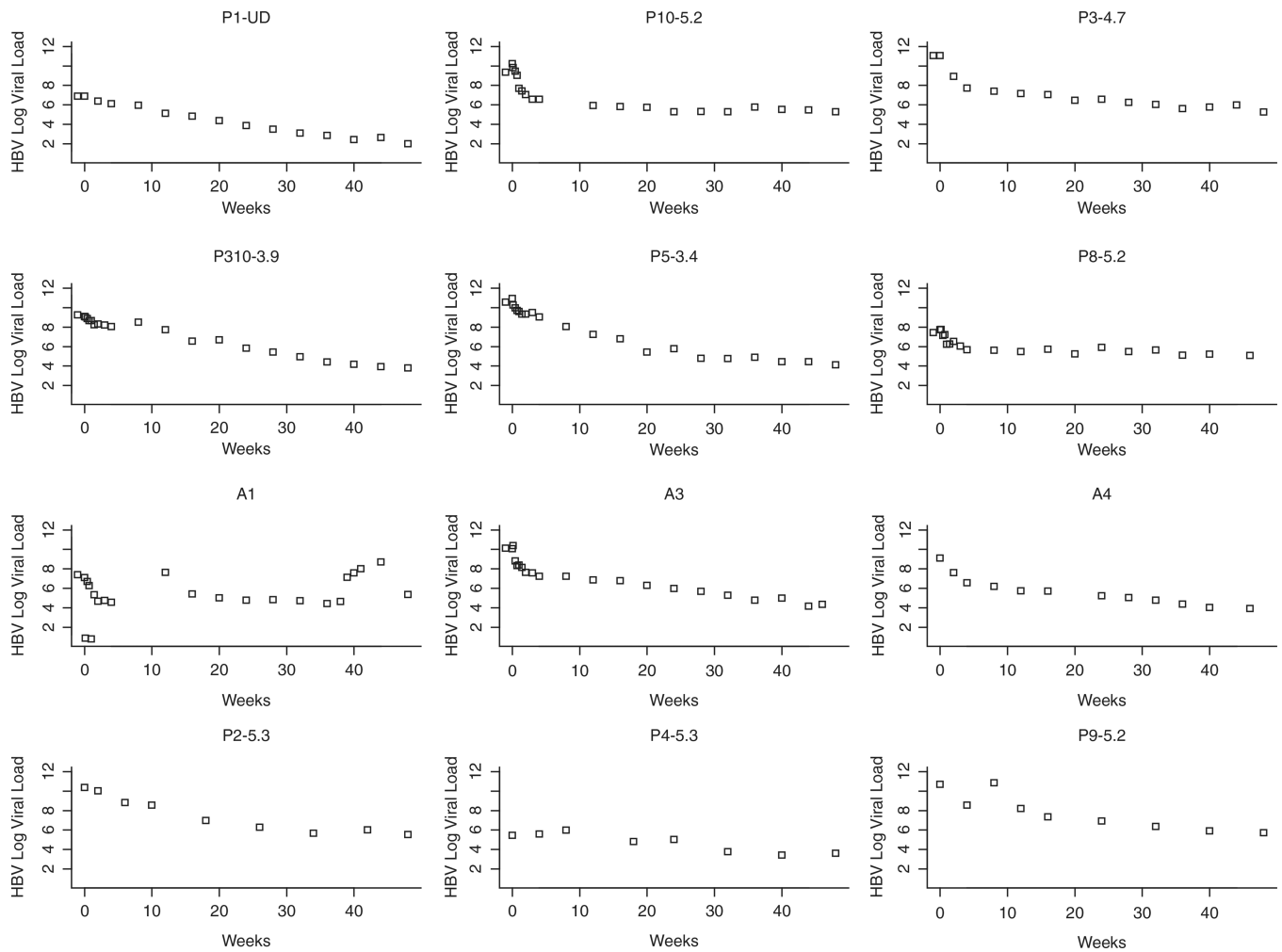


Figure 2. Graphs of the 12 HBV+/HIV+ individuals. Hepatitis B virus (HBV) decay represented by the slope depicts the same trends toward a more rapid/steeper slope in the first 10 to 12 weeks. Subjects 10, 12, 15, and 18 portray similar trends with very linear slope. Subject 2 shows a more erratic trend. The numbers above each graph represent the number at randomization.

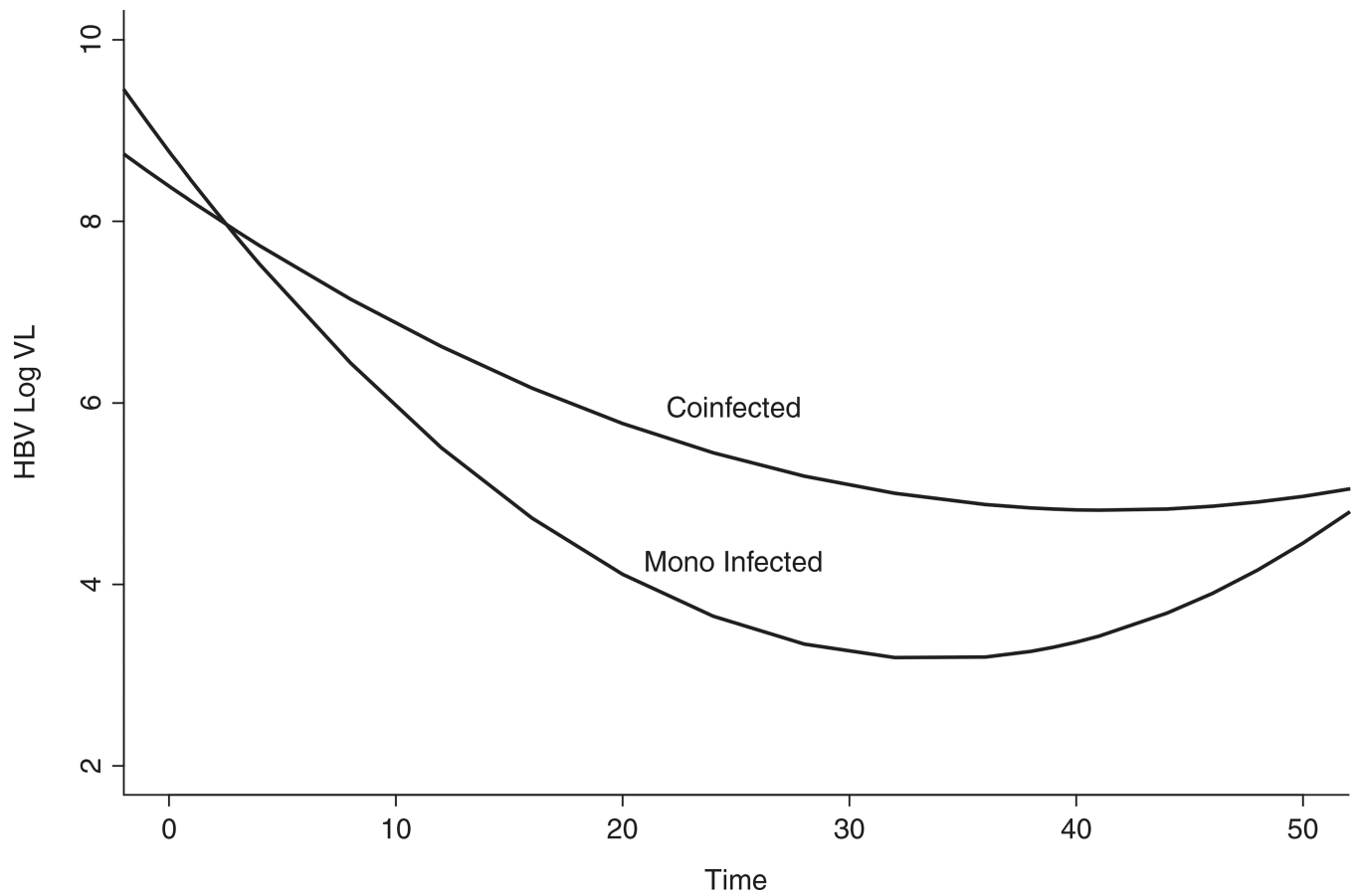


Figure 3. Quadratic and linear terms fit a curve of monoinfected and coinfecting subjects' hepatitis B virus (HBV) decay over time (weeks). The difference between these 2 patterns was statistically significant ($P = .001$, by approximate chi-square test). VL = viral load.

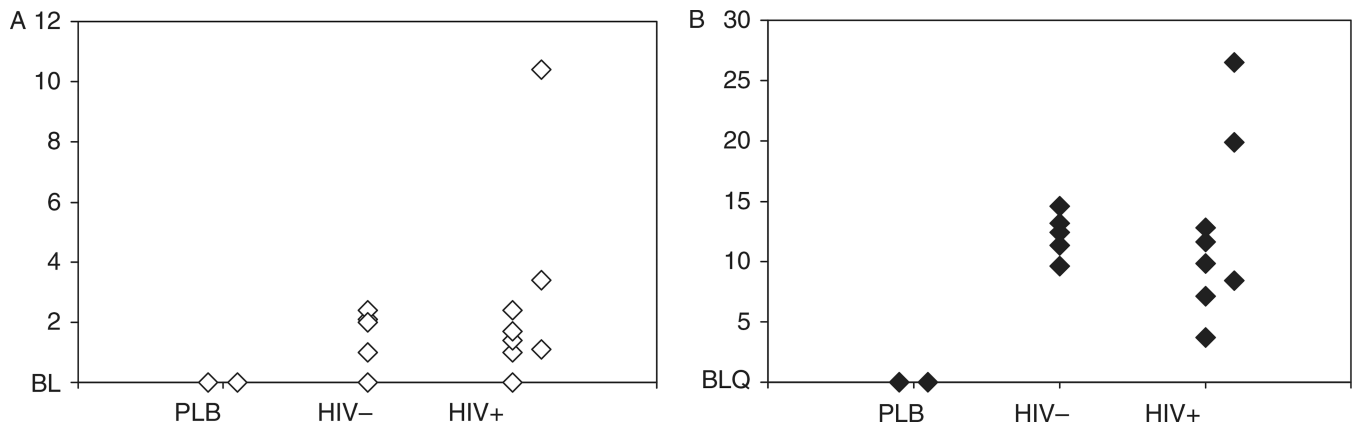


Figure 4. Adefovir pharmacokinetics trough (panel A) and peak (panel B) levels of adefovir in plasma. Peak measured after 1 hour of oral dose. BL = baseline; BLQ = below the level of quantification; PLB = placebo.

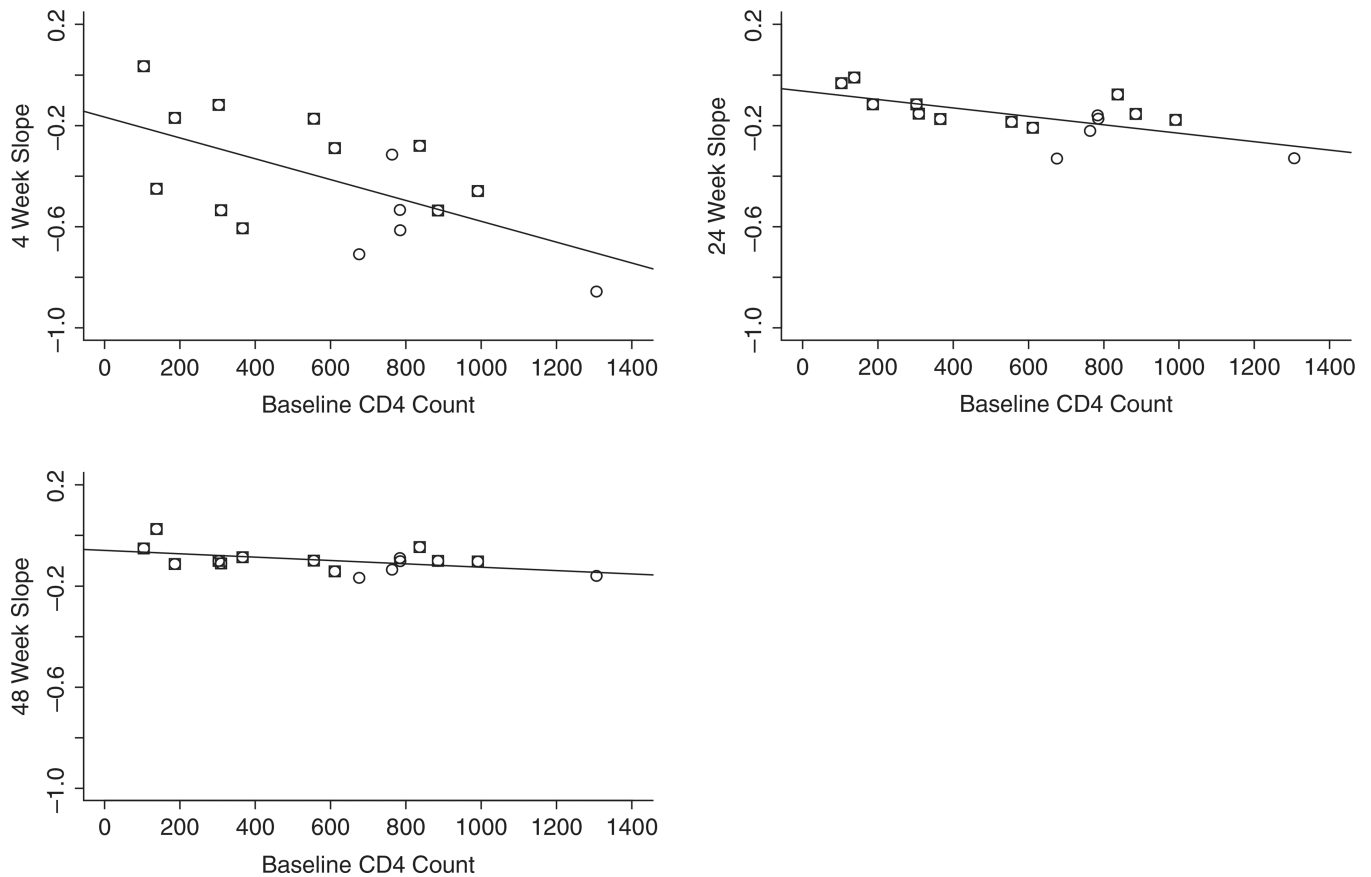


Figure 5.

The circles representing mono-infected patients are at the right of the graphs, indicating high CD4+ T-cell counts. Note that patients with higher CD4+ T cell counts had steeper declines in hepatitis B virus (HBV) viral load ($P = .016$, $.006$, and $.056$, for the relationship between CD4+ T-cell count HBV viral decline slope over 4, 24, and 48 weeks, respectively). The squares represent coinfecting patients.

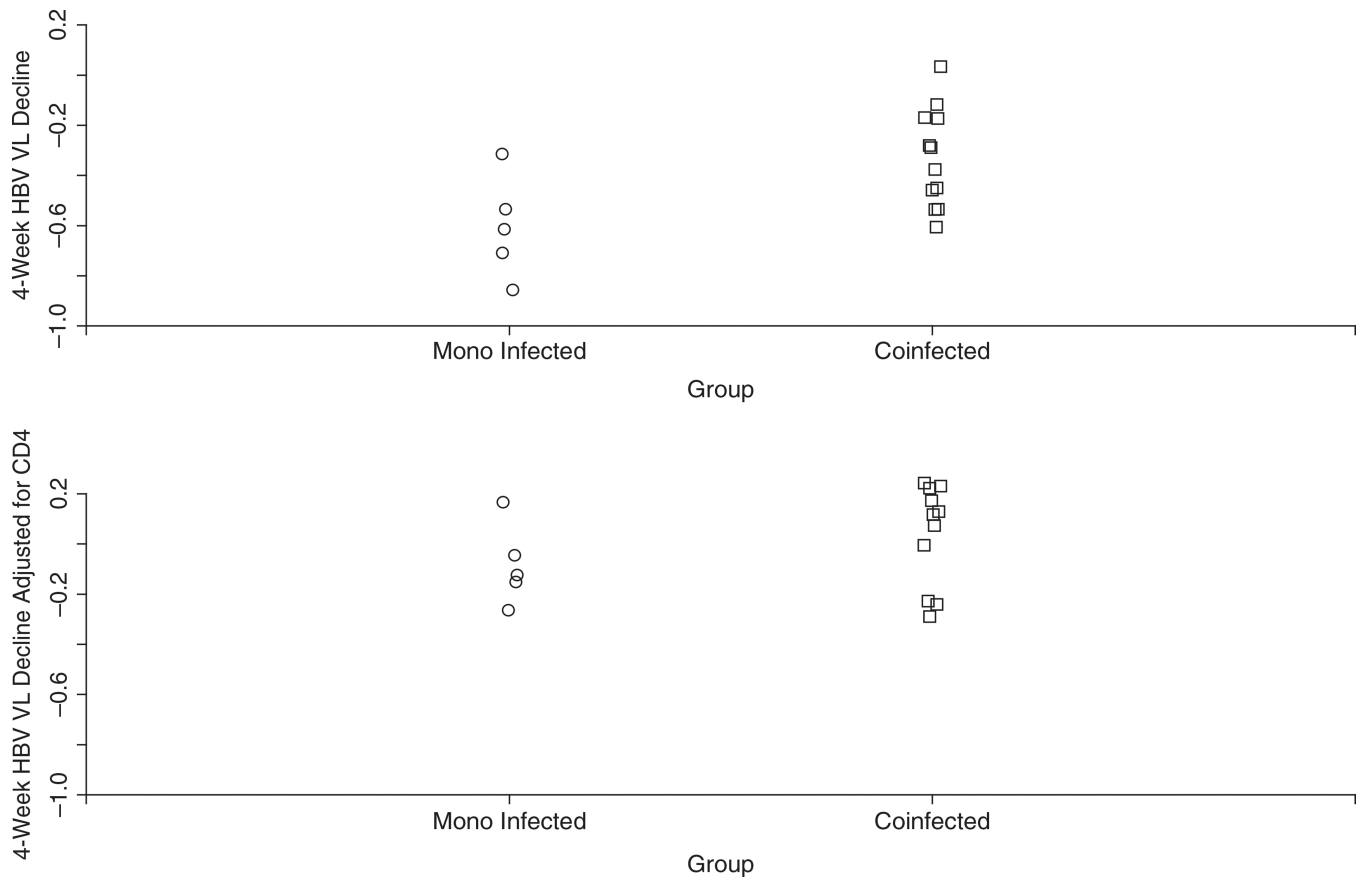


Figure 6. CD4⁺ T-cell count versus hepatitis B virus (HBV) viral decay in plasma of monoinfected (*squares*) and coin-fected (*circles*). The difference in viral decay between monoinfected and coinfecting subjects is largely dependent on CD4⁺ cell counts (top panel), such difference disappears when adjusted by CD4⁺ T-cell counts (bottom panel).

Table 1

Baseline characteristics of the chronic hepatitis B virus (HBV) patients by HIV infection status

	HBV+/HIV-	HBV+/HIV+
No.	5	12
Median age, years (IQR)	40 (36 to 46)	38.5 (36.75 to 47.25)
Gender	Male	Female
Race, n		
Asian	2	0
African American	1	1
Caucasian	2	11
Median CD4+, cells/mm ³ (IQR)	816 (773 to 918)	303 (163 to 576)
Median plasma HBV DNA, copies/mL (IQR)	19E+9 (2.16E+7 to 33.7E+8)	3.88E+7 (53.9E+5 to 26.5E+8)
Median plasma HIV-1 RNA, copies/mL (IQR)	<50	1,148 (445 to 1,189)

Table 2
A. Baseline and 48-week relevant clinical characteristics of 17 patients including hepatitis B virus (HBV) genotype and baseline mutations

Patient	Age	Race	HIV	Baseline CD4, %	HBV VL, copies/mL	HIV VL, copies/mL	Liver fibrosis	HBV genotype	No. of mutations	CODONS present and MT or WT
A1	40	White	(+)	163 (16)	24,200,000	<50	4	A	1	80 WT, 173 WT, 180/181 MT/WT, 236 WT
A3	47	White	(+)	309 (39)	26,500,000,000	347	4	A/G	3	80 WT, 173 MT, 180/181 MT/WT, 204 MT, 236 WT
A4	65	White	(+)	238 (33)	1,240,000,000	1556	4	A/G	3	80 WT+MT, 173 WT, 180/181 WT + MT/WT, 204 MT, 236 WT
N101	40	White	(-)	918(34)	252,000,000	<50	1	A	3	80 WT, 173 WT+MT, 180/181 MT/WT, 204 MT, 236 WT, 184 WT, 194 WT, 202 WT, 250 WT+MT
N102	30	Black	(-)	652 (36)	82,000,000,000	<50	3	A	3	80 WT, 173 MT, 180/181 MT/WT, 204 MT, 236 WT
N103	46	Asian	(-)	1169(37)	19,000,000,000	<50	3	A	3	80 WT+MT, 173 WT, 180/181 WT + MT/WT, 204 WT+MT, 236 WT
N104	17	Asian	(-)	816(40)	33,700,000,000	<50	3	C	2	80 WT+MT, 173 WT, 204 MT, 236 WT
N105	71	White	(-)	773 (38)	2,160,000,000	<50	3	A	2	80 WT, 173 WT, 180/181 MT/WT, 204 MT, 236 WT
P1	35	White	(+)	271 (20)	7,700,000	<50	1	A/G	3	80 WT, 173 MT, 180/181 MT/WT, 204 MT, 236 WT
P10	40	Black	(+)	396 (23)	18,200,000,000	<50	0	A	2	80 WT, 173 WT, 180/181 MT/WT, 204 MT, 236 WT
P2	37	White	(+)	558 (29)	3,880,000,000	<50	3	A	3	80 WT, 173 WT, 180/181 MT/WT, 204 MT, 236 WT
P3	37	White	(+)	979 (25)	114,000,000,000	<50	3	A	3	80 WT, 173 WT+MT, 180/181 MT/WT, 204 MT, 236 WT
P310	48	White	(+)	163 (16)	1,260,000,000	739	4	G	3	80 WT, 173 WT+MT, 180/181 MT/WT, 204 MT, 236 WT
P4	37	White	(+)	87(5)	55,300,000,000	<50	1	A	3	80 WT, 173 WT+MT, 180/181 MT/WT, 204 MT, 236 WT
P5	32	White	(+)	576 (28)	86,800,000,000	1907	3	A	3	80 WT, 173 WT+MT, 180/181 MT/WT, 204 MT, 236 WT
P8	57	White	(+)	775 (28)	53,900,000	152	3	A	2	80 WT, 173 WT, 180/181 MT/WT, 204 MT, 236 WT
P9	36	White	(+)	852 (32)	7,300,000,000	<50	3	A	2	80 WT, 173 WT, 180/181 MT/WT, 204 MT, 236 WT

B. Hepatitis B virus serology status of all patients before and after treatment

Patient	Base line										48 Weeks				
	HBsAg	HBcAg	antiHBc	antiHBs	antiHBc	ALT	AST	HBsAg seroconversion	ALT	AST	HBsAg	HBcAg	anti HBc	antiHBs	antiHBc
N101	(+)	(+)	(-)	(+)	(+)	86	182	No	27	16	(+)	(+)	(-)	(+)	(+)
N102	(+)	(+)	(-)	(-)	(+)	175	374	Yes	35	40	(+)	(-)	(+)	QNS	(+)
N103	(+)	(+)	(-)	(+)	(+)	175	220	No	41	42	(+)	(+)	(-)	Grayzone	(+)
N104	(+)	(+)	(-)	(-)	(+)	36	58	No	37	66	(+)	(+)	(-)	(-)	(+)
N105	(+)	(+)	(-)	(-)	(+)	116	136	No	36	34	(+)	(+)	(-)	(-)	(+)
P1	(+)	(+)	(-)	(-)	(+)	106	255	No	40	53	(+)	(+)	(-)	(-)	(+)

B. Hepatitis B virus serology status of all patients before and after treatment

Patient	Base line										48 Weeks									
	HBsAg	HBsAg	antiHBc	antiHBs	antiHBc	ALT	AST	ALT	AST	HBsAg seroconversion	ALT	AST	HBsAg	HBsAg	anti HBc	antiHBs	antiHBc			
P2	(+)	(+)	(-)	(-)	(+)	94	80	111	55	No	94	80	(+)	(+)	(-)	(-)	(+)			
P3	(+)	(+)	(-)	(-)	(+)	139	270	46	54	No	139	270	(+)	(+)	(-)	(-)	(+)			
P4	(+)	(+)	(-)	(-)	(+)	40	83	49	82	No	40	83	(+)	(+)	(-)	(-)	(+)			
P5	(+)	(+)	(-)	(-)	(-)	134	208	42	49	No	134	208	(+)	(+)	(-)	(-)	(+)			
P8	(+)	(+)	(-)	(-)	(+)	54	49	34	35	No	54	49	(+)	(+)	(-)	(-)	(+)			
P9	(+)	(+)	(-)	(-)	(+)	40	56	45	64	No	40	56	(+)	(+)	(-)	(-)	(+)			
P10	(+)	(+)	(-)	(-)	(-)	54	80	39	48	No	54	80	(+)	(+)	(-)	(-)	(+)			
P310	(+)	(+)	(+)	(-)	(+)	124	131	56	33	No	124	131	(+)	(+)	(-)	(-)	(+)			
A1	(+)	(+)	(-)	(-)	(+)	56	38	34	20	No	56	38	(+)	(+)	(-)	(-)	(+)			
A3	(+)	(+)	(-)	(-)	(+)	71	66	99	85	No	71	66	(+)	(+)	(-)	(-)	(+)			
A4	(+)	(+)	(-)	(-)	(+)	51	28	80	40	Yes	51	28	(+)	(+)	(-)	(-)	(-)			

Note: Subject A2 (patient 18) died 24 weeks into the study. MT = mutations; VL = viral load; WT = wild type.

Note: Grayzone = equivocal results; QNS = quantity not sufficient.