Emerging Pharmacology: Inhibitors of Human Immunodeficiency Virus Integration

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Key Words

AIDS, HIV, antiretrovirals, integrase

Abstract

The first integrase inhibitor licensed to treat HIV-1 infection was approved in late 2007, more than a decade after the introduction of the first inhibitors of the HIV-1 reverse transcriptase and protease. The unique biochemical and molecular mechanism of action of this novel class of antiretroviral drugs is the fundamental basis for their activity in treating multidrug-resistant HIV-1 infection and is important for understanding both the cellular and in vivo pharmacology and metabolism of these agents. In addition, available pharmacokinetic and drug interaction data for raltegravir and elvitegravir, the two integrase inhibitors that are the most advanced in clinical development to date, are reviewed.

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INTRODUCTION

Background and Medical Need

Since the first reports of Acquired Immune Deficiency Syndrome (AIDS) in the early 1980s, there has been significant progress in the treatment of HIV-1 infection. The identification of HIV-1 as the causative agent of AIDS catalyzed efforts to develop antiviral agents directed against the three virally encoded enzymes that are essential for HIV-1 replication: reverse transcriptase, protease, and integrase. These efforts quickly resulted in the identification and development of two different classes of reverse transcriptase inhibitors (the nucleosides and nonnucleosides) and inhibitors of the viral protease. As an understanding of HIV-1 replication elucidated the molecular mechanisms of viral fusion and entry, inhibitors preventing these processes were identified. By 2007, more than 21 different agents targeting the viral reverse transcriptase and protease were licensed to treat HIV-1 infection, and T20, an injectable peptide inhibitor of viral fusion, had been available for four years. The year 2007 marked a significant milestone in the history of antiretroviral drug development; after more than a decade since the introduction of the concept of three-drug combination therapy or highly active antiretroviral therapy (HAART), two entirely new classes of oral antiretroviral agents received FDA approval: Maraviroc, a CCR5 receptor antagonist that blocks viral entry, and raltegravir, the first inhibitor of HIV-1 integrase.

The advent of HAART as the standard of care for the treatment of HIV-1 infection was seminal in reducing the morbidity and mortality associated with HIV-1 infection and progression to AIDS (1, 2). Combination antiretroviral therapy dramatically suppresses HIV-1 replication and reduces the plasma HIV-1 viral load, resulting in significant reconstitution of the immune system (3–7). Combination therapy using agents directed against at least two distinct molecular targets is also the underlying basis for forestalling drug resistance. However, despite the many advances in diagnosis and treatment, the HIV-1 epidemic continues. It is estimated that 39.5 million people are currently infected worldwide. With 4.3 million new infections and 2.9 million deaths in 2006, HIV/AIDS remains one of the leading causes of infectious disease–related mortality worldwide (8).

Although HAART has significantly improved morbidity and mortality, because HIV-1 is a chronic viral infection and there is currently no cure, the prospective of maintaining therapy for the lifetime of a patient also presents significant challenges. The potential for persistent viral replication in compartments and reservoirs may continue to drive pathogenic disease processes. Adverse effects and poor tolerability associated with therapy are still issues for some patients, and suboptimal pharmacokinetics and drug interactions with antiretroviral agents and/or concomitant medications can also impact clinical outcomes (9). In addition, for all commonly prescribed antiretroviral agents, both evolved and transmitted drug resistance is a reality. For example, an analysis of viremic patients receiving treatment for HIV-1 infection in urban centers across the United States in the late 1990s revealed the incidence of three-class drug resistance to be slightly more than 13%, and in several studies the prevalence of transmitted drug resistance that affected susceptibility to one or more antiretroviral agents was estimated to be in the range of 23% (10–12). Transmitted drug resistance can have both immediate and long-term clinical consequences. Transmitted drug resistance is associated with decreased treatment responses, including both a prolonged time to virologic suppression following the initiation of therapy and decreased durability of the therapeutic response (12, 13). If undiagnosed, transmitted resistance also has the potential to facilitate the development of collateral multi-class drug resistance affecting any or all of the concomitant agents in the regimen.

In light of the limitations of current HIV-1 therapies, particularly in patients with multidrug-resistant infections, approval of the first integrase inhibitors has been eagerly anticipated. Here

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we review the role of integrase in HIV-1 replication and the unique mechanism of action of the class of integrase inhibitors known as strand transfer inhibitors. The drug metabolism profiles as well as available drug interaction data are summarized for raltegravir and elvitegravir, the two integrase strand transfer inhibitors that are the most advanced in clinical development to date.

HIV Replication and Antiretroviral Therapies

Although the HIV-1 life cycle presents many potential opportunities for therapeutic intervention, current drug discovery efforts have focused on and exploited only a limited number of these processes (reviewed in 14 and 15) (**Figure 1**).

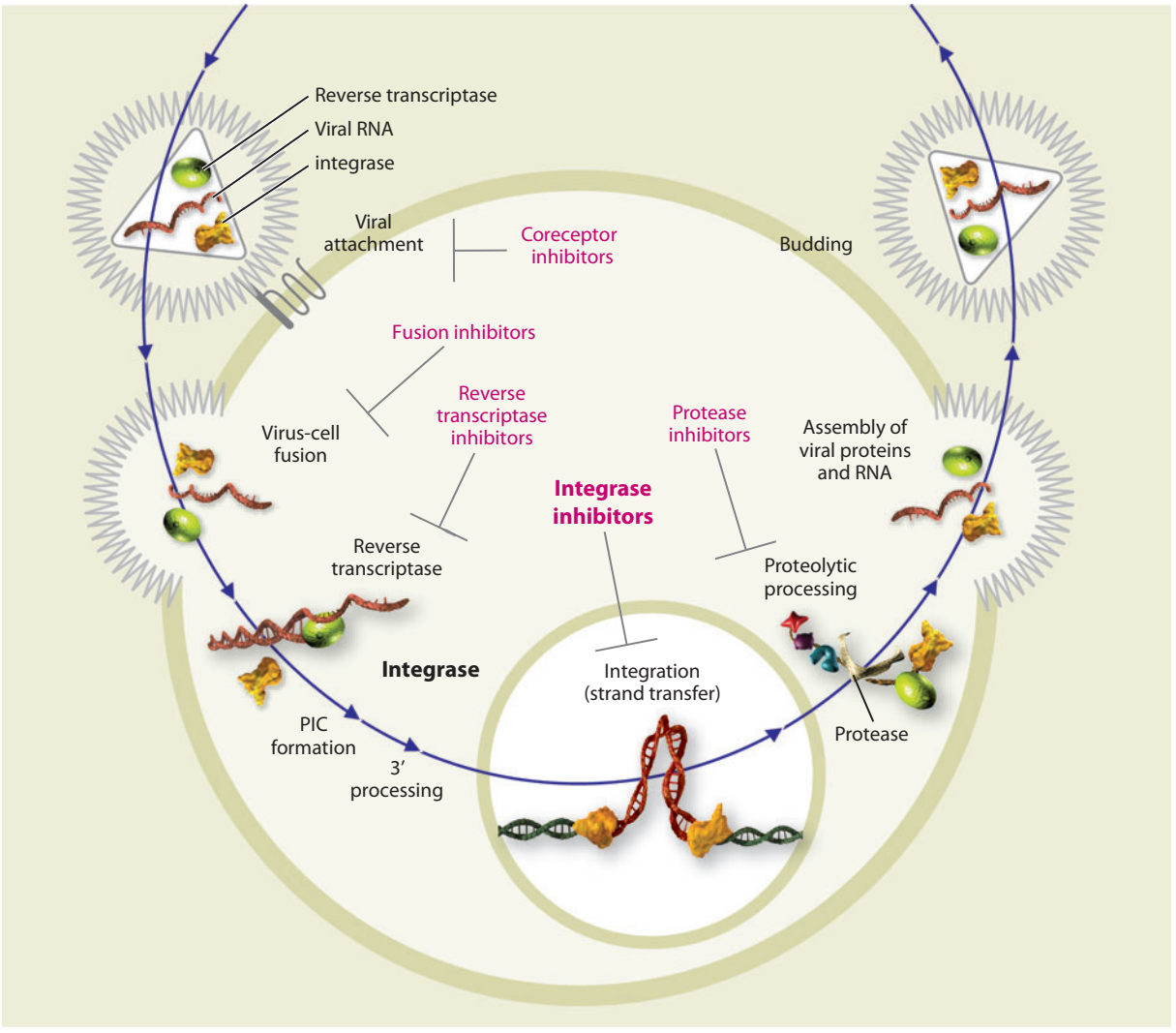

Figure 1

The HIV-1 life cycle and antiretroviral agents.

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The first step in the HIV-1 life cycle is viral entry, the target for two distinct classes of antiretroviral agents: the CCR5 antagonists and fusion inhibitors. The HIV-1 envelop gp120/gp41 has affinity for the CD4 receptor and targets HIV-1 to CD4+ immune cells. Interaction of the HIV-1 envelope with CD4 is followed by binding to an additional coreceptor, either the CC chemokine receptor CCR5 or the CXC chemokine receptor CXCR4. The disposition of these coreceptors on the surface of lymphocytes as well as the surface of monocyte/macrophages and the sequence of the viral envelope determine the tropism of the virus for different cell types and the susceptibility of infection to inhibition by CCR5 antagonists. These sequential receptor binding events induce conformational changes in the viral envelope, exposing a hydrophobic domain on gp41 that is principally responsible for mediating viral fusion and the target of fusion inhibitors (T20 or enfuvirtide). Fusion of the viral envelope to the host cell membrane allows for uncoating of the viral core and the release of the viral enzymes and RNA.

The HIV-1 reverse transcriptase is the target for two classes of antiretroviral agents, the nucleoside inhibitors (NRTIs) and non-nucleoside inhibitors (NNRTIs). Reverse transcriptase is a multifunctional enzyme with RNA-dependent DNA polymerase, RNase-H, and DNA-dependent DNA polymerase activities, all of which are required to convert the single-stranded viral RNA into double-stranded DNA. Although they differ with respect to their site of interaction on the enzyme and molecular mechanism, NRTIs and NNRTIs affect the polymerization activity of the enzyme and block formation of full-length viral DNA. The completion of reverse transcription is required for formation of the viral preintegration complex (PIC). Integrase inhibitors bind to the enzyme in the context of the viral PIC and therefore need to be present only after the reverse transcription process is complete. Integrase inhibitors prevent the insertion or integration of the viral DNA into the cellular DNA. Integration is required to maintain the viral DNA in the infected cell and is essential for expression of HIV-1 messenger RNA, viral proteins, and new viral RNA genomes. Viral proteins are assembled and transported to the cell surface, where the HIV-1-encoded protease enzyme is responsible for the maturation of the viral particles into infectious virions. Protease inhibitors block processing of the viral polyprotein and prevent the production of infectious viral particles.

As outlined above, integrase inhibitors act on a distinct viral target at a point in the HIV-1 replication cycle that differs from all other classes of antiretroviral drugs. Moreover, as discussed further below, the biological mechanism of action and molecular properties of integrase inhibitors such as raltegravir, the most well studied compound in the class, have important implications for understanding the pharmacology and pharmacodynamics of these agents.

INTEGRASE INHIBITORS

Integrase Biology and Biochemistry

In contrast to the early discovery and subsequent rapid clinical development of reverse transcriptase and protease inhibitors, integrase—the third of the three major enzymes required for HIV-1 replication—followed the first ARV agents after more than a decade (16–19). Although HIV-1 integrase is known to influence several stages of the HIV-1 replication cycle, including reverse transcription, integration, and viral assembly (20, 21), the enzyme's primary role is in integration, the process wherein the viral DNA is irreversibly inserted into the cellular DNA of the host. Integrase is required for each of the three sequence-specific events critical for integration: assembly with the viral DNA, 3′ endonucleolytic processing, and strand transfer. In the 3′ processing reaction, integrase removes the terminal 3′ dinucleotide from each end of the DNA, leaving a recessed-3′-OH at both termini. In the strand transfer reaction, integrase nicks the cellular or

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target DNA once on each strand and covalently links each 5′ phosphate to one of the recessed 3′ ends of the viral DNA. In the final, nonspecific step, the integrated intermediate is repaired by cellular enzymes to create the intact double-stranded product. In the context of HIV-1 replication, these events proceed in a stepwise manner, with the rate-limiting event being strand transfer. In activated cells, within several hours after infection, reverse transcription is completed and integrase binds and processes the viral DNA. The subsequent reaction, strand transfer, occurs after the PIC has been transported into the nucleus.

To date, HIV-1 integrase is the only protein known to be absolutely required to catalyze each of the three specific steps in integration, and is sufficient to perform these activities in vitro. The structure of the full-length integrase enzyme has yet to be determined; however, in conjunction with biochemical analyses, the structures of each of the three subdomains have substantially advanced an understanding of enzymatic function and mechanism (reviewed in 21 and 22). In the absence of a relevant inhibitor-bound complex for either raltegravir or elvitegravir, the unliganded subdomain structure of the catalytic core domain (amino acids 51–212 in HIV-1 integrase) has also suggested implications relevant for understanding integrase inhibitor mechanism and pharmacology. The catalytic core domain includes the critical active site residues aspartates D64 and D116 as well as glutamate E152, which are conserved among all retroviral integrases. This DDE motif coordinates the divalent metal ion cofactor(s) required for the phosphodiester bond cleavage/formation reactions of 3′ processing and strand transfer (23, 24). The metal binding architecture of the integrase active site is a common feature of many magnesium-dependent phosphotransferases and is the key structural element exploited in the mechanism of action of all integrase strand transfer inhibitors.

Inhibitor Mechanism

The 4-aryl-2,4-diketobutanoic acids (or diketo acids) exemplified by L-731988 (**Figure 2*a***) represent the prototype for integrase strand transfer inhibitors (25). These compounds were the first integrase inhibitors demonstrated to have antiviral activity directly as a consequence of their effect on HIV-1 integration. In biochemical assays and in cells, these compounds inhibit HIV-1 strand transfer and integration without affecting either assembly or processing of the viral DNA. Studies to understand the biochemical and molecular basis of inhibition have identified distinct

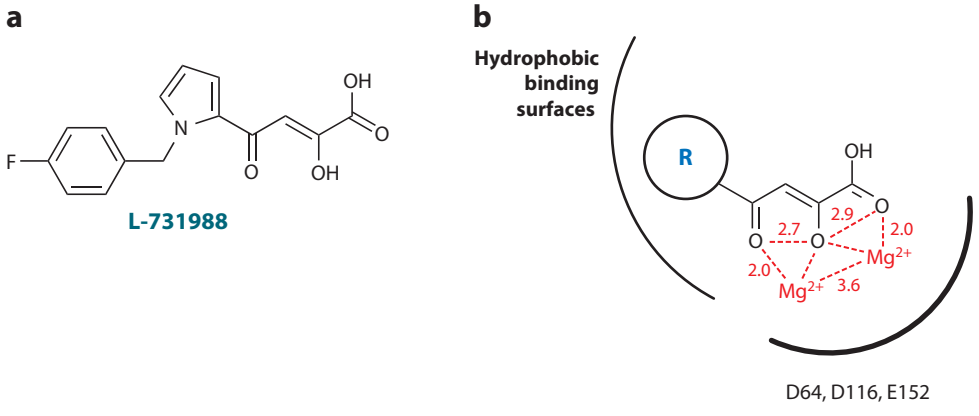

Figure 2

A prototypical integrase strand transfer inhibitor (InSTI): (*a*) the diketo acid L-731988 and (*b*) a model for InSTI active site interaction.

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biochemical and biological properties that characterize compounds with this mechanism of action. These inhibitors only bind with high affinity to integrase when the enzyme is in a specific complex with viral DNA (26). The inhibitor-bound complex is not competent to bind the cellular or target DNA substrate, and the net result is selective inhibition of strand transfer. In biological systems, blocking strand transfer and integration allows the viral DNA to be metabolized by cellular enzymes. Although most of the unintegrated viral DNA may be degraded, alternate metabolic pathways involving recombination and repair produce 1 and 2 long terminal repeat (LTR) circular DNA by-products. The net result of either process is an irreversible block of HIV-1 replication. LTR circles have become a defining feature of integrase strand transfer inhibitors, but were first noted with integration-defective viruses containing mutations in the integrase coding region (27, 28).

The biological and biochemical action of integrase strand transfer inhibitors distinguishes them functionally and mechanistically from other antiretroviral agents. As these inhibitors bind only to the enzyme in complex with viral DNA, they are not involved until several hours after infection when the process of reverse transcription is complete. However, inhibition is functionally reversible. Together, these two characteristics suggest such compounds may have to be continuously present to be effective.

Medicinal Chemistry

Binding of integrase strand transfer inhibitors to the integrase-DNA complex is strictly dependent on divalent metal. The specific chemical nature of the pharmacophore has been shown to affect relative activity in biochemical assays depending on whether magnesium or manganese is used in the reaction. Importantly, although nonacid pharmacophore replacements exhibit only a modest loss in binding affinity, such compounds are inactive as inhibitors. Thus, sequestration of the active site metals by the pharmacophore is critical for inhibition, whereas the affinity of integrase strand transfer inhibitors appears to be determined largely (although not exclusively) by the pendant substituents (29). On the basis of these observations as well as structure activity analyses of inhibitors and information derived from X-ray crystallography studies of integrase and other metal-dependent phosphotransferase enzymes, a model for the interaction between the inhibitor pharmacophore and the metals at the integrase active site was developed (29) (**Figure 2*b***). The bond lengths and angles for the diketo acid pharmacophore used in this model were derived from the crystal structure of 5-CITEP [1-(5-chloroindol-3-yl)-3-hydroxy-3-(2H-tetrazol-5-yl)-propenone)] and structural information based on the two active site metals in the crystal structure of ASV integrase (30). This model is also consistent with the observation that the resistance mutations that are selected with a variety of integrase strand transfer inhibitors affect residues that are proximal to those that coordinate the metal cofactors at the integrase active site (31, 32).

Subsequent to the identification of the first strand transfer inhibitors, many structurally diverse analogs elaborating novel, isosteric replacements for the diketo acid pharmacophore have been reported (reviewed in 33). These analogs have been designed not only to improve upon intrinsic potency and antiviral efficacy but also to obviate pharmacologic liabilities such as cell penetration and protein binding. Notable among these compounds are the 8-hydroxy-(1,6)-naphthyridine carboxamides, L-870810 and L-870812 (31, 34, 35), which provided proof of concept for the efficacy of integrase strand transfer inhibitors as antiretroviral agents in vivo. Raltegravir (MK-0518) and elvitegravir (GS-9137, JTK303) are the two integrase strand transfer inhibitors to reach advanced clinical development (36–38). These compounds are distinct from either the diketo acids or the naphthyridines, and each is from a different chemical series (**Figure 3**). Although

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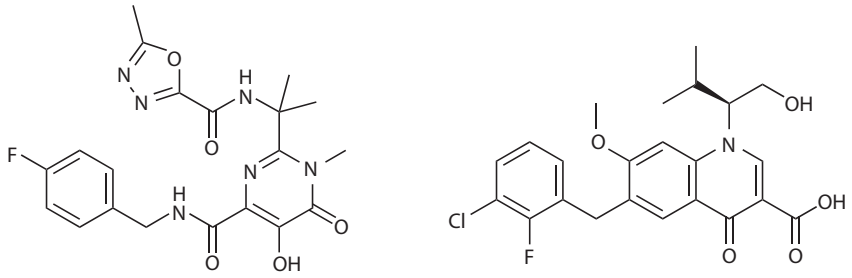

Figure 3

Chemical structures of raltegravir (MK-0518) and elvitegravir (JTK-303/GS9137).

these inhibitors exhibit a range of chemical diversity, in each case the critical elements of the metal-binding pharmacophore encompassed in the original diketo acid series are preserved. The conservation of the metal pharmacophore in these compounds, particularly as it relates to the apparent invariant need for a primary hydroxyl in all potent inhibitors with this mechanism, makes all integrase strand transfer inhibitors subject to extensive metabolism via glucuronidation.

PHARMACOKINETICS AND DRUG METABOLISM

The clinical pharmacokinetics of raltegravir and elvitegravir differ based on the distinct absorption, distribution, metabolism, and excretion pathways of the two compounds and thus will be discussed separately below.

Raltegravir Pharmacokinetics

Raltegravir is an orally administered drug that is rapidly absorbed with a time to maximal concentration of approximately three hours when administered in the fasted state. Raltegravir area under the concentration-time curve (AUC) and maximal concentration (C_{max}) increase dose proportionally from 100 to 1600 mg. Raltegravir trough concentration or concentration at 12 hours postdose ($C_{12\,hr}$) increases dose proportionally from 100 to 800 mg and slightly less than dose proportionally from 100 to 1600 mg. The apparent terminal half-life of raltegravir is approximately nine hours, with a shorter α-phase half-life of approximately one hour accounting for much of the AUC (39). Typical concentration-time profiles following single-dose administration of raltegravir are shown in **Figure 4**. The therapeutic dose and schedule is 400 mg administered twice daily, and steady state is achieved rapidly within approximately two days. There is little to no accumulation in AUC and C_{max}, and modest accumulation in $C_{12\,hr}$ (39a). In HIV-1-infected patients administered 400 mg raltegravir twice daily as monotherapy, a geometric mean $AUC_{0-12\,hr}$ of 14.3 μM·hr and $C_{12\,hr}$ of 142 nM were characterized (38).

Raltegravir is administered without regard to food, although food has been shown to affect the pharmacokinetic profile (41). Varying meal types differing in fat content have resulted in increases and decreases in raltegravir plasma concentrations (D.M. Brainard, L.A. Wenning, and M. Iwamoto, unpublished data). Overall, the food-effect studies have not resulted in predictable changes secondary to food. In the pivotal phase III studies, raltegravir was administered without regard to food. Overall, the pharmacokinetic variability resulting from ingestion with or without food has not been shown to result in clinically meaningful differences in efficacy.

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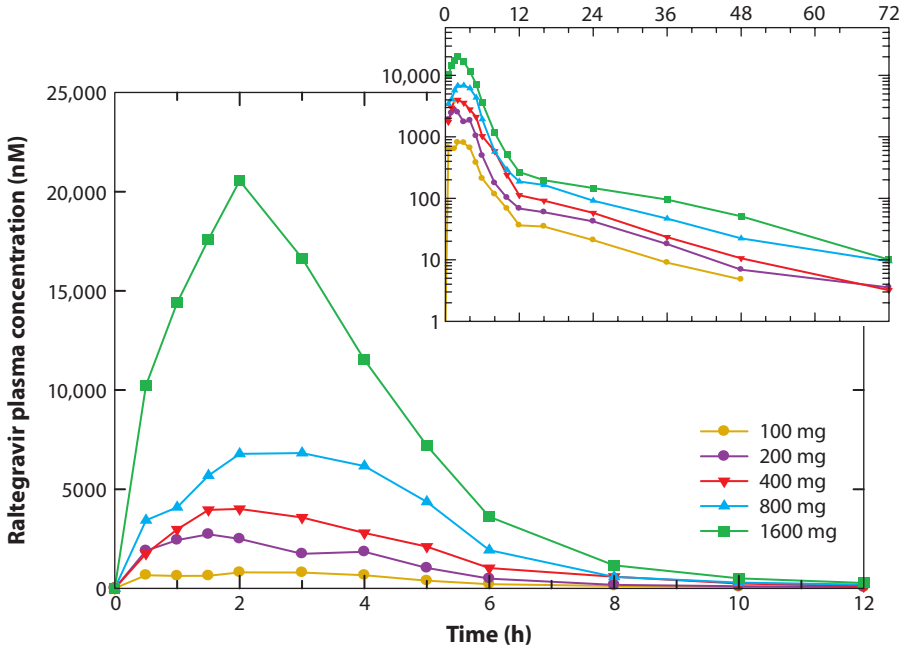

Figure 4

Arithmetic mean raltegravir plasma concentration profiles following single-dose administration of 100, 200, 400, 800, or 1600 mg to healthy male and female subjects (40) ($N = 20$; inset: semilog scale).

Raltegravir Metabolism

In preclinical studies, raltegravir was metabolized predominantly in the liver via the UDP-glucuronosyltransferase (UGT)-mediated pathway. In vivo and in vitro studies using isoform-selective chemical inhibitors and cDNA-expressed UGTs showed that UGT1A1 is the primary enzyme responsible for the formation of raltegravir-glucuronide (40). In vitro studies demonstrate that raltegravir is not a substrate for cytochrome P450 (CYP) enzymes and does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A or induce 3A4 (43). Similarly, raltegravir is not an inhibitor of UGTs (UGT1A1 and UGT2B7) or P-glycoprotein (P-gp)-mediated transport (40).

In clinical studies, metabolism via UGT1A1-mediated glucuronidation is the major pathway of elimination of raltegravir, with a minor component of elimination via kidney (~9% of total dose excreted unchanged into urine). The only metabolite detected in humans was the phenolic hydroxyl glucuronide, and this metabolite does not have antiviral activity (42). In a human absorption, distribution, metabolism, and excretion (ADME) study, ~51 and 32% of a radiolabeled raltegravir dose (parent and metabolite) was excreted in the feces and urine, respectively. The major circulating entity in plasma was the parent compound (69% of the total drug-related material in plasma), whereas most of the drug-related material in urine was accounted for by the glucuronide derivative (72% of the drug-related material in urine). In feces, only parent compound was detected, but it is likely that a good fraction of the raltegravir detected in feces is derived from hydrolysis of the glucuronide derivative secreted in bile as observed in preclinical species (42).

Effects of intrinsic and extrinsic demographic factors on the pharmacokinetics of raltegravir were evaluated. Results from the analyses indicate that the demographic factors of gender, age (adults ≤65 years), body mass index, hepatic function impairment (moderate), renal function

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impairment (severe), race, and HIV infection status do not have clinically meaningful effects on the pharmacokinetics of raltegravir, and no dose adjustment is warranted for these factors (41). Additionally, there is no evidence that the UGT1A1 *28/*28 polymorphism alters raltegravir pharmacokinetics to a clinically meaningful extent (42a).

Raltegravir Drug-Drug Interactions

The effect of raltegravir on the pharmacokinetics of other agents as well as the effect of other agents on the pharmacokinetics of raltegravir were examined. On the basis of the metabolic profile and preclinical interaction data, raltegravir has a low propensity to be involved in clinically meaningful drug interactions.

Effect of raltegravir on coadministered drugs. In vitro results indicated that raltegravir is generally not expected to alter the pharmacokinetics of coadministered drugs. At concentrations up to 100 μM, raltegravir is not an inhibitor of the major CYP450 isozymes, several major UGTs, or P-gp. Additionally, raltegravir was not found to be a time-dependent inhibitor of CYP3A4 nor an inducer of CYP3A4 (43).

Clinical interaction studies were conducted with midazolam, tenofovir, etravirine, and a triphasic oral contraceptive, which demonstrated minimal effects of raltegravir on the respective pharmacokinetics (**Table 1**) (43–46).

Effect of coadministered drugs on raltegravir. There is low propensity for coadministered drugs to meaningfully alter the pharmacokinetics of raltegravir. Raltegravir is eliminated primarily by metabolism via UGT1A1, and studies were conducted evaluating the effect of inducers and inhibitors of drug metabolizing enzymes (including UGT1A1) on raltegravir pharmacokinetics. Results are summarized in **Table 2**.

As anticipated, raltegravir plasma levels were increased with coadministration of atazanavir, consistent with the known inhibitory effect of atazanavir on UGT1A1 (47). The increases, however, were on the whole modest and not considered clinically meaningful based on the overall safety database inclusive of patients receiving raltegravir in conjunction with atazanavir (41).

Both ritonavir-boosted tipranavir and rifampin decreased plasma levels of raltegravir (48, 49). The interaction is likely secondary to a modest inductive effect of tipranavir and rifampin on the metabolism of raltegravir. In both cases, raltegravir $C_{12\,hr}$ value was most impacted. The prescribing information states that caution should be used when coadministering raltegravir with rifampin or other strong inducers of UGT1A1. For tipranavir, the decreases are not considered to be clinically meaningful based on the clinical efficacy database (40). Clinical efficacy data are available in patients

Table 1 Summary of raltegravir drug-drug interactions: effect of raltegravir on coadministered agent pharmacokinetics

Coadministered agent	AUC[a] GMR (90% CI)	C_{max} GMR (90% CI)	C_{trough}[b] GMR (90% CI)
Ethinyl Estradiol	0.98 (0.93, 1.04)	1.06 (0.98, 1.14)	–
Etravirine	1.10 (1.03, 1.16)	1.04 (0.97, 1.12)	1.17 (1.10, 1.26)
Midazolam	0.92 (0.82, 1.03)	1.03 (0.87, 1.22)	–
Norelgestromin	1.14 (1.08, 1.21)	1.29 (1.23, 1.37)	–
Tenofovir	0.90 (0.82, 0.99)	0.77 (0.69, 0.85)	0.87 (0.74, 1.02)

[a] $AUC_{0-\infty}$ for midazolam; $AUC_{0-24\,hr}$ for tenofovir, ethinyl estradiol and norelgestromin; $AUC_{0-12\,hr}$ for etravirine.
[b] $C_{12\,hr}$ for etravirine; $C_{24\,hr}$ for tenofovir; "–", not done.
GMR, Geometric mean ratio; CI, Confidence interval.

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Table 2 Summary of raltegravir drug-drug interactions: effect of coadministered agent on raltegravir pharmacokinetics

Coadministered agent	AUC[c] GMR (90% CI)	C_{max} GMR (90% CI)	$C_{12\,hr}$ GMR (90% CI)
Atazanavir[a]	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)	1.95 (1.30, 2.92)
Atazanavir/ritonavir[b]	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)	1.77 (1.39, 2.25)
Efavirenz[a]	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)	0.79 (0.49, 1.28)
Etravirine[b]	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)	0.66 (0.34, 1.26)
Omeprazole[a]	3.12 (2.13, 4.56)	4.15 (2.82, 6.10)	1.46 (1.10, 1.93)
Rifampin[a]	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)	0.39 (0.30, 0.51)
Ritonavir[a]	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)	0.99 (0.70, 1.40)
Tenofovir[b]	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)	1.03 (0.73, 1.45)
Tipranavir/ritonavir[b]	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)	0.45 (0.31, 0.66)

[a]Multiple doses of concomitant medication plus single dose of raltegravir.
[b]Multiple doses of concomitant medication plus multiple doses of raltegravir.
[c]$AUC_{0-\infty}$ for single doses of raltegravir; $AUC_{0-12\,hr}$ for multiple doses of raltegravir.
GMR, Geometric mean ratio; CI, Confidence interval (41, 45, 46a).

coadministered tipranavir in conjunction with raltegravir and no difference in efficacy was seen relative to the complementary cohort. No data are available in patients coadministered rifampin and raltegravir; as such, caution should be used with coadministration (41).

Raltegravir is sparingly soluble in media with low pH, and solubility increases at higher pH. An omeprazole interaction study in healthy subjects resulted in increased plasma concentrations of raltegravir likely secondary to the pH-altering effects of omeprazole (46a). A high prevalence of achlorhydria has been reported in HIV-1 infected individuals (50), and as such the effect of omeprazole may differ in this population. Evaluation of population pharmacokinetics in the phase III studies revealed that the pharmacokinetics of raltegravir was not meaningfully altered with gastric pH altering agents (L.A. Wenning, unpublished data). Furthermore, safety subgroup analyses did not reveal a difference in the safety profile of raltegravir with coadministration (H. Teppler, unpublished data). Additional investigation is warranted to fully evaluate the interaction in HIV-1 infected patients.

Other drugs assessed had less of an inductive or inhibitory effect on raltegravir pharmacokinetics. Overall, the data suggest raltegravir to have a relatively low propensity to be involved in clinically meaningful drug interactions.

Elvitegravir Pharmacokinetics and Metabolism

Elvitegravir is an orally administered drug with high bioavailability and low clearance when coadministered with boosting doses of ritonavir (51). It is rapidly absorbed with a time to maximal concentration of approximately three hours when administered in the fasted state. When administered alone, elvitegravir demonstrates slightly less than dose proportional pharmacokinetics (52). Ritonavir boosting significantly increases plasma levels of elvitegravir. Effects are seen at ritonavir doses as low as 20 mg, with maximal increase in elvitegravir exposure at 100 mg ritonavir. Coadministration with ritonavir results in a ~20-fold increase in AUC and an increase in the half-life of elimination from three to ten hours (51, 53).

Metabolism via oxidation by CYP3A4/5 and secondarily by glucuronidation via UGT1A1/3 is the major pathway of elimination, with a minor component of elimination via the renal system. The resulting major metabolites have reduced activity compared with elvitegravir and are not believed

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to contribute significantly to antiviral activity (54). In a human ADME study with radiolabeled elvitegravir and boosting doses of ritonavir, >90% of the circulating plasma was present as the parent compound. Radiolabeled compound was excreted primarily in the feces (94.8%), with a minor amount in the urine (6.7%). Fecal radioactivity consisted primarily of parent compound (36%) and an oxidative metabolite (46%). Urine was comprised of low levels of various metabolites (55).

Elvitegravir Drug-Drug Interactions

The effect of elvitegravir on the pharmacokinetics of other agents as well as the effect of other agents on the pharmacokinetics of elvitegravir were examined. On the basis of the metabolic profile and preclinical interaction data, elvitegravir has some modest potential to be involved in clinically meaningful drug interactions.

Effect of elvitegravir on coadministered drugs. Elvitegravir has been shown in vitro to possess the potential to induce CYP3A4 (53). Additionally, the majority of studies conducted with elvitegravir utilized boosting doses of ritonavir, which possesses both inhibitory and inductive potential on a number of drug-metabolizing enzymes. A number of clinical interaction studies were conducted to assess the effect of elvitegravir-ritonavir on the pharmacokinetics of coadministered drugs. Results are summarized in **Table 3**. Overall, elvitegravir-ritonavir effects were relatively

Table 3 Summary of elvitegravir drug-drug interactions: effect of elvitegravir/ritonavir on coadministered agent pharmacokinetics

Coadministered agent	AUC[a] GMR (90% CI)	C_{max} GMR (90% CI)	C_{trough}[b] GMR (90% CI)
Abacavir	0.835 (0.807, 0.864)	0.876 (0.820, 0.936)	–
Amprenavir	0.991 (0.906, 1.08)	0.979 (0.905, 1.06)	1.01 (0.853, 1.20)
Atazanavir (with 200 mg elvitegravir)	0.792 (0.736, 0.853)	0.843 (0.782, 0.909)	0.655 (0.591, 0.726)
Atazanavir (with 85 mg elvitegravir)	0.886 (0.796, 0.987)	0.960 (0.861, 1.107)	0.826 (0.719, 0.949)
Darunavir	0.887 (0.823, 0.956)	0.894 (0.850, 0.941)	0.828 (0.737, 0.929)
Didanosine	0.859 (0.749, 0.986)	0.841 (0.674, 1.05)	–
Emtricitabine	1.11 (1.07, 1.15)	1.15 (1.09, 1.22)	1.04 (0.965, 1.12)
Etravirine	0.982 (0.898, 1.07)	1.05 (0.937, 1.17)	0.896 (0.827, 0.971)
Lopinavir	0.966 (0.853, 1.09)	0.992 (0.88, 1.12)	0.923 (0.787, 1.08)
Maraviroc	2.86 (2.33, 3.51)	2.15 (1.71, 2.69)	–
Ritonavir (with darunavir)	0.861 (0.767, 0.966)	0.893 (0.742, 1.07)	0.822 (0.735, 0.920)
Ritonavir (with etravirine)	0.877 (0.808, 0.951)	0.976 (0.862, 1.10)	0.706 (0.637, 0.782)
Ritonavir (with fosamprenavir)	0.946 (0.857, 1.05)	0.895 (0.751, 1.07)	1.01 (0.920, 1.10)
Ritonavir (with maraviroc)	0.982 (0.910, 1.06)	0.918 (0.784, 1.07)	1.03 (0.887, 1.20)
Ritonavir (with tipranavir)	0.991 (0.863, 1.14)	1.06 (0.882, 1.26)	1.10 (0.917, 1.33)
Stavudine	1.07 (1.05, 1.08)	0.996 (0.934, 1.06)	–
Tenofovir	1.07 (1.03, 1.12)	1.01 (0.933, 1.10)	1.08 (1.02, 1.15)
Tipranavir	0.889 (0.800, 0.988)	0.916 (0.838, 1.00)	0.889 (0.774, 1.02)
Zidovudine	0.860 (0.798, 0.926)	0.881 (0.765, 1.01)	–

[a] $AUC_{0-\infty}$ for abacavir, didanosine, and stavudine; $AUC_{0-24\,hr}$ for atazanavir, emtricitabine, ritonavir (with maraviroc) and tenofovir; $AUC_{0-12\,hr}$ for amprenavir, darunavir, etravirine, lopinavir, maraviroc, other ritonavir, tipranavir, and zidovudine.

[b] $C_{24\,hr}$ for atazanavir, emtricitabine, ritonavir (with maraviroc), and tenofovir; $C_{12\,hr}$ for amprenavir, darunavir, etravirine, lopinavir, other ritonavir, and tipranavir; "–", not done.

GMR, Geometric mean ratio; CI, Confidence interval (54, 56–66).

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Table 4 Summary of elvitegravir drug-drug interactions: effect of coadministered agent on elvitegravir pharmacokinetics

Coadministered agent	$AUC_{0-24\,hr}$ GMR (90% CI)	C_{max} GMR (90% CI)	$C_{24\,hr}$ GMR (90% CI)
Abacavir/ritonavir	0.967 (0.925, 1.01)	0.950 (0.897, 1.01)	1.06 (1.01, 1.13)
Atazanavir/ritonavir	2.00 (1.85, 2.16)	1.85 (1.69, 2.03)	2.88 (2.53, 3.27)
Atazanavir/ritonavir (85 mg elvitegravir in combination versus 150 mg elvitegravir control)	1.07 (0.951, 1.21)	0.909 (0.814, 1.02)	1.38 (1.18, 1.61)
Darunavir/ritonavir	1.11 (0.991, 1.22)	1.13 (1.03, 1.24)	1.18 (1.06, 1.31)
Didanosine/ritonavir	0.967 (0.925, 1.01)	0.950 (0.897, 1.01)	1.06 (1.01, 1.13)
Emtricitabine/tenfovir disoproxil fumarate/ritonavir	1.02 (0.963, 1.09)	0.984 (0.904, 1.07)	1.14 (1.04, 1.24)
Etravirine/ritonavir	1.06 (1.00, 1.13)	1.07 (1.01, 1.13)	1.06 (0.970, 1.16)
Fosamprenavir/ritonavir	0.934 (0.879, 0.992)	0.999 (0.906, 1.10)	0.963 (0.898, 1.03)
Lopinavir/ritonavir	1.75 (1.50, 2.04)	1.52 (1.29, 1.79)	2.38 (1.81, 3.13)
Maraviroc/ritonavir	1.07 (0.964, 1.18)	1.01 (0.887, 1.15)	1.09 (0.947, 1.26)
Stavudine/ritonavir	0.987 (0.939, 1.04)	0.960 (0.899, 1.03)	1.24 (1.17, 1.33)
Tipranavir/ritonavir	0.924 (0.787, 1.08)	1.06 (0.894, 1.26)	0.904 (0.698, 1.17)
Zidovudine/ritonavir	1.05 (0.993, 1.11)	1.05 (0.983, 1.13)	1.15 (1.04, 1.26)

Multiple doses of concomitant medication plus multiple doses of elvitegravir and ritonavir with the exception of abacavir, didanosine, and stavudine, which were administered as a single dose. GMR, Geometric mean ratio; CI, Confidence interval (54, 56–66).

modest. With maraviroc coadministration, maraviroc plasma levels were increased consistent with ritonavir CYP3A inhibition. Atazanavir exposures were modestly reduced with 200 mg elvitegravir, but not affected with an 85 mg dose.

Effect of coadministered drugs on elvitegravir. Elvitegravir metabolism is mediated through CYP3A4/5 and UGT1A1/3 and may be affected by inducers and inhibitors of these enzymes. Studies were conducted evaluating various antiretroviral agents as well as antacids and omeprazole. Results are summarized in **Table 4**. Overall, the effects on elvitegravir pharmacokinetics were relatively modest.

Atazanavir and lopinavir coadministration increased plasma levels of elvitegravir likely secondary to inhibitory effects on CYP3A and UGT1A. A reduced dose of elvitegravir is recommended with coadministration of either atazanavir or lopinavir (57, 64). Coadministration of elvitegravir with Al^{3+}/Mg^{2+}-containing antacids resulted in decreased plasma levels of elvitegravir ~40 to 50%, whereas antacid administration staggered by two hours or coadministration with omeprazole did not have a meaningful effect on elvitegravir pharmacokinetics. Thus, proton pump inhibitors may be coadministered with elvitegravir but antacid administration should be staggered by at least two hours (67).

Pharmacokinetics and Pharmacodynamics

An exposure-response relationship between drug trough concentrations and the decline in HIV RNA with short-term monotherapy treatment has been suggested for both raltegravir and elvitegravir. For raltegravir, a potential association was observed between raltegravir trough concentration (C_{trough}) and both change from baseline in log_{10} HIV RNA and the slope of decline in HIV RNA following 10 days of monotherapy treatment with various twice-daily dosing regimens. Similar relationships were not observed with raltegravir AUC or C_{max} in this study (40). In a

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10-day study containing various doses of once- or twice-daily elvitegravir with or without ritonavir boosting, elvitegravir trough concentrations appeared to be related to change from baseline (CFB) in $\log_{10}$ HIV RNA according to a simple E_{max} relationship [$CFB = E_{max} * C_{trough}/(EC_{50} + C_{trough})$] with an E_{max} (maximum effect) of 2.32 $\log_{10}$ change from baseline and an EC_{50} (concentration that results in 50% of maximum effect) of 14.4 ng ml^{-1}. No such relationship was evident for either C_{max} or AUC of elvitegravir in this study (36). These results suggest that C_{trough} may be a sensitive pharmacokinetic parameter to predict viral response for integrase inhibitors, and that at least short-term efficacy may be associated with maintenance of therapeutic concentrations across a dosing interval.

The clinical significance of an association between C_{trough} and viral response for integrase inhibitors following short-term monotherapy treatment, however, is not yet clear for longer-term treatment with combination therapies. For raltegravir, for example, no associations were observed between C_{trough} and a variety of measures of treatment outcome (including HIV RNA <400 copies ml^{-1}, HIV RNA <50 copies ml^{-1}, virologic failure, change from baseline in log10 HIV RNA, and various mutations associated with resistance to raltegravir) following 16 weeks of treatment in combination with optimized background therapy in two phase III studies in treatment-experienced patients, and patients with the lowest C_{trough} values (below the in vitro IC_{95}) had a similar probability of a successful treatment outcome compared with the rest of the study population (68). Some relationships were observed in these phase III studies between treatment outcome and the average of all collected raltegravir concentration data for a particular patient, using a sparse sampling scheme where one pharmacokinetic (PK) sample was collected per visit. Because the sparse sampling scheme is likely to underestimate peak concentrations, this average concentration parameter likely represents something in between the true average raltegravir plasma concentration in these patients and the trough concentration, and, in light of the considerable interoccasion variability in the pharmacokinetics of raltegravir (41), it may be a better measure of overall exposure to raltegravir on long-term dosing than C_{trough} because it represented sampling on more occasions. The observed pharmacokinetic/pharmacodynamic (PK/PD) relationships for raltegravir in the phase III studies were generally shallow for patients with additional active agents in their optimized background therapies, and did not suggest a threshold raltegravir concentration known to be associated with reduced efficacy. Some other factors in these studies, such as baseline HIV RNA and naïve use of darunavir, were more influential on efficacy outcome than raltegravir PK parameters (68).

Although short-term monotherapy data initially suggested the importance of C_{trough} for raltegravir, extensive analyses in longer-term phase II and phase III clinical studies have not supported these preliminary findings. The apparently complex relationship between the PK target and efficacy may also be, in part, a function of the unique mechanism of action of integrase strand transfer inhibitors relative to other antiretroviral agents. As these inhibitors result in a functionally irreversible inhibition of the HIV-1 replication cycle, strand transfer inhibitors do not have to be present continuously during the infection process. Thus, maintaining a high drug concentration throughout the dosing interval, including trough, could be less critical for efficacy and durability than has been observed with other drug classes.

CLINICAL IMPLICATIONS

Efficacy and Future Directions

Integrase inhibitors in combination with optimized background therapy provide an important option for patients who are treatment experienced and in whom current therapy is unable to

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effectively suppress HIV-1 RNA l replication owing to drug resistance. As a new drug class, it is expected that these agents should have activity against all current drug-resistant HIV-1 variants. Raltegravir specifically has demonstrated efficacy in treatment-experienced patients who are failing therapy with multidrug-resistant HIIV-1 infection in both the phase II and phase III clinical trials with increasing effectiveness observed when coadministered in combination with other active agents (37). As the clinical success of agents with new mechanisms of action, including both CCR5 antagonists and integrase inhibitors, is established it will become important to reevaluate the current long- and short-term strategies in HIV-1 patient management throughout the spectrum of disease. The use of a novel agent such as raltegravir as part of combination therapy in highly treatment-experienced patients may decrease the complexity of treatment with improved efficacy, better safety, and tolerability. However, the robust efficacy phase II study of raltegravir in combination with NRTIs in treatment-naïve patients also suggests integrase inhibitors may someday have a role in first-line HAART regimens (38). Larger studies of these agents and an exploration of the sundry combination options now available are required to address the best approaches for including integrase inhibitors in an overall strategy for managing lifelong therapy for HIV-1 infected patients.

Finally, given the continuing success of antiretroviral therapy, a better understanding of the potential pharmacologic implications and complications in an aging population is needed, as are studies in a variety of special populations such as hepatitis C virus (HCV)-coinfected patients, ethnic minorities, and women. In addition, an exploration of drug penetration in potential sanctuary sites, reservoirs, and different cell types is becoming an area of growing interest for HIV-1 pathogenesis. Although these data for integrase inhibitors in particular are currently limited, it is in general an area that has not been extensively studied for most antiretroviral agents. With the new options available for the treatment of HIV-1 infection, the question of whether specific drugs or drug classes may offer advantages relative to these pharmacologic features has now become one of increasing relevance with potentially important clinical consequences that must be explored for integrase inhibitors as well as all other antiretrovirals that are the mainstay of current therapy.

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DISCLOSURE STATEMENT

All authors are employed by Merck and Co. and were involved in the discovery and development of raltegravir.

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