Integrase Strand Transfer Inhibitors in HIV Therapy

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ABSTRACT

HIV drug resistance has been one of the major obstacles to HIV eradication and has contributed to the need for the constant development of new antiretroviral drugs over the past 25 years. With the recent approval of dolutegravir for human therapy by the U.S. Food and Drug Administration, health practitioners may soon have access to three integrase strand transfer inhibitors to treat individuals living with HIV. Here, we review the use of raltegravir, elvitegravir, and dolutegravir for use in first- and second-line HIV treatment regimens and the issue of HIV resistance against integrase inhibitors.

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INTRODUCTION

Current highly active antiretroviral therapy (HAART) against HIV infection has, until recently, typically consisted of two reverse transcriptase inhibitors and a ritonavir-boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment-naïve adults [1]. HIV drug resistance threatens the long-term efficacy of HAART in both developed and developing country settings (reviewed in [2–4]) and this has led to the development of a new class of drugs termed integrase inhibitors. As is the case for all

antiretroviral drugs, HIV has the ability to acquire resistance against integrase inhibitors and this occurs through discrete mutations in the integrase coding sequence (reviewed in [5–8]). These mutations can be analyzed according to several genotyping resistance interpretation algorithms.

The issue of whether various integrase inhibitors may be used sequentially, i.e., in a sequential strategy, is a subject of great potential importance. Indeed, this concept has been studied from the beginnings of the field of antiretroviral therapy to develop strategies that might enable patients to benefit from newer classes of drugs, even if they had previously failed therapy while on older compounds against which resistance had developed [3]. In some cases, newer compounds could be used even within single drug classes to provide patient benefit in the event of resistance. A good example of this has been the use of ritonavir-boosted darunavir (DRV) that has a high genetic barrier for resistance for use in the place of earlier protease inhibitors such as nelfinavir (NFV) and ritonavir-boosted lopinavir (LPV) that have lower genetic barriers to resistance [9–12]. Due to the fact that ritonavir helps to maintain higher levels of PIs in the blood and tissues of treated individuals, the action of these compounds is prolonged and their genetic barrier for resistance is increased.

It has also long been established that members of different drug families may be used even if resistance has developed against members of other drug classes. As an example, the development of drug resistance to the NNRTI family of compounds can often be confronted through the use of protease inhibitors, since no cross-resistance exists between these two drug classes. More recently, newer NNRTI compounds that have somewhat distinct resistance profiles have also been

developed to provide benefits to patients when these compounds are used as a part of a second-line regimen [13].

In this context, the discovery of integrase strand transfer inhibitors (INSTIs) is important as a means of extending therapeutic options for individuals living with HIV. The integrase gene and enzyme of HIV were recognized early to be a potential therapeutic target and were shown to be susceptible to inhibition by oligonucleotides and synthetic peptides as early as 1995 [14, 15]. However, a seminal study only described the first promising small compound targeting integrase in 2000 [16]. This, in turn, has led to the development of all currently approved integrase inhibitors.

In the USA, INSTIs currently available for HIV treatment include raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). Integration is a two-step reaction catalyzed by the HIV integrase protein (reviewed in [17, 18]). The first step consists of the processing of the 3′ end of the newly retrotranscribed double-stranded viral DNA and is followed by the strand transfer reaction that results in the irreversible insertion of the viral genome into the host DNA. RAL, EVG, and DTG specifically inhibit the strand transfer step of integration [16, 19]. INSTIs have demonstrated long-term safety and efficacy [20–24] for the treatment of individuals living with multiple HIV subtypes [25–27]. Here, we review the use of INSTIs in first- and second-line HIV treatment regimens, as well as the potential to use these drugs sequentially after treatment failure as well as the issue of resistance.

METHODS

The analysis in this article is based on previously conducted studies, and does not

involve any new studies of human or animal subjects performed by any of the authors. Clinical studies reviewed in this manuscript were deemed important to the field of HIV integrase inhibitors by the authors. Most of these studies included large cohorts of patients. We also searched PubMed using the terms "raltegravir", "elvitegravir", and "dolutegravir" as well as both the previous and brand names for these drugs.

INTEGRASE INHIBITORS FOR FIRST- AND SECOND-LINE TREATMENT

INSTIs have been used in clinical trials in antiretroviral treatment-naïve individuals living with HIV (Table 1) [24, 28–47]. Both RAL [24, 28–32] and cobicistat (c)-boosted EVG [33, 34] have demonstrated non-inferiority to efavirenz (EFV) when co-administered in combination with tenofovir (TDF)/ emtricitabine (FTC). EVG/c is also non-inferior to ATV/r when combined with TDF/FTC [35, 36]. Non-inferiority was also demonstrated for DTG compared to EFV in the SPRING-1 (A Dose Ranging Trial of GSK1349572 and 2 NRTI in HIV-1 Infected, Therapy Naive Subjects) study in which patients were randomized to receive either TDF/FTC or abacavir (ABC)/lamivudine (3TC) [37, 38]. More recently, the SINGLE (A Trial Comparing GSK1349572 50 mg Plus Abacavir/Lamivudine Once Daily to Atripla) study compared DTG/abacavir ABC/3TC to EFV/TDF/FTC and showed that the former regimen offered a superior virological response than the latter [39]. Although EVG is co-formulated in a single pill with cobicistat (c) plus FTC/TDF, RAL and DTG might also be able to be co-formulated with nucleoside drugs, and all of the INSTIs can probably be co-

formulated with protease inhibitors for use in first-line treatment [48–54].

Importantly, INSTIs can be used for second-line treatment against HIV strains that are resistant against other drug classes, including NRTI, NNRTI, and PI [55–62] (Table 1). In particular, RAL was shown to be efficacious for patients who displayed resistance to three classes of drugs other than INSTIs [58]. In addition, RAL combined with a ritonavir-boosted PI was non-superior to ritonavir-boosted PIs plus two or three NRTIs in patients who had previously failed NNRTI-based treatments [40]. RAL was also non-inferior to LPV/r as a second-line drug for patients who had failed regimens consisting of a NNRTI and two NRTIs [41].

Treatment-experienced patients can also benefit from the use of INSTIs for reasons of toxicity, convenience, or absence of drug interactions [41, 63, 64]. Although switching from LPV/r/TDF/FTC to RAL/DRV/r in individuals with suppressed viral load resulted in sustained viral suppression, it did not improve renal function at week 48 [42]. In contrast, RAL has a positive impact on bone mineral density compared to standard second-line treatments [5]. Whether treatment intensification with INSTIs might benefit individuals with suppressed viral loads is beyond the scope of this review [65–69].

Studies have compared the efficacy of the different INSTIs in suppressing HIV viral load. In the 145 Study, EVG demonstrated non-inferiority to RAL at weeks 48 and 96 in highly treatment-experienced patients [43, 44]. DTG was non-inferior to RAL in attainment of viral suppression in treatment-naïve individuals at week 48 [45]. In contrast, DTG performed better than RAL in highly treatment-experienced INSTI-naïve individuals who were enrolled in a

Table 1 Summary of the major clinical trials reviewed in this publication

Study name	Tested regimen		Reference regimen	Antiviral activity of the tested regimen compared to the reference regimen	References
STARTMRK, Protocol 004, QDMRK	RAL + TDF/FTC	vs.	EFV + TDF/FTC	Non-inferiority	[24, 28–32]
GS-US-236-0102	EVG/c + TDF/FTC	vs.	EFV + TDF/FTC	Non-inferiority	[33, 34]
GS-236-0103	EVG/c + TDF/FTC	vs.	ATV/r + TDF/FTC	Non-inferiority	[35, 36]
SPRING-1	DTG + TDF/FTC or ABC/3TC	vs.	EFV + TDF/FTC or ABC/3TC	Non-inferiority	[37, 38]
SINGLE	DTG + ABC/3TC	vs.	EFV + TDF/FTC	Superiority	[39]
Study 145	EVG + PI/r + 3rd drug	vs.	RAL + PI/r + 3rd drug	Non-inferiority	[43, 44]
SPRING-2	DTG + TDF/FTC or ABC/3TC	vs.	RAL + TDF/FTC or ABC/3TC	Non-inferiority	[45]
SAILING	DTG + 1 or 2 active drugs	vs.	RAL + 1 or 2 active drugs	Superiority	[46]
EARNEST	RAL + boosted PI	vs.	Boosted PI + 2 or 3 NRTIs	Non-inferiority	[40]
Second-Line	RAL + LPV/r	vs.	LPV/r + 2 or 3 NRTIs	Non-inferiority	[41]
FLAMINGO	DTG + TDF/FTC or ABC/3TC	vs.	DRV/r + TDF/FTC or ABC/3TC	Superiority	[47]

RAL raltegravir, *TDF* tenofovir disoproxil fumarate, *FTC* emtricitabine, *EFV* efavirenz, *EVG/c* cobicistat-boosted elvitegravir, *ATV/r* ritonavir-boosted atazanavir, *ABC* abacavir, *3TC* lamivudine, *DTG* dolutegravir, *PI* protease inhibitor, *LPV/r* ritonavir-boosted lopinavir

study termed SAILING (A Study of GSK1349572 Versus Raltegravir (RAL) With Investigator Selected Background Regimen in Antiretroviral-Experienced, Integrase Inhibitor-Naive Adults) [46]. Overall INSTI-based regimens have shown low toxicity and an absence of unfavorable drug–drug interactions. The yearly costs of the various INSTI-containing regimens are comparable among the three drugs, i.e., approximately 30,000 USD/year [70].

SEQUENTIAL STRATEGY FOR THE USE OF INTEGRASE INHIBITORS AND THE ISSUE OF RESISTANCE

The concept of sequential strategy in regard to integrase inhibitors has not been fully explored. Although little information is available on this subject, the following facts are well-known. First, it is unlikely that RAL and EVG will ever

be able to be used sequentially in therapy, since the resistance profiles of these two compounds overlap to considerable extent [5, 6]. The only possibility for use of these compounds in sequential fashion might be if a change in therapy is contemplated at a time that resistance has not yet developed against either of these agents. The rationale for such a substitution could include the fact that RAL is a twice-daily drug and that some patients might prefer to be on the once-daily regimen of co-formulated EVG/c/TDF/FTC. In contrast, there are some patients who cannot take a pharmacological booster such as cobicistat for reasons of drug interactions and who might need instead to take the twice-daily regimen of RAL, complemented by two members of the nucleoside family of drugs [70].

The use of DTG to rescue patients who have first developed resistance to RAL has also been studied and documented [71]. In almost all cases, it appears as though some measure of patient benefit can be obtained if DTG is used to treat individuals who have developed resistance to either RAL or EVG, after the development of mutations in the integrase gene that follow one of the well-described resistance pathways for these compounds. However, it should also be noted that DTG may not be as effective in this setting as it is in first-line therapy. Indeed, the VIKING (A Pilot Study Assessing the Integrase Inhibitor GSK1349572 in HIV-infected Persons With Virus Resistant to Raltegravir) clinical trials in which DTG was used to rescue patients who first developed resistance against RAL showed that patients will have to receive DTG bid dosing at a total intake that is double the dose of DTG that is commonly used in first-line therapy [71]. The results also suggest that patients who first develop mutations that follow the RAL/EVG 148/140 mutational

pathway are less likely to respond to DTG than are INSTI-naïve individuals. This raises the important question of whether DTG can be saved for use as part of a second-line regimen, instead of being used in first-line therapy. Clearly, patients who have failed RAL or EVG and who have few other treatment options might benefit from the use of DTG and should be treated with this drug. However, this does not mean that DTG should be saved for use in later treatment regimens. In support of this, the FLAMINGO (Dolutegravir Compared to Darunavir/Ritonavir, Each in Combination With Dual Nucleoside Reverse Transcriptase Inhibitors (NRTIs) in ART-naive Subjects) study recently demonstrated the superiority of DTG over DRV/r in first-line therapy, when patients also received two nucleos(t)ides [47].

SHOULD DTG BE USED AS A FIRST-LINE DRUG?

The danger of delaying the use of DTG is that significant numbers of individuals who develop resistance to RAL and/or EVG may, by that time, have lost their ability to respond in fully efficacious fashion to DTG. For example, the results of the VIKING studies raise the issue of durability of responsiveness to a DTG-based regimen in second-line therapy after relevant INSTI mutations for RAL and EVG are already in place.

Further information on this topic is provided by the results of the SAILING study that evaluated the use of RAL vs. DTG in a context in which previously treatment-experienced patients had received therapy with many other types of drugs but not with INSTIs. Moreover, the patients in this trial had developed resistance against many of the compounds that were used

in prior therapy. Accordingly, almost all of them had compromised background regimens that involved the use of the various antiretroviral compounds that were employed. The results of the SAILING study show clearly that DTG outperformed RAL in terms of percentage of patients who achieved significant drops in viral load [46]. This is important, as it suggests that DTG is a more potent compound than RAL when either of these drugs is used in a salvage setting for patients who have previously failed traditional drug regimens that did not include an INSTI. At the same time, patients in the RAL arm of the trial who developed resistance against the latter compound did so due to development of mutations that are associated with the latter drug. In contrast, patients in the DTG arm of the trial developed resistance in very few cases. Two individuals developed the R263K mutation [72] that had earlier been shown to be of potential significance for DTG on the basis of tissue culture selection studies [73]. Accordingly, it appears that resistance to DTG in the clinic may be very difficult to develop, even in the case of patients who have previously failed other drug regimens

and who are currently being treated with DTG, almost in the context of functional monotherapy. This suggests that it may be very difficult to develop resistance against DTG under circumstances in which this compound is used as part of a first-line INSTI regimen. This may be because the mutations that develop against DTG, when the latter is used in first-line therapy, are ones that significantly diminish viral replication capacity [73, 74].

In contrast, the use of DTG as part of a second-line INSTI regimen may be more laden with problems, given the fact that mutations at positions 148, 140, and elsewhere within the viral genome, that are associated with resistance to RAL and EVG, may interfere with the ability of DTG to perform well. Moreover, the use of DTG to treat previously INSTI-experienced patients, with resistance to RAL and/or EVG, may lead to the selection of additional mutations that may further compromise therapy and cause cross-resistance [71]. Notably, in vitro studies suggest that the very rare individuals who may fail DTG treatment following emergence of the R263K mutation

Table 2 Representation of the potential evolution of HIV-1 following therapy of previously treatment-naïve individuals with raltegravir, elvitegravir, or dolutegravir

Treatment-naïve patients			
Treatment initiation	Primary resistance mutations	Compensatory mutations	Clinical outcome
Raltegravir/ elvitegravir	E92Q, Y143R/C, N155H, Q148R/H/K	Y143C/T97A; Y143R/T97A; Y143G/L74M/T97A; Y143C/L74 M/T97A/E138A	Virological failure
		N155H/L74M; E92Q/N155H	
		E92Q/T66I; E92Q/S153A; E92Q/H51Y/L68V	
		Q148H/K/R + E138A/K; Q148H/K/R + G140S/A; Q148H/E138A/G140S/Y143H	
Dolutegravir	R263 K	None	Viral suppression

In rare cases, the emergence of resistance mutations in patients treated with raltegravir or elvitegravir can lead to virological failure (top). Virological failure with resistance mutations in treatment-naïve patients treated with dolutegravir has not been reported (bottom)

may still be treatable with RAL but not with EVG [74]. As stated, the results of the VIKING studies showed that many patients who possessed mutations at positions 148 and 140 within integrase did not respond well to DTG [71]. In addition, such patients commonly developed additional mutations associated with the RAL/EVG resistance pathway. Thus, the potential sequential use of integrase inhibitors may be problematic, and the use of DTG in second-line regimens after resistance has developed against either RAL or EVG may ultimately represent a hazard to the long-term performance of DTG in the clinic. Of course, the choice of which INSTI to use in first-line regimens will be made by physicians in consultation with their patients based on considerations of drug efficacy, tolerability, safety, and ease of dosing. A summary of resistance pathways involving the use of various INSTIs to treat patients in first-line therapy can be found in Table 2.

CONCLUSION

INSTIs are the most recent class of antiretroviral drugs. INSTIs can and should be used as part of first- and second-line regimens to treat individuals living with HIV. Due to its high genetic barrier for resistance, DTG may be used to treat patients who have previously failed treatment with RAL or EVG, but only under the circumstances described above. Overall, INSTIs are a major advance in the management of individuals living with HIV.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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