Safety, Tolerability, and Efficacy of KP-1461 as Monotherapy for 124 Days in Antiretroviral-Experienced, HIV Type 1-Infected Subjects

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Abstract

Treatment of HIV infection with conventional antiretroviral therapy (ART) is a lifelong challenge with significant long-term risks of adverse events and treatment failure-induced HIV resistance being major concerns. One potential alternative to standard treatment is the use of viral decay accelerators, antiviral agents that theoretically can drive the rate of viral mutation beyond the compensatory capacity of the virus, thereby inducing viral extinction. One such drug, KP-1461, was tested in a population of HIV-infected persons not receiving ART to assess the safety, tolerability, and efficacy of the strategy *in vivo*. Of 24 highly treatment-experienced HIV-infected patients who received at least one dose of KP-1461, 13 completed the planned 4 months of monotherapy. The drug was generally well tolerated; it did not significantly affect either HIV viral load or CD4 lymphocyte count over the period of dosing. Pharmacokinetic sampling suggested adequate drug exposure was achieved. There were no new mutations induced by KP-1461 that changed viral susceptibility to standard antiretroviral agents. After the study was completed, analysis of more than 7 million base pairs of HIV samples from study patients and controls demonstrated changes in the pattern of viral mutations that differed significantly from what would be encountered naturally. The identified alterations were consistent with an effect resulting from KP-1461's proposed mechanism of action. These findings suggest that the novel antiretroviral approach illustrated by this study should be further investigated, particularly given the relatively good tolerability and the demonstrated excellent safety in this limited cohort study.

Introduction

THE DEVELOPMENT AND WIDESPREAD introduction of combination antiretroviral therapy (ART) into clinical practice have transformed HIV infection from a relentlessly progressive disease with high mortality into a chronic manageable medical condition with a generally favorable outcome.^{1–5}

While the benefits of contemporary ART approaches are quite apparent, treating HIV-infected patients remains a challenge for which improved therapeutic strategies are needed. Currently available antiretroviral drugs work by inhi-

bition of a single viral enzyme function or by blocking a specific receptor site used by the virus. These inhibitory therapeutic strategies may select for viral resistance, sometimes accompanied by cross-resistance to other drugs, potentially leading to loss of activity within an entire antiretroviral class. Resistance to antiretroviral agents is facilitated by the high levels of viral replication and the high rates of viral mutation that are characteristic of HIV infection.^{6,7} This current paradigm of therapy requires medication to be continuously present, necessitating administration of ART for life since latently infected cells are not significantly affected by current treatment strategies.⁸

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In an attempt to exploit the intrinsically high mutation rate of HIV, a novel approach to ART using an agent that amplifies the error rate of base incorporation occurring during HIV transcription is being investigated. Previous work has shown that viruses like HIV can sustain only a certain level of viral mutation before exceeding their viability threshold, experiencing loss of virological integrity, and being eliminated.⁹ While this concept has been studied *in vitro* in HIV and other viruses, it has not been evaluated *in vivo*.⁹⁻¹³ This strategy, termed viral decay acceleration (VDA), was studied in a cohort of 24 HIV-infected persons with multiclass antiretroviral drug resistance using the drug KP-1461, administered as monotherapy, in a safety and mechanism validation study.

Materials and Methods

KP-1461-201 was a Phase 2a, open-label, single-arm, multicenter, mechanism validation study designed to evaluate the safety, tolerability, and efficacy of KP-1461 as monotherapy in antiretroviral-experienced, HIV-1-infected subjects. The primary endpoint was the safety and tolerability of KP-1461 administered for 124 days to HIV-infected persons not concurrently receiving ART. The secondary endpoint was to determine the virologic and immunologic efficacy of KP-1461 in this population. Eligible subjects had received prior non-suppressive ART and/or had documented HIV resistance to multiple ART classes, including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Participants were required to be off all ART for ≥ 16 weeks prior to screening. The screening phase required at least two visits occurring within 42 days prior to the baseline visit. Exclusion criteria included recent opportunistic infection, pregnancy/breastfeeding, significant baseline laboratory abnormalities, active hepatitis B infection, or the need for treatment of hepatitis C infection (HCV) during the study (note that HCV infection alone was not an exclusionary criterion). After informed consent was obtained, study subjects completed the first screening visit including safety laboratory testing, HIV RNA measurement, and CD4 lymphocyte assays. Study eligibility required participants to have a stable CD4 count > 250 cells/ml off ART at screening. Those persons without a prescreening visit CD4 count measured off ART within the previous 6 months underwent an additional screening CD4 assay after ≥ 21 days following the initial screen to establish the pretreatment baseline value.

All subjects underwent a second screening visit to complete data used to ascertain baseline parameters (mean of two visits used). The pretreatment CD4 count was assessed using historical data for a period of 5 months (155 days) prior to the baseline visit. All CD4 counts measured during this period were averaged and the mean value was calculated as the pretreatment CD4 count prior to the baseline measure.

The treatment phase commenced at the baseline (BL) visit (< 42 days from first screening visit). Qualified participants were instructed to take a 1600 mg oral dose of KP-1461 twice daily on an empty stomach and were reevaluated at days 8, 15, 29, 43, 57, 71, 85, 99, 113, and 125 (end of treatment). Adherence was assessed at each visit by pill count and interview. All subjects taking at least one dose of study medication had posttreatment evaluations done 7 and 30 days after the last dose of KP-1461 was taken.

Persons who initiated conventional ART between post-treatment days 8 and 30 were asked to return 30 and 60 days after starting this regimen in order to assess for potential new ART resistance that might be attributable to KP-1461. HIV RNA measurements (Roche Amplicor HIV-1 Monitor Test with a lower limit of detection of 50 copies/ml, Covance Laboratories, Indianapolis, IN) were done at BL, day 15, and at all subsequent treatment phase visits as well as at the 30-day posttreatment visit and 30 and 60 days after study drug discontinuation in those who reinitiated ART after the study conclusion. CD4 counts were measured by flow cytometry at BL, days 29, 57, 71, 85, 99, 113, 125, and at the 30-day post-treatment visit as well as at days 30 and 60 post-ART reinitiation, as applicable. If during the course of KP-1461 treatment, the CD4 count fell below 200 cells/ml, confirmed by a second sample obtained 2 weeks later, study subjects were considered to have met a study endpoint and KP-1461 was discontinued. These persons were referred back to their clinicians for further management.

The mean change from baseline in viral load at study day 125 was compared to a reference reduction in HIV RNA of 0.3 log₁₀ copies considered to represent a minimum true treatment effect. This degree of viral load change was felt to represent the least change that could be ascribed to treatment effect since natural viral variation and the reproducibility of the viral load assay may range as great as 0.3 log₁₀ copies.

Blood samples for reverse transcriptase activity (The Reverse Transcriptase Assay, colorimetric, Roche Diagnostics Corporation, Indianapolis, IN) were collected at BL and at all subsequent treatment phase visits. Blood samples for genotype and phenotype HIV resistance testing (PhenoSense GT, Monogram Biosciences, South San Francisco, CA) were collected during screening, at BL, and at study days 57, 85, and 125. Resistance testing was also done at posttreatment day 30 and at the day 30 and 60 follow-up visits in those who initiated ART.

Safety parameters were assessed by history and physical examination and by measurement of hematologic and chemistry profiles at every visit. Adverse event severity was graded in accordance with the standards established by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS scale).

In previous *in vitro* work, KP-1212 was shown to induce HIV viral ablation at concentrations of 0.4-4 ng/ml. To determine if appropriate drug concentrations were achieved in this study, a planned sparse sampling methodology was changed to an average trough concentration measure (WinNonLin 4.1, PharSight Corporation, Mountain Oaks, CA) due to limited sampling. Predose concentrations of parent compound KP-1461 and active moiety KP-1212 were measured using a validated LC-MS/MS process (Tandem Labs, Salt Lake City, UT) on study days 7, 14, 28, 56, and 112.

The study was conducted in accordance with the clinical research guidelines defined in the U.S. 21 CFR Parts 50, 56, the principles enunciated in the World Assembly Declaration of Helsinki and its most recent amendments, and the principles defined by the International Conference on Harmonization. The study was approved by the investigational review boards (IRB) of each participating institution and listed publicly at www.clinicaltrials.gov (NCT00129294). The study was conducted between July 2007 and July 2008.

Results

Twenty-seven persons enrolled in the trial, 24 of whom received at least one dose of KP-1461. Most study participants were male [20/24 (83.3%)], white [15/24 (62.5%)], and had long-standing HIV infection with a mean time since HIV diagnosis of 15 years. The median age was 47.5 years (range 34–63 years) and the median pretreatment CD4 cell count (as defined above) was 429 cells/ μ l (20%) with a range of 252 to 834 cells/ μ l (13–32%). At the baseline visit (just prior to KP-1461 dosing), the median CD4 count for the 23 treated patients with available counts was 299 cells/ μ l (20%) with a range of 133 to 469 cells/ μ l (11–32%), and the median viral load was 68,450 copies/ml with a range of 6,030 to 750,000 copies/ml. Patients had been treated with a variety of antiretroviral agents prior to study entry (Table 1); none had previously been diagnosed with an opportunistic infection.

Subject disposition is shown in Table 2. The full 124 day course of KP-1461 was completed by 13/24 (54.2%) study subjects. Two deaths occurred during the course of the study but neither was considered to be related to the study drug (one due to arteriosclerotic cardiovascular disease on day 15 of treatment and the other to multiple trauma secondary to a motor vehicle accident on day 57 of treatment).

Adverse events

The majority of study subjects (23/24) reported at least one adverse event (AE) during the dosing period (in decreasing frequency reported): gastrointestinal disorders (12 subjects, 50%), infections/infestations (11 subjects, 46%), nervous system disorders (9 subjects, 38%), respiratory disorders (8 subjects, 33%), and skin disorders (7 subjects, 29%). The most commonly reported AEs were upper respiratory tract infection in five subjects (21%), sinusitis, headache, and pharyngolaryngeal pain, each reported in four subjects (17%), and nausea, fatigue, and dizziness, each reported in three subjects (13%). The majority of AEs were mild to moderate (DAIDS grades 1–2) in severity. There were six AEs of grade 3 or 4,

TABLE 2. STUDY SUBJECT DISPOSITION

only one of which (nausea) was considered to be probably related to the study drug.

Study site investigators assessed the potential relationship of AEs to study drug, and based on these judgments, 12/24 subjects (50%) experienced at least one AE considered to be possibly related to the study drug. The most frequently reported study drug-related AEs were gastrointestinal disorders [10 subjects (42%) with nausea being most common—3/24 (12.5%)] followed by nervous system disorders [five subjects (21%), dizziness (2), and dysgeusia (2)]. No other study drug-related AE occurred in more than one patient. Two patients discontinued treatment due to adverse events, one for headache and nausea and one due to esophagitis.

There were no consistent laboratory abnormalities observed in the study population, either in frequency or in trends over time. Three study subjects experienced grade 3 laboratory changes [two elevations in creatine kinase (CK) and one increased alanine aminotransferase/aspartate aminotransferase (ALT/AST)]. There were no grade 4 laboratory abnormalities. The CK abnormalities were episodic and were not consistently present in either patient. The ALT/AST elevation occurred in a study subject whose baseline ALT was mildly abnormal (grade 1). It increased to a grade 2 level on study day 85 and to grade 3 on study day 113 and remained grade 3 thereafter. The AST was normal at baseline and increased to grade 1 at study day 29 and to grade 2 on day 113. AST briefly reached grade 3 1 week after finishing the study and subsequently declined to grade 2. This patient (negative for hepatitis B at screening, hepatitis C not done at screening and not part of the past medical history reported at screening) had no liver-related symptoms during the study.

Antiretroviral drug resistance

Because the proposed mechanism of action of KP-1461 is to accelerate the rate of mutation within the HIV genome, it is critical to determine if administration of the drug is associated with increased levels of resistance to currently available

TABLE 1. PRIOR ANTIRETROVIRAL THERAPY

Drug class	Medication	N = 24
NRTI	Lamivudine (3TC)	7 (29.2%)
	Stavudine (d4T)	1 (4.2%)
	Tenofovir (TDF)	15 (62.5%)
	Abacavir (ABC)	6 (25%)
	Didanosine (DDI)	6 (25%)
	Emtricitabine (FTC)	8 (33.3%)
	Zidovudine (ZDV)	5 (20.8%)
NNRTI	Efavirenz (EFV)	4 (16.7%)
	Etravirine (ETV)	1 (4.2%)
	Nevirapine (NPV)	2 (8.3%)
PI	Atazanavir (ATV)	9 (37.5%)
	Fosamprenavir (FOS-APV)	3 (12.5%)
	Nelfinavir (NFV)	1 (4.2%)
	Darunavir (DRV)	1 (4.2%)
	Saquinavir (SQV)	1 (4.2%)
	Lopinavir (LPV)	4 (16.7%)
	Ritonavir (RTV)	15 (62.5%)
Entry inhibitors	Enfuvirtide (T-20)	1 (4.2%)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

antiretroviral drugs. To determine if this was an issue, resistance data were collected prior to initiation of KP-1461 and at three intervals during the treatment period. All but one of the 24 participants who received at least one dose of KP-1461 had pretreatment genotype/phenotype antiretroviral resistance data. At baseline, there were numerous mutations in reverse transcriptase and protease indicative of prior treatment failure while on multiple antiretroviral agents. Similarly, decreased phenotypic susceptibility to multiple ART agents at baseline was common and consistent with the histories of the study participants.

To identify changes in the patterns of antiretroviral resistance during the study, the resistance tests done during the trial were examined for meaningful changes in genotypic and phenotypic resistance. Review of the individual patient resistance tests showed no patterns suggestive of evolution of significant antiretroviral drug resistance over time that could be construed as a consequence of drug pressure. Most changes appeared to occur randomly and appeared to represent shifts in prevalent virus populations sampled at differing time intervals. The number of new mutations occurring during the first 8 weeks of treatment was greater than the number observed between week 8 and the end of the study, but there was no corresponding difference in CD4 lymphocyte numbers or levels of viral replication related to the different mutation rates. Examination of the phenotypic resistance tests done before, during, and after treatment with KP-1461 revealed changes in drug susceptibility in 15/23 (65%) study subjects, involving drugs from all three major classes of antiretroviral therapy available at the time the trial was conducted (NRTIs, NNRTIs, and PIs). Most changes were transient and those that persisted were all increases in drug susceptibility. No instances of decreased susceptibility to any antiretroviral agent were observed during KP-1461 dosing or following completion of the treatment period.

Nine study participants initiated ART at intervals ranging from 8 to 30 days after discontinuation of KP-1461. All experienced a decline in HIV RNA greater than 2 log₁₀ copies on the regimen prescribed.

Treatment outcome

Because this was not intended to be a true efficacy study, no placebo arm was included. To explore outcomes for evidence of a possible treatment effect, the subset of 13 persons who completed the full 124 days of treatment was assessed. Change in HIV RNA and CD4 cell count were determined between baseline and the last dose of study drug for both groups. In addition, a variety of parameters including reverse transcriptase activity and viral sequencing were examined in the 13 study completers.

There was a small nonsignificant decrease in HIV RNA over the dosing period in the 13 study completers with a median decline in HIV RNA of 20,700 copies RNA/ml plasma. During the treatment period, CD4 lymphocyte numbers decreased slightly with a median loss of 40 cells/mm³ among the 13 study completers (Table 3). In general, it appeared that over the 124-day period of treatment, KP-1461 showed neither significant beneficial nor detrimental effects on HIV RNA or on CD4 lymphocyte counts. Measures of reverse transcriptase activity (not shown) and viral resistance phenotype (see previous section) were not affected by KP-1461 treatment.

TABLE 3. VIROLOGIC AND IMMUNOLOGIC OUTCOMES

<i>Patients</i>	<i>Δ log₁₀ RNA (per ml)</i>	<i>Δ CD4 cells (per μl)</i>
Completers from baseline to end of treatment		
Patient 1	-0.26	-40
Patient 2	0.19	-104
Patient 3	-0.3	-129
Patient 5	-0.31	-142
Patient 6	0.49	106
Patient 7	-0.07	-131
Patient 8	-0.36	-32
Patient 10	-0.2	27
Patient 13	-0.76	68
Patient 17	-0.19	-3
Patient 20	-0.27	-168
Patient 21	0.08	-106
Patient 22	-0.41	-5
Discontinued patients from baseline to last dose		
Patient 9	0.38	36
Patient 11	0.01	19
Patient 12	-0.24	-128
Patient 14	0.18	ND
Patient 16	0.28	-53
Patient 18	-0.76	-86
Patient 19	-0.04	ND
Patient 24	0.4	-51
Patient 25	-0.15	-47
Patient 26	0.17	-36
Patient 27 ^a	-1.39	-32

^aPatient 27's viral load was stable (4.36±0.1) before and during treatment, except for a spike of 1.4 log₁₀ copies per ml at baseline. ND, not determined.

Pharmacokinetics

Trough concentrations obtained during the study did not show an accumulation of KP-1461 or its primary metabolite over time. During the study a total of 97 predose (trough) samples were obtained at a time 11.85±0.02 h (mean±95% CI) following the previous dose. Steady-state concentrations were achieved by day 7 and the previously reported KP-1461 half-life of 1.5 h was confirmed. KP-1461 troughs ranged from 89 to 134 ng/ml, while KP-1212 troughs ranged from 34 to 55 ng/ml (Fig. 1). Although a dose-effect relationship was unable to be determined, concentrations measured were considered to be comparable to those previously published.¹⁴

Discussion

The primary endpoint of this study was achieved, demonstrating safety and tolerability of twice daily dosing of 1600 mg of KP-1461 administered for 124 days. These results confirmed the phase I findings.¹⁴ Recruitment for this study was challenging given the requirement that study participants be both antiretroviral treatment experienced and not currently receiving ART. A wide variety of reasons were given as to why participants were not on ART at the time of enrollment. Many described previous widespread intolerance to all available antiretroviral agents as a rationale for not being on ART. Thus, the enrolled population was a group for whom medication tolerability was generally poor. In addition, the study participants entered the trial with

FIG. 1. Arithmetic mean with standard deviation of KP-1461 and KP-1212 trough concentrations from days 7 to 112.

considerable accumulated resistance to the available classes of ART.

Given the significant challenges to adherence and tolerability that were clearly present in this study population, the outcomes data overall are relatively favorable. Only two participants discontinued treatment for adverse events that may have been related to the study drug. Gastrointestinal side effects were the most commonly observed adverse events considered potentially associated with the study drug.

In contrast to other approved HIV treatments, KP-1461 is designed to be incorporated into the HIV viral genome, generating mutations that propagate throughout the viral population and ultimately exceed the capacity of the virus to compensate for the changes incurred. Intuitively, acceleration of the pace of HIV evolution/mutation seems to be an undesirable objective, particularly if it involves mutations in portions of the genome that encode the enzymes that serve as antiretroviral targets. Theoretically, this accelerated mutation rate could increase antiretroviral drug resistance, perhaps creating an increasingly resistant virus and therefore diminishing future therapeutic options.^{9–11} Given this potential concern regarding KP-1461 as the first-in-class VDA agent, it was essential to understand what, if any, antiretroviral drug resistance changes might be identified during the course of KP-1461 dosing.

Importantly, there was no evidence that the administration of KP-1461 increased antiretroviral drug resistance. The few cases in which changes in resistance were identified appeared to occur randomly and without a consistent pattern, generally reverting to baseline over time. Thus, safety as related to antiretroviral resistance was established, and concerns that KP-1461, designed to intentionally increase the HIV mutation rate, might worsen antiretroviral resistance patterns by accelerating resistance at critical ART target sites, were not validated. Nonetheless, continued vigilance is required with further development of KP-1461.

This study did not, however, provide virologic evidence for a “proof-of-mechanism” for the concept for viral decay accelerators as a therapeutic option (a secondary objective of the study). No significant antiretroviral activity was observed.

In this study, 13 HIV-1-infected, antiretroviral treatment-experienced patients received KP-1461 for 4 months as monotherapy, a time limit imposed by the FDA because long-term safety data in animal models were not available at the time of the IND filing. The proposed mechanism of action of KP-1461 as a viral decay accelerator suggests its action occurs in two stages of variable duration depending on the fitness of the viral population being treated. The first stage consists of increasing the rate and therefore the numbers of mutations occurring during replication. The second stage occurs when the accumulated mutations exceed the error threshold of the virus, resulting in diminishing rates of viral replication as demonstrated by reduced HIV RNA viral load. The limited duration of dosing in this study may have precluded demonstration of the second phase of the VDA mechanism of action. Importantly, though, treatment with KP-1461 was not associated with any significant adverse events and had no discernible harmful effect on HIV replication or on antiretroviral resistance—thus it fulfilled the precept of “first, do no harm.”

Despite the lack of measurable clinical effect in this trial, additional analysis suggests that significant benefit may be achievable with more prolonged dosing. A comprehensive examination of the evolution of HIV populations in study participants in this trial strongly suggests that the first phase of the VDA mechanism of action was well underway.¹⁵ By means of an extensive analysis of viral sequences involving more than 7 million base pairs from the first 10 subjects to complete treatment in this trial and 10 control patients, evidence of an alteration in the mutation spectrum of HIV was identified. Mutations referred to as “private mutations” (those occurring in recent rounds of viral replication) revealed changes consistent with the proposed mechanism of action of KP-1461. These findings suggest that the novel antiretroviral approach illustrated by this study should be further investigated, particularly given the relatively good tolerability and the demonstrated excellent safety in this limited cohort study.

Conclusions

Administration of the novel investigational agent KP-1461 for 4 months as monotherapy in a population of highly antiretroviral treatment-experienced HIV-infected patients with resistance to multiple antiretroviral agents resulted in no demonstrable effect on HIV viral load or CD4 lymphocyte counts. The drug was safe and generally well tolerated and, importantly, did not lead to the accumulation of any significant new resistance mutations. The unique proposed mechanism of action of the drug, acting to amplify the naturally high error rate of base incorporation occurring during HIV transcription, was intended to exceed the compensatory capacity of the virus, ultimately leading to viral extinction. While a clinical effect was not seen in the study, additional work suggests the mechanism of action was in fact being achieved and that the concept of treating HIV-infected patients with a “viral decay accelerator” remains worth exploring, likely with an improved drug formulation. Additional studies are being considered for subsequent drug development.

If the promise of this drug is borne out in future studies, it would represent a major advance in the management of

HIV-infected patients. The main challenge of currently available antiretroviral agents—avoiding the development of resistance—would not be an issue for viral decay accelerators since the generation of mutations in the viral genome would in fact be the goal of treatment. Moreover, there would be no preexisting resistance among HIV-infected persons, even those with highly resistant viruses. Although there is clearly much that needs to be done to make this speculation become reality, the promise of this compound is such that additional research studies are essential.

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References

- Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed via <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail>. Accessed on March 29, 2012.
- Thompson MA, Aberg JA, Cahn P, *et al.*: Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA* 2010;304:321–333.
- Mocraft A, Vella S, Benfield TL, *et al.*: Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998;352:1725–1730.
- Hogg RS, Yip B, Chan KJ, *et al.*: Rates of disease progression by baseline CD4 cell count and viral load after initiating triple drug therapy. *JAMA*. 2001;286(20):2568–2577.
- Palella FJ Jr, Deloria-Knoll M, Chmiel JS, *et al.*: Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4 strata. *Ann Intern Med* 2003;138:620–626.
- Hirsch MS, Gunthard HF, Schapiro JM, *et al.*: Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis* 2008;47:266–285.
- Palella FJ Jr, Armon C, Buchacz K, *et al.*: The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: A cohort study. *Ann Intern Med* 2009;151:73–84.
- Chun TW, Engel D, Berrey MM, *et al.*: Early establishment of a pool of latently infected, resting CD4(+) T cells during primary HIV-1 infection. *Proc Natl Acad Sci USA* 1998;95:8869–8873.
- Loeb LA, Essigmann JM, Kazazi F, *et al.*: Lethal mutagenesis of HIV with mutagenic nucleoside analogs. *Proc Natl Acad Sci USA* 1999;96:1492–1497.
- Harris KS, Brabant W, Styrchak S, *et al.*: KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. *Antiviral Res* 2005;67:1–9.
- Anderson JP, Daifuku R, and Loeb LA: Viral error catastrophe by mutagenic nucleosides. *Annu Rev Microbiol* 2004;58:183–205.
- Crotty S, Maag D, Arnold J, *et al.*: The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen. *Nature Med* 2000;6:1375–1379.
- Partiente N, Sierra S, Lowenstein P, and Domingo E: Efficient extinction by combinations of a mutagen and antiviral inhibitors. *J Virol* 2001;75:9723–9730.
- Clay PG, McRae MP, and Laurent JP: Safety, tolerability, and pharmacokinetics of KP-1461 in phase I clinical studies: A single oral dose study in non-HIV-infected adults, and a 14-day dose-escalating study in highly antiretroviral-experienced HIV-infected adults. *J Int Assoc Physicians AIDS Care* 2011;10:232–238.
- Mullins J, Heath L, Hughes J, *et al.*: Mutations of HIV-1 genomes in a clinical population treated with the mutagenic nucleoside KP1461. *PLoS ONE* 2011;6:e15135.

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