PERSPECTIVE

HIV-1 Integrase Inhibitor Resistance and Its Clinical Implications

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With the approval in 2007 of the first integrase inhibitor (INI), raltegravir, clinicians became better able to suppress virus replication in patients infected with human immunodeficiency virus type 1 (HIV-1) who were harboring many of the most highly drug-resistant viruses. Raltegravir also provided clinicians with additional options for first-line therapy and for the simplification of regimens in patients with stable virological suppression. Two additional INIs in advanced clinical development—elvitegravir and S/GSK1349572—may prove equally versatile. However, the INIs have a relatively low genetic barrier to resistance in that 1 or 2 mutations are capable of causing marked reductions in susceptibility to raltegravir and elvitegravir, the most well-studied INIs. This perspective reviews the genetic mechanisms of INI resistance and their implications for initial INI therapy, the treatment of antiretroviral-experienced patients, and regimen simplification.

Although the era of highly active antiretroviral (ARV) therapy began in 1996, it was not until a decade later, with the licensing of 4 new ARVs belonging to 4 ARV classes, that it became possible to fully suppress HIV-1 replication in a high proportion of the most heavily treated HIV-infected individuals. Darunavir, the protease inhibitor (PI) with the highest genetic barrier to resistance, and maraviroc, the first CCR5 inhibitor, were approved in 2006. Raltegravir (RAL; Merck Laboratories), the first integrase inhibitor (INI), was approved in 2007, and etravirine, the first non-nucleoside reverse transcriptase inhibitor (NNRTI) shown to be useful for treating patients in whom previous NNRTIs were ineffective, was approved in 2008. Of these 4 new ARVs, the development of RAL may have had the greatest effect on current ARV treatment strategies.

RAL, however, may not be unique among INIs. Two other INIs in advanced clinical development—elvitegravir (EVG; Gilead Sciences) and S/GSK1349572 (GlaxoSmithKline)—may be equally efficacious. However, resistance to RAL and EVG develops rapidly in vitro and, in the absence of other active ARVs, in vivo. Although S/GSK1349572, which is earlier in its clinical development than EVG, appears to have a higher genetic barrier to resistance than RAL or EVG, its efficacy at treating RAL-resistant viruses is incomplete. Understanding INI resistance is therefore critical to use of INIs for initial therapy, the treatment of ARV-experienced patients, and regimen simplification.

INTEGRASE STRUCTURE AND FUNCTION AND INHIBITOR DISCOVERY

Following reverse transcription, integrase (IN) cleaves the conserved dinucleotides GT from the 3′ ends of double-stranded HIV-1 DNA, leaving 2 CA overhangs (the 3′-processing reaction). IN remains bound to each of the 3′ ends, circularizing the HIV-1 preintegration complex (PIC). IN then binds the host protein, lens epithelial-derived growth factor (LEDGF), which translocates the PIC to the nucleus, where IN catalyzes a nucleophilic attack of the viral 3′-hydroxy ends on the phosphodiester bonds of host genomic DNA (the strand-transfer reaction). Although IN catalyzes both the 3′-processing and strand-transfer reactions, only those compounds that specifically inhibit

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strand transfer have been effective INIs. Indeed, the development of a high-throughput screening assay for the identification of strand-transfer inhibitors that *bind IN in complex with viral DNA* heralded the modern era of INI development [1].

HIV-1 IN contains 288 amino acids encoded by the 3′ end of the HIV-1 *pol* gene. It is composed of 3 functional domains. The catalytic core domain (CCD), which encompasses amino acids 51 to 212, contains the catalytic triad D64, D116, and E152 and the viral DNA binding site. D64 and D116 coordinate the positioning of a metallic cationic cofactor (Mg^{++} or Mn^{++}), which is essential for IN function. The N-terminal domain (NTD), which encompasses amino acids 1 to 50, is characterized by an HHCC zinc-binding motif. Its primary role appears to be to facilitate IN multimerization through its extensive contacts with adjacent CCD monomers. The C-terminal domain (CTD), which encompasses amino acids 213 to 288, binds host DNA nonspecifically.

There are published crystal structures of the HIV-1 IN CCD plus CTD domains, the CCD plus NTD domains, the CCD bound to LEDGF, and the CCD bound to an active site inhibitor, the prototype diketo acid inhibitor 5CITEP (reviewed in [2–4]; see Figure 1). But the relative conformation of the CCD, NTD, and CTD domains and the tetrameric state of functional HIV-1 IN has been inferred primarily from crystallographic studies of the homologous IN of the prototype foamy virus (PFV) [5]. The applicability of the PFV IN structure to HIV-1 IN is validated by the consistency of the PFV IN structure with HIV-1 IN biochemical data and by the ability of PFV IN to co-crystallize with RAL and EVG [5–6].

HIV-1 IN inhibitors are structurally diverse molecules that contain a motif for binding the essential divalent metal cations Mg^{++} or Mn^{++} and a hydrophobic region for binding within the cavity formed by integrase and the 3′ HIV-1 DNA ends containing the terminal CA dinucleotide. RAL, EVG, and S/GSK1349572 displace viral DNA in the active site and contact several active site amino acids—including those in a mobile loop extending between positions 140 and 149 [2–4].

INTEGRASE INHIBITOR RESISTANCE

The principles of INI resistance parallel those of nucleoside reverse transcriptase inhibitor (NRTI), NNRTI, and PI resistance: (1) INI resistance is caused by primary mutations that reduce INI susceptibility in combination with secondary mutations that further decrease virus susceptibility and/or compensate for the decreased fitness associated with the primary mutations; (2) there is a genetic barrier to INI resistance, defined by the number of mutations required for the loss of clinical INI activity; and (3) there is extensive but incomplete cross-resistance among the INIs.

Mutations Associated With INI Resistance

Table 1 summarizes data on 39 mutations at 26 INI positions derived from (1) in vitro passage experiments in the presence of RAL [9–10], EVG [7–9], or 572 [11]; (2) in vivo data on mutations that emerged in individuals receiving RAL [12–19] or EVG [20]; and (3) in vitro susceptibility data of site-directed mutants and clinical HIV-1 isolates to RAL, EVG, and S/GSK1349572 [7–11, 18, 21–23]. Nineteen mutations at 10 positions (T66IAK, E92QV, F121Y, Y143RCH, P145S, Q146P, S147G, Q148HRK, V151AL, and N155HS) reduce susceptibility to either RAL or EVG by 5-fold or higher. Seven of these 19 mutations (E92V, F121Y, P145S, Q146P, V151AL, and N155S), however, have not been reported in published sequences from patients receiving RAL or EVG. Twenty mutations at 16 additional positions are accessory mutations that contribute to INI resistance only in the presence of primary INI resistance mutations. G140SAC (±E138KA) and T97A are particularly important accessory mutations because of the marked contribution these mutations make to INI resistance and viral fitness in HIV-1 strains containing Q148 [24–26] and Y143 [18, 21] mutations, respectively.

With the exception of one report of transmitted INI resistance [27], fewer than .1% of INI-naive individuals harbor viruses with primary INI resistance mutations [28–29]. As a corollary, naturally occurring resistance to RAL and the other INIs in advanced clinical development is currently absent. Although secondary INI resistance mutations occur in INI-naive patients, these mutations do not interfere with the virological response to RAL-containing regimens [2, 29–30]. Table 1 does not show highly polymorphic mutations that have been only weakly associated with INI selective drug pressure or decreased susceptibility such as V72I, T124A, M154IL, K156N, V165I, V201I, I203M, T206S, and D232N (reviewed in [28, 31]).

Table 2 shows the most common patterns of INI resistance mutations in published HIV-1 IN sequences from individuals receiving RAL [32]. Among 192 viral isolates from 105 RAL-treated individuals, 121 viruses contained mutations belonging to one of the 3 most commonly reported RAL-resistance mutation pathways: (1) Q148HRK ± G140SA ($n = 58$), (2) N155H ± E92Q ($n = 38$), and (3) Y143CR ± T97A ($n = 25$). The remaining 71 viruses from 44 individuals included 50 viruses without primary INI resistance mutations, 18 viruses with mutations belonging to more than one of the 3 most common mutational pathways, and 3 with primary mutations not belonging to any of the 3 common mutational pathways. Despite the fact that one mutation such as Y143R, Q148HKR, or N155H is often sufficient to reduce RAL susceptibility more than 10-fold—particularly in site-directed mutagenesis experiments—

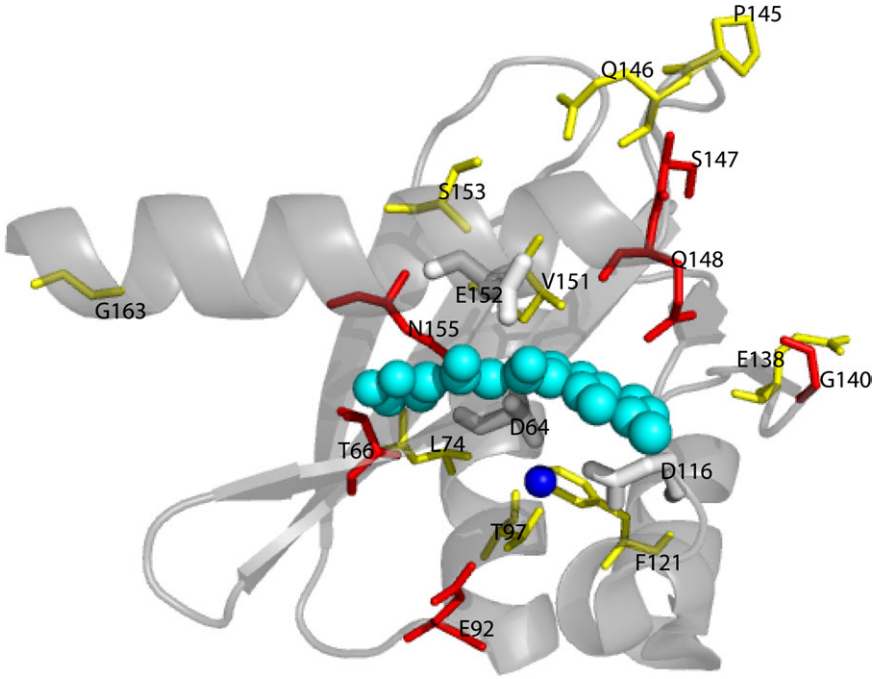

Figure 1. HIV-1 integrase (IN) inhibitor resistance mutations superimposed on a crystal structure of the IN central core domain bound to a prototype diketo acid inhibitor (5CITEP; PDB 1QS4) [54]. IN residues 56 to 165 are displayed in gray cartoon mode to represent secondary structural properties. 5CITEP is represented using cyan spheres. Active site residues D64, D116, and D152 are in white. Sites associated with the most commonly occurring primary mutations are in red (T66, E92, G140, S147, Q148, and N155). Sites associated with the most common accessory mutations (L74, T97, E138, V151, S153, and S163) and with primary mutations that have been observed solely in vitro (F121, Q145, and P146) are in yellow. Mg^{++} is a blue sphere. Residues 141 to 144, which form part of the highly mobile loop extending between G140 and G149, were not resolved in this crystal structure.

most RAL-resistant viruses obtained from RAL-treated patients have 2 or more RAL resistance mutations.

Most published INI susceptibility data have been produced by Monogram's PhenoSense assay, Virco's Antivirogram assay, and various permutations of HeLa-$CD4^{+}$ reporter gene assays. Although these assays frequently yield divergent results, the relative reductions in susceptibility associated with different mutation patterns is consistent among the different assays.

Q148 is a critical part of the IN active site believed to interact with the terminal adenosine and preterminal cytosine of the reactive viral DNA strand. Q148HRK decreases susceptibility to each of the INIs but also markedly decreases IN function. The replication defect associated with Q148HKR, however, is largely reversed by mutations at position 140 and, to a lesser extent, at position 138 [21, 24]. In clinical isolates, viruses with Q148 plus G140 mutations have >150-fold reduced susceptibility to RAL and EVG and up to 10- to 20-fold reduced susceptibility to S/GSK1349572 particularly when a third INI resistance mutation is also present (Table 2).

The second-most common pathway to RAL resistance includes N155H. N155H lies at the base of the catalytic site, where it may form a hydrogen bond with the active site residue E152 and directly interfere with IN metal binding [2]. N155H reduces susceptibility to RAL and EVG but not S/GSK1349572. N155H alone decreases replication capacity less than that of viruses with Q148 mutations alone. The addition of E92Q to N155H further decreases RAL and EVG susceptibility but does not rescue viral fitness [21]. Therefore, viruses with N155H ± E92Q are often outcompeted by viruses with G140 + Q148 mutations [21, 24].

Y143RC is the third-most common pathway to RAL resistance. When RAL binds IN, it induces a stacking interaction with Y143 [5, 34]. Substitution of Y with C or R removes this favorable interaction. S/GSK1349572 and EVG do not appear to contact Y143, and viral susceptibility to these INIs is not affected by Y143 mutations (Table 2). T97A markedly increases Y143RC-mediated RAL resistance [18, 21]. Y143H usually occurs as part of an electrophoretic mixture and may represent a transition between Y and R (TAC/T [Y] => CAC/T [H] => CGC/T [R]).

The Genetic Barrier to INI Resistance

The genetic barrier to INI resistance is lower than that of the PIs and most NRTIs. First, INI resistance is usually selected more rapidly during in vitro passage experiments with INIs than with most NRTIs and PIs [7–10]. Second, virological failure on an INI-containing regimen often occurs within the first several months of therapy and is often accompanied by INI resistance mutations [12, 19, 35]. In Merck Protocol 005, 35 of

Table 1. Integrase Inhibitor (INI) Resistance Mutations: Prevalence in INI-Naive and Raltegravir-Treated Individuals and Estimated Effect on Susceptibility to Raltegravir (RAL), Elvitegravir (EVG), and S/GSK1349572 (572)

Wild Type (Consensus Subtype B)*	Position*	Mutation*	Naive* (%; *n*= 4,435)	RAL Rx* (%; *n*= 105)	RAL Fold†	EVG Fold†	572 Fold†	In vitro and In vivo Selection Data§
Primary RAL and/or EVG INI Resistance Mutations Observed In vivo								
T	66	I	0	0	1	15	1	In vitro and in vivo by EVG [2, 7–8].
		A	.1	1.8	1	10	1	In vitro and in vivo by EVG [2, 9] and rarely by RAL [2, 35].
		K	0	0	10	80	2	In vitro and in vivo by EVG [2, 9].
E	92	Q	0	8.5	5	30	2	In vitro and in vivo by RAL and EVG [2, 12–14].
Y	143	C	0	4.8	4	1	1	In vitro and in vivo by RAL [12, 14–16, 19]. Y143H usually occurs as part of a mixture with Y143RC.
		R	0	12	20	1	1	
		H	.1	2.4	2	1	1	
S	147	G	.1	0	1	8	NA	In vitro and in vivo by EVG [2, 7].
Q	148	H	0	35	20	6	1¶	In vitro and in vivo by RAL and EVG [2, 9, 12, 14–16, 19]
		R	0	14	30	100	1¶	
		K	0	3.8	40	70	1¶	
N	155	H	0	46	20	40	1	In vitro and in vivo by RAL and EVG [2, 12–16, 19].
Primary RAL and/or EVG INI Resistance Mutations Observed Solely In vitro								
E	92	V	0	0	3	20	4	In vitro by EVG and GS-9160 [9, 22].
F	121	Y	0	0	5	10	1	In vitro by RAL and EVG [7, 9].
P	145	S	0	0	1	>150	1	In vitro by EVG [9].
Q	146	P	0	0	1	10	NA	In vitro by EVG [7].
V	151	A	0	0	5	5	NA	In vitro by GS-9160 [22].
		L	.1	.9	8	30	4	In vitro by L870,812 [9]. Reported in one patient receiving RAL [16]
N	155	S	0	0	10	40	1	In vitro by S-1360 [9]
Accessory RAL/EVG Resistance Mutations								
H	51	Y	0	2.9	3	4	NA	In vitro and in vivo by EVG [2, 7] and in vivo by RAL [18].
V	54	I	.5	1.0	1	1	NA	In vitro by RAL [10]
L	68	V	.8	0	1	1	NA	In vivo by EVG [2].
L	74	M	2.5	10	1	1	1	In vivo by RAL usually with N155H [12, 14–15].
Q	95	K	.1	1.9	1	1	NA	In vitro by EVG and RAL [2, 7].
T	97	A	2.2	17	1	1	NA	In vivo by RAL usually with Y143 mutations [13, 16, 18, 21].
H	114	Y	0	0	1	4	NA	In vitro by EVG [8].
T	125	K	0	0	1	1	NA	In vitro by L-870,812 [9].
A	128	T	.5	1.0	1	1	NA	In vitro by RAL and EVG [8, 10].
E	138	K	0.1	1.9	1	1	1	In vitro and in vivo by RAL and EVG usually with Q148 mutations [2, 35]
		A	0	3.8	1	1	1	
G	140	S	.1	36	1	1	1	In vitro and in vivo with Q148HR in patients receiving RAL [12, 14–16, 19, 35] and EVG [2]. G140AC is a less well-studied variant in this position [9, 22].
		A	0	2.9	1	1	1	
		C	0	0	1	1	1	
V	151	I	2.9	16	1	1	1	In vitro and in vivo by RAL [9, 14, 19, 48]. In vitro by EVG [9].
S	153	Y	0	0	1	3	2.5	In vitro by EVG [2].
E	157	Q	2.0	2.9	2.5	2.5	NA	In vitro by EVG [7] and rarely in vivo by RAL [13].

Table 1. (*Continued*)

Wild Type (Consensus Subtype B)*	Position*	Mutation*	Naive* (%; *n*= 4,435)	RAL Rx* (%; *n*= 105)	RAL Fold†	EVG Fold†	572 Fold†	In vitro and In vivo Selection Data§
G	163	R	.5	8.6	1	1	NA	In vivo by RAL [12, 35].
		K	.4	3.8	NA	NA	NA	
S	230	R	.1	3.8	1	1	NA	In vitro by RAL and EVG [8].
R	263	K	.1	1.9	1	5	NA	In vitro by EVG [2]

NOTE. *Direct PCR sequences of HIV-1 group M plasma viruses from 4,435 INI-naive individuals [29]. The RAL-Rx % is the no. of patients with a virus sequence containing a mutation divided by the number of RAL-treated patients (n = 105) obtained from 12 published references in the Stanford HIV Drug Resistance Database [32]. Although several RAL-treated individuals had multiple sequences, no mutation was counted more than once per individual. †In vitro susceptibility in the absence of other INI resistance mutations. Most data were derived from site-directed mutants. When data were available from multiple studies or determined using multiple assays the fold resistance approximates the median of the multiple results. §S-1360, L-870,812, and GS-9160 are investigational INIs. ¶Site-directed mutants with Q148H, Q148R, or Q148K do not decrease 572 susceptibility. However, viruses having one of these mutations in combination with E138K and/or G140S may have up to 10- to 20-fold decreased 572 susceptibility [11, 33].

38 subjects with virological failure developed RAL-resistant viruses [35], and in the BENCHMRK trials 64 of 94 with virological failure who underwent genotypic resistance testing had RAL-resistant viruses [12]. Likewise, a high proportion of subjects who developed virological failure while receiving EVG in the phase II trial GS-153-105 developed EVG-resistant viruses [2]. Third, the substitution of RAL for lopinavir/ritonavir (LPV/r) in the SWITCHMRK trial in patients with stably suppressed HIV-1 infection was associated with an increased risk of virological rebound [36]. Fourth, although RAL resistance mutations have been associated with decreased replication capacity [25–26], no clinical benefit has been observed from continuing RAL in patients with high-level RAL resistance [37], presumably because most primary RAL resistance mutations occur in combination with accessory compensatory mutations [24–26].

The genetic barrier to INI resistance, however, may not be as low as that of lamivudine, emtricitabine, or the NNRTIs nevirapine and efavirenz. In contrast to the NNRTIs, RAL has been highly effective at treating ARV-experienced individuals with few therapeutic options. In the BENCHMRK trials, RAL-containing regimens often

Table 2. Phenotypic Susceptibility Data Associated With the Most Common INI Resistance Mutation Patterns Present in 192 Virus Isolates From 105 Patients

	No. of Unique Viruses†		Published In vitro Susceptibility Data§		
Primary Mutations*	Without accessory mutations	With accessory mutations	Raltegravir	Elvitegravir	S/GSK1349572
148H + 140S	26	18	>150 [2, 9, 11, 21–23]	>150 [2, 9, 11, 22–23]	3 [11]
148R + 140S	5	0	>150 [9, 11, 21, 23]	>150 [9, 23]	8 [11]
148R + 140A	2	1	>150 [21, 23]	>150 [23]	NA
148R	5	0	10 to 50 [8–9, 11, 21]	90 to 150 [8–9, 11]	1 [11]
148K	1	0	25 to 40 [2, 9–11, 21]	80 [2, 9–11]	1 [11]
Totals	39	19			
155H	11	24	10 to 30 [8–11, 21–22]	20 to 50 [2, 8–11, 22]	1 [11]
155H + 92Q	1	2	80 to 150 [11, 21]	125 to 150 [2, 11]	3 [11]
Totals	12	26			
143R	7	1	15 to 20 [11, 21]	2 [11]	1 [11]
143R + 97A	2	7	>150 [21]	NA	NA
143C + 97A	2	4	>150 [18, 21]	NA	NA
143C	0	2	3 to 4 [11, 21]	1.5 [11]	1 [11]
Totals	11	14			

NOTE. The viral sequences in this table were obtained from 12 published references in the Stanford HIV Drug Resistance Database [32].

*G140SA and T97A are in this column because of their strong association with Q148 and Y143 mutations, respectively. Accessory mutations include the mutations in the second half of Table 1 (except G140SA and T97A). Viruses with primary mutations belonging to more than one pathway are not shown. †The totals of these 2 columns consist of 121 viruses containing one of the 3 most common raltegravir-associated mutational patterns. §In vitro susceptibility data obtained using the PhenoSense assay, the Antivirogram, or one of the generic HeLa-CD4$^+$ reporter gene assay variants. Viruses containing G140 + Q148 mutations may have up 10- to 20-fold decreased S/GSK1349572 susceptibility when a third INI resistance mutation is present [11, 33].

Table 3. Integrase Inhibitor Clinical Trials and Associated Drug Resistance Data

Trial Type	Clinical Trial*	Trial Design†	Virological Outcome and INI Resistance
Initial ARV Therapy	Protocol 004 [38]	Phase II randomized blinded dose-ranging trial of RAL (100, 200, 400, or 600 mg) BID + TDF/3TC vs. EFV + TDF/3TC	At 2, 4, and 8 weeks, all RAL treatment arms had a more rapid plasma HIV-1 RNA decrease than the EFV arm. At week 48, 84% of both arms had plasma HIV-1 RNA levels <50 copies/mL.
	STARTMRK [39]	Phase III randomized blinded trial of RAL + TDF/FTC (n= 281) vs. EFV + TDF/FTC (n= 282)	Both arms had similar virological efficacy. Among 84 patients with VF defined as confirmed plasma HIV-1 RNA levels >50 copies/mL, 12 of 39 RAL recipients vs. 9 of 45 EFV recipients had plasma HIV-1 RNA levels high enough for genotypic resistance testing. Four of 12 RAL recipients and 5 of 9 EFV recipients had INI and NNRTI resistance, respectively [40].
	Protocol GS-236-014 [41]	Phase II randomized blinded trial of EVG + the novel pharmacokinetic enhancer cobicistat + TDF/FTC (''QUAD'' n= 48) vs. EFV + TDF/FTC (n= 23)	At week 48, 90% of EVG (''QUAD'') vs. 83% of EFV recipients had plasma HIV-1 RNA levels <50 copies/mL.
	SPRING-1 [42]	Phase II randomized blinded dose-ranging trial of 572 (10, 25, or 50 mg) QD (n= 155) vs. EFV (n= 50) in combination with TDF/FTC or abacavir/3TC	At 24 weeks, >90% of subjects in each of the 3 572 arms had plasma HIV-1 RNA levels <50 copies/mL.
	SPARTAN [43]	Pilot randomized open-label study of RAL + ATV 300 mg BID (n= 63) vs. ATV/r + TDF/FTC QD (n= 31)	Five of 6 RAL-treated subjects with VF and plasma HIV-1 RNA levels >400 copies/mL developed RAL resistance.
	PROGRESS [44]	Phase III randomized blinded study of RAL + LPV/r (n= 101) vs. TDF/FTC + LPV/r BID (n = 105)	One of 4 RAL-treated subjects with VF and plasma HIV-1 RNA levels >400 copies/mL developed RAL resistance.
Regimen Simplification	EASIER [45]	Phase III randomized open-label trial of RAL vs. continued enfuvirtide in subjects with plasma HIV-1 RNA levels <400 copies/mL for ⩾3 months	At week 24, 88% of subjects in both arms had plasma HIV-1 RNA levels <50 copies/mL. INI resistance mutations emerged in 3 of 39 subjects with low-level viremia (defined as plasma HIV-1 RNA levels <1,000 copies/mL).
	SWITCHMRK 1 and 2 [36]	Phase III randomized blinded trial of RAL (n= 353) vs. continued LPV/r (n= 354) in subjects with plasma HIV-1 RNA levels <50 copies/mL for ⩾3 months	At week 24, 84.4% of subjects receiving RAL vs. 90.6% receiving LPV/r maintained plasma HIV-1 RNA levels <50 copies/mL. Eight of 11 RAL-treated subjects with VF and plasma HIV-1 RNA levels >400 copies/mL developed RAL resistance mutations.
	SPIRAL [46]	Phase IV 48-week randomized open-label trial of RAL 400 vs. continued RTV-boosted PI in subjects with plasma HIV-1 RNA levels <50 copies/mL for ⩾6 months	At week 48, 89.2% of subjects receiving RAL vs. 86.6% receiving continued RTV-boosted PI maintained plasma HIV-1 RNA levels <50 copies/mL. Week 48 RAL resistance data were not described.
	ODIS [47]	Pilot open-label randomized trial of RAL 800 mg QD (n= 177) vs. RAL 400 mg BID (n= 35) as a substitute for continued RTV-boosted PI in subjects with plasma HIV-1 RNA levels <50 copies/mL for ⩾6 months	At week 24, 6.4% of those receiving RAL QD vs. 2.9% of those receiving RAL BID (P = .2) had virological failure. All but one virological failure occurred in patients with a history of prior NRTI resistance.

Table 3. (*Continued*)

Trial Type	Clinical Trial*	Trial Design†	Virological Outcome and INI Resistance
Late-Stage Therapy: INI Naive	Protocol 005 [48]	Phase II blinded dose-ranging trial of RAL 200, 400, or 600 mg BID + OBR (n= 133) vs. placebo + OBR (n= 45)	At 24 weeks, the mean plasma HIV-1 RNA decrease was >1.8 log copies/mL in each of the RAL recipients vs. .35 log copies/mL in the placebo recipients. Among 38 RAL recipients with VF, 35 had RAL resistance [35].
	BENCHMRK 1 and 2 [12]	Phase III randomized blinded trials of RAL (n= 462) vs. placebo (n= 267) + OBR in subjects with 3-class resistant virus	At week 16, 62% of RAL recipients vs. 35% of placebo recipients had plasma HIV-1 RNA levels <50 copies/mL. Sixty-four of 94 subjects with VF had RAL resistance to IN mutations at positions 143, 148, or 155 usually in combination with one or more accessory INI resistance mutations.
	ANRS 139 TRIO [49]	Phase II open-label trial of RAL + DRV/r + etravirine + OBR in subjects with 3-class resistant virus (n= 103)	At week 48, 86% had plasma HIV-1 RNA levels <50 copies/mL. The 14 subjects with VF generally had low-level viremia (median plasma HIV-1 RNA levels of 90 copies/mL); none had INI resistance mutations [30].
	Protocol GS-183-105 [20]	Phase IIb randomized dose-ranging trial of RTV (100 mg)-boosted EVG (20, 50, or 125 mg) QD + OBR (n= 205) vs. RTV-boosted PI + OBR (n= 73). Adding DRV or TPV to EVG/r was permitted later in the trial and used after week 16.	The EVG 20 mg arm was discontinued at week 8. The 125 mg EVG dosage regimen produced a significantly greater decrease in plasma HIV-1 RNA levels than the comparator RTV-boosted PI arm. However, plasma HIV-1 RNA levels <50 copies/mL occurred mainly in those EVG recipients who also received enfuvirtide or subsequently added TPV or DRV. EVG resistance occurred commonly among EVG recipients with VF.
Late-Stage Therapy: INI Experienced	VIKING [33]	Phase II single-arm study of 572 50 mg QD as RAL replacement × 10 days followed by 572 50 mg + OBR × 23 weeks (n= 27). The initial primary end point was a plasma HIV-1 RNA decrease ⩾.7 logs by day 11.	In the 18 subjects with viruses having mutations belonging to the N155H or Y143 pathways, the mean plasma HIV-1 RNA decrease by day 11 was 1.8 log copies/mL. Three of 5 subjects with Q148H + G140S had an RNA decrease ⩾.7 logs by day 11. None of 4 subjects with a Q148 mutation plus ⩾2 additional mutations at positions 74, 138, and 140 had an RNA decrease ⩾.7 logs.

NOTE. RAL, raltegravir; EVG, elvitegravir; 572, S/GSK1349572; TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; EFV, efavirenz; RTV, ritonavir; ATV, atazanavir; TPV, tipranavir; DRV, darunavir; LPV/r, lopinavir/ritonavir; ARV, antiretroviral; BID, twice daily; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; PI, protease inhibitor; QD, once daily; VF, virological ⩾failure.

*Clinical trials are ordered according to their year of publication. †Raltegravir dosage was 400 mg twice daily unless otherwise specified. Other regimens and antiretrovirals were used at standard dosages unless otherwise specified.

produced complete virological suppression despite the absence of other highly active ARVs [12]. In addition, most patients with low-level virological rebound while receiving RAL do not develop INI resistance mutations. For example, none of the 14 subjects in the ANRS 139 TRIO trial with virological rebound developed INI resistance mutations [30] (Table 3). It has also been extremely difficult to select for S/GSK1349572 resistance in vitro,

suggesting that this INI has a higher genetic barrier to resistance than RAL or EVG [11].

INI Cross-Resistance

The 2 most commonly occurring RAL-associated mutation pathways—Q148HRK + G140SAC and N155H ± E92Q—both cause high-level EVG resistance. In contrast, the third RAL-associated mutation pathway, Y143CR ± T97A, does not confer EVG cross-resistance. Similarly, the common EVG-associated resistance mutations T66I [8–9] and S147G [2, 7] do not confer RAL cross-resistance. S/GSK1349572 is fully active in vitro against viruses with N155H ± E92Q or Y143CR ± T97A. However, susceptibility to S/GSK1349572 is reduced by about 10- to 20-fold by mutations at positions Q148HRK ± G140SAC ± E138KA [11, 33].

CLINICAL IMPLICATIONS OF INTEGRASE INHIBITOR RESISTANCE

RAL was first approved because of its effectiveness in the treatment of 3- and 4-class experienced HIV-infected individuals. It was subsequently approved for first-line therapy because of the noninferiority of tenofovir (TDF) + emtricitabine (FTC) + RAL compared with the standard-of-care first-line regimen TDF + FTC + efavirenz (EFV). RAL has since found a third role as a well-tolerated substitute for enfuvirtide or ritonavir-boosted PIs in patients with stable virological suppression (''regimen simplification'').

The novel stage at which INIs block HIV-1 replication has prompted intensification studies designed to eradicate HIV-1 from long-lived cellular reservoirs or to eliminate low-level residual viremia that emanates from this reservoir. These studies have shown that RAL intensification does not appear to reduce the size of the latent virus reservoir or eliminate low-level residual viremia [50–52]. One study has shown that in some patients the latent HIV-1 reservoir is replenished by ongoing low-level replication because telltale episomal viral forms accumulate in some patients receiving RAL intensification [53].

Initial ARV Therapy

Table 3 summarizes published clinical trials in which INIs were used for initial ARV therapy [38–39, 41–44]. In the phase III STARTMRK trials, RAL + TDF/FTC twice daily was as effective as the standard-of-care regimen (EFV + TDF/FTC once daily) [39]. As a result, published guidelines have recommended RAL + TDF/FTC as a preferred first-line regimen.

In a viral dynamic substudy of the phase II trial Protocol 004 [38], RAL-containing treatment was shown to accelerate the decline in plasma HIV-1 RNA levels relative to EFV-containing treatment. The accelerated decline in virus levels appears to result from INI-induced prevention of the release and production of virions from cells with unintegrated forms of HIV-1 DNA. This accelerated decline, however, has not been shown to provide a unique clinical benefit presumably because the longer period of detectable viremia in patients not receiving INIs is caused by virions produced from unintegrated viral DNA that are unable to infect new cells in the presence of active reverse transcriptase or protease inhibition.

In an interim 48-week analysis of the phase IIb trial comparing 48 subjects receiving EVG + cobicistat (an investigational pharmacokinetic enhancer) + TDF/FTC with 23 subjects receiving EFV + TDF/FTC, the EVG- and EFV-containing arms demonstrated similar virological efficacy [41]. In a dose-ranging 24-week phase II study of S/GSK1349572, at least 90% of subjects receiving each of the 3 S/GSK1349572 dosages had plasma HIV-1 RNA levels below 50 copies/mL [42].

In the NRTI-sparing PROGRESS trial, RAL 400 mg BID + LPV/r 400/100 mg BID produced virological responses similar to the standard-of-care regimen TDF/FTC + LPV/r 400/100 mg BID [44] (Table 3). Four subjects in the RAL-containing arm met the protocol-defined criteria for virological failure and genotypic resistance testing, and one had INI resistance. In the 24-week NRTI-sparing SPARTAN trial, open-label RAL 400 mg BID + atazanavir (ATV) 300 mg BID in 63 patients was similar in efficacy to the standard-of-care arm (ATV/r + TDF/FTC) [43]. However, among the 11 RAL recipients with virological failure, 5 developed RAL resistance, suggesting that despite the clinical efficacy of RAL + ATV, the regimen may be associated with a higher risk of INI resistance at the time of virological failure. The clinical trial was halted because of the frequent occurrence of INI resistance and hyperbilirubinemia [43].

Regimen Simplification

One controlled comparative trial [45] and multiple open-label pilot studies have shown that patients with stable virological suppression on an enfuvirtide-containing regimen can substitute RAL for enfuvirtide without risking virological rebound. The substitution of RAL for a boosted PI, however, has not been uniformly successful. In the large randomized double-blinded controlled SWITCHMRK trial, RAL regimen simplification was less efficacious than continued LPV/r: 84% of 353 RAL recipients versus 91% of 354 suppressed subjects continuing LPV/r maintained a plasma HIV-1 RNA level of fewer than 50 copies/mL by week 24 [36]. Moreover, 8 of the 11 RAL recipients with virological failure developed RAL resistance. In contrast, in the phase IV open-label SPIRAL trial, RAL substitution was at least as efficacious as the boosted PI arm: 89% versus 87% of subjects, respectively, maintained plasma HIV-1 RNA levels of fewer than 50 copies/mL over the 48-week study period [46].

The higher risk of virological failure associated with RAL in the SWITCHMRK compared with the SPIRAL trial is consistent with the

observation that failure in SWITCHMRK was associated with previous NRTI failure, so LPV/r was more effective than RAL in the context of a compromised background regimen. In contrast, in the SPIRAL trial about one-half of the subjects in the comparator arm received ATV/r and fosamprenavir/r, PIs with a lower genetic barrier to resistance than LPV/r. Subjects in the SPIRAL trial also had a longer baseline history of virological suppression (⩾6 months versus ⩾3 months) than those in the SWITCHMRK trial, placing the SPIRAL trial participants at a lower risk of virological failure.

ARV-Experienced Patients

The phase III randomized double-blind controlled BENCHMRK trial demonstrated the efficacy of RAL for highly ARV-experienced patients (Table 3). The phase II GS-183-105 trial compared several different ritonavir-boosted EVG (EVG/r) dosages with an optimized ritonavir-boosted PI-containing regimen. In GS-183-105, the superiority of EVG/r relative to the comparator arm was less than that in the BENCHMRK trials because in GS-183-105, EVG/r was compared with a boosted PI and an optimized background regimen. In contrast, in the BENCHMRK trials, RAL was compared solely with an optimized background regimen. A double-blinded phase III study directly comparing the safety and efficacy of EVG/r with RAL has been fully enrolled (NCT00708162).

Although the treatment of highly ARV-experienced patients with ARV regimens containing RAL or EVG has been successful in the majority of patients in these trials, virological failure and INI resistance occurred in a large proportion of subjects whose optimized background regimen contained no additional active ARVs. The successful use of RAL for treating highly ARV-experienced patients in clinical practice has also been high, particularly when it is part of a regimen containing one or more recently approved ARVs such as darunavir, maraviroc, or etravirine [49].

The VIKING trial is a phase II single-arm study of S/GSK1349572 QD administered to subjects with RAL-resistant viruses in whom a previous RAL-containing regimen had been unsuccessful [33]. For the first 10 days of the trial, S/GSK1349572 was given as functional monotherapy (ie, in combination with existing ARVs for those subjects who had already discontinued RAL or as replacement for RAL for those subjects still receiving it). In the 18 subjects with viruses having mutations in the N155 or Y143 mutational pathways, the mean RNA decrease was 1.8 logs by day 11. In contrast, the virological response was poorer in patients with viruses having Q148 pathway mutations. Although 3 of 5 subjects with Q148H + G140S had an RNA decrease ⩾.7 logs by day 11 (the primary end point), none of 4 subjects with a Q148 mutation plus 2 or more additional mutations at positions 74, 138, and 140 had an RNA decrease ⩾.7 logs. Whether or not the 10- to 20-fold decreased susceptibility to S/GSK1349572 associated with a Q148 mutation plus one or more mutations can be overcome with a higher S/GSK1349572 dosage (50 mg twice daily) is being evaluated in a second cohort of this trial (NCT00950859; http://clinicaltrials.gov).

There have been no studies of RAL or EVG in patients infected with viruses containing INI resistance mutations or having a history of previous INI therapy. Therefore, there are no clinically validated genotypic susceptibility scores or phenotypic cutoffs yet for these INIs. However, treatment with RAL is unlikely to be effective at treating viruses containing one of the major RAL resistance mutations such as Y143CR, Q148HRK, and N155H. Likewise, treatment with EVG is unlikely to be effective at treating viruses containing one of the major EVG resistance mutations such as T66IAK, E92Q, S147G, Q148HRK, and N155H.

CONCLUSIONS

The potency and tolerability of RAL have made it an important option for first-line therapy, the treatment of highly ARV-experienced patients, and regimen simplification. RAL's relatively low genetic barrier to resistance, coupled with the high level of cross-resistance within the INI class, calls for clinicians to be familiar with the studies that define RAL's optimal use. The investigational INIs EVG and S/GSK1349572 are also being studied for first-line therapy and the treatment of highly ARV-experienced patients. If these INIs are approved and prove to be as well tolerated as RAL, they are also likely to be used for regimen simplification. S/GSK1349572 may also prove useful at treating a significant subset of patients who have RAL-resistant viruses.

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