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DOLUTEGRAVIR efficacy in HIV infected patients

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ABSTRACT

In the past years there have been numerous discoveries regarding treatment of patients with HIV. If at first the doctors watched as patients live longer, now we want these patients to live better with regimens potent, safe, individualized and without side effects. HAART has revolutionized “the world HIV” and caused a significant reduction in mortality, and morbidity associated with HIV-related opportunistic infections. However, side effects associated with HAART, metabolic toxicity (such as abnormal fat distribution, abnormal lipid and glucose metabolism, and bone loss) and the large number of pills led to decreased patient adherence.

Keywords: Dolutegravir, HAART, efficacy, resistance, safety

Introduction

In the past years there have been numerous discoveries regarding treatment of patients with HIV. If at first the doctors watched as patients live longer, now we want these patients to live better with regimens potent, safe, individualized and without side effects. HAART has revolutionized “the world HIV” and caused a significant reduction in mortality, and morbidity associated with HIV-related opportunistic infections. However, side effects associated with HAART, metabolic toxicity (such as abnormal fat distribution, abnormal lipid and glucose metabolism, and bone loss) and the large number of pills led to decreased patient adherence. Now, we need potent regimens, more simple, with a minimum number of pills, with administration of up to twice a day (if possible once a day) and with a safety profile more favorable.

There are six major types of drugs used to treat HIV/AIDS. These antiretroviral drugs are grouped by how they interfere with steps in HIV replication (Table I):

Reverse Transcriptase Inhibitors prevent the HIV enzyme reverse transcriptase (RT) from converting single-stranded HIV RNA into double-

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Table I - Antiretroviral Drugs Classes

NRTI	NNRTI	Protease Inhibitors (PI)	Fusion Inhibitors	Entry inhibitor	Integrase Inhibitors
abacavir (ABC, Ziagen)	delavirdine (DLV, Rescriptor),	atazanavir (ATV, Reyataz)	enfuvirtide (T20, Fuzeon)	maraviroc (MVC, Selzentry)	raltegravir (RLV, Isentress)
didanosine (ddI, Videx)	efavirenz (EFV, Sustiva)	darunavir (DRV, Prezista)			elvitegravir EVG (as coformulation only)
emtricitabine (FTC, Emtriva)	nevirapine (NVP, Viramune)	fosamprenavir (FSV, Telzir, Lexiva)			dolutegravir(DLV, Tivicay)
lamivudine (3TC, Epivir)	etravirine (ETR, Intelence)	indinavir (Crixivan)			
stavudine (d4T, Zerit)	rilpivirine (RPV, Edurant)	lopinavir/ritonavir (Kaletra)			
tenofovir (TDF, Viread)		nelfinavir (NFV, Viracept)			
zalcitabine (ddC, Hivid)		saquinavir (SQV, Invirase)			
zidovudine (ZDV, AZT Retrovir)		tipranavir (TPV, Aptivus)			

stranded HIV DNA—a process called reverse transcription. There are two types of RT inhibitors:

1. Nucleoside/nucleotide RT inhibitors (NRTIs) known as nucleoside analogues or “nukes” and were the first agents available for the treatment of HIV Infection. NRTIs interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase and termination of the DNA chain[1]. Without the DNA, HIV is unable to make functional copies of itself

2. Non-nucleoside RT inhibitors (NNRTIs) bind to RT, interfering with its ability to convert HIV RNA into HIV DNA. NNRTIs (Efavirenz, in particular) are part of preferred initial regimens [2].

Protease Inhibitors (PI) interfere with the HIV protease enzyme, which normally cuts long chains of HIV proteins into smaller individual proteins. PI prevent subsequent cleavage of polypeptides and thus prevent assembling new viral particles [3].

Fusion Inhibitors interfere with the virus’s ability to fuse with a cellular membrane, preventing HIV from entering a cell.

Entry inhibitor (Chemokine Receptor Antagonists) interfere with the virus’ ability to bind

to receptors on the outer surface of the cell it tries to enter. When receptor binding fails, HIV cannot infect the cell.

Integrase Inhibitors block the HIV enzyme integrase, which the virus uses to integrate its genetic material into the DNA of the cell it has infected.

Multi-class Combination Products combine HIV drugs from two or more classes, or types, into a single product (Table II).

Table II - Multi-class Combination Products

Combivir (retrovir + epivir) (ZDV/3TC)
Kivexa (abacavir + epivir) (ABC/3TC)
Trizivir(retrovir +epivir+ abacavir) (ZDV/3TC/ABC)
Truvada (tenofovir + emtricitabine) (TDF/FTC)
Atripla (efavirenz + tenofovir + emtricitabine) (EFV/ TDF/FTC)
Kaletra (lopinavir + ritonavir) (LPV/r)
Complera (rilpivirine + tenofovir + emtricitabine) (RPV /TDF/FTC)
Stribild (formerly Quad) (elvitegravir + cobicistat + tenofovir + emtricitabine) (EVG/COBI /TDF/FTC)
Triumeq (formerly Trii) (dolutegravir + abacavir + lamivudine) (DTG/ABC/3TC)

The standard of care for treatment of HIV-1 infection involves the use of a combination of at least three ART drugs belonging to different classes [2].

At present there are four options that combine drugs from two different groups into a complete HIV drug regimen. A patient prescribed one of these combinations takes only one tablet, once a day (Atripla, Complera, Triumeq and Stribild) [2].

Integrase inhibitors are a new class of antiretroviral agents and have the role of to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. The first integrase inhibitor approved by the U.S. Food and Drug Administration (FDA) on October 12, 2007 was raltegravir followed by elvitegravir on August 27, 2012 and dolutegravir which was approved by the FDA on August 13, 2013 and by the European Commission for use throughout the European Union on January 16, 2014 [4, 5, 6].

Pharmacodynamics

Dolutegravir is metabolized primarily by uridine diphosphate glucuronyltransferase (UGT)1A1, with renal elimination of unchanged drug being extremely low (< 1% of the dose). Fifty-three percent of the total oral dose is excreted unchanged in the feces but it is unknown if all or part of this is due to unabsorbed drug or some percentage of biliary excretion of the glucuronide conjugate which can be further degraded to form the parent compound in the gut lumen [7]. Thirty-one percent of the total oral dose is excreted in urine in which consists of the ether glucuronide of dolutegravir (18.9%), a metabolite formed by oxidation at the benzylic carbon (3.0%), and its hydrolytic N-dealkylation product (3.6%) [8].

DTG has a minor role of cytochrome P450 (CYP)3A. Based on data from extensive in-vitro studies examining DTG and potential inhibition (or induction) of enzymes or transport proteins, DTG is not expected to affect the PK of drugs that are substrates of these key CYP enzymes or transport

proteins [9], (Table3).

Table III - Drug interaction potential of DTG [9]

Key enzymes	Transport proteins
CYP1A2	P-gp
CYP2A6	BCRP
CYP2B6	OATP1B1
CYP2C8/9	OATP1B3
CYP2C19	OCT
CYP2D6	MRP2
CYP3A	MRP4
UGT1A1	MATE2-K
UGT2B7	

UGT, UDP-glucuronosyltransferase; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OATP, organic anion-transporting polypeptide; MRP, multi-drug resistance protein; MATE, Multidrug and toxin extrusion protein

Pharmacokinetics study demonstrated that DTG does not induce or inhibit the CYP3A isozyme in vivo [10]. Geometric least squares (GLS) mean ratio (MDZ+DTG/MDZ alone) was 0.945 (90% CI: 0.82–1.10), plasma MDZ AUC_{0–t} was similar with MDZ + DTG 25 mg versus MDZ alone and reduction in exposure of DTG with midazolam = $1 - 0.945 = 0.055 = 5.5\%$ [10].

Dolutegravir has a long half-life (~14 hours) with steady-state achieved after ~5 days[10]. This was demonstrated by MinS et al, in healthy volunteers, who observed that t_{1/2} was 13–15 hours following single administration of DTG, T_{max} was 0.5–3 hours and DTG was still detectable in plasma up to 72 hours after single dosing [9]. In HIV infected patients PK variability was low-to-moderate (CV 25–50%), Median T_{max} was 1.5–2.5 hours and mean t_{1/2} was 11–12 hours after multiple doses [10].

Song I et al demonstrated that low, moderate and high fat meals increased DTG (50mg) AUC_{0–∞} by 33%, 41% and 66%, respectively but this increase in DTG exposure is not anticipated to impact clinical safety, and therefore DTG can be taken without regard to meals [11].

Dolutegravir is highly protein bound (≥98.9%) to human plasma proteins.[6]. The median dolutegravir

concentration in the CSF (cerebrospinal fluid) was 18 ng/mL after 2 weeks of treatment [6]. A Phase IIIb study assessed the distribution of DTG in CSF: DTG concentrations observed in CSF at both Week 2 and Week 16 exceeded the in-vitro IC₅₀ against wild-type viruses (0.2 ng/mL) for all subjects, suggesting that DTG was able to achieve therapeutic concentrations in the CSF. DTG concentrations in CSF were similar to unbound DTG concentrations in plasma at Week 16, there were statistically significant correlations between DTG CSF and plasma (both total and unbound) concentrations (levels were similar to those observed at Week 2) [12].

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the active site and blocking the strand transfer step to retroviral DNA integration, an essential step of the HIV replication cycle and will result in an inhibition of viral activity [8].

Medical use

Dolutegravir is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg who are treatment-naïve or treatment-experienced [9].

Clinical trials

Efficacy

Efficacy and Safety of Dolutegravir were studied in 4 ART-naïve clinical trials (SPRING-1, SPRING-2, SINGLE, FLAMINGO) in 1 ART-experienced, INI-naïve (integrase inhibitor – naïve) study (SAILING) and in 1 antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1 (VIKING-3 study)

In SPRING-1, 205 patients were randomly (1:1:1:1) in a phase 2b, multicentre, dose-ranging study, treatment-naïve adults. The patients received 10 mg, 25 mg, or 50 mg dolutegravir versus 600 mg efavirenz associated with NRTI (tenofovir plus emtricitabine or abacavir plus lamivudine). Week 16 response rates to viral loads of at most 50 copies per mL were 93% for all doses of dolutegravir and 60% for efavirenz; week 48 response rates were 87% for all doses of dolutegravir and 82% for efavirenz [13]. The author concluded that Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses [13].

SPRING-2 was a 96 week, phase 3, randomized, double-blind, active-controlled, non-inferiority study. Patients were randomly assigned (1:1), 411 patients received dolutegravir 50 mg once daily and 411 raltegravir 400 mg twice daily plus an NRTI backbone (tenofovir/emtricitabine or abacavir/lamivudine).

At 48 weeks, 361 (88%) patients in the dolutegravir group achieved an HIV-1 RN. A value of less than 50 copies per mL compared with 351 (85%) in the raltegravir group (adjusted difference 2.5%; 95% CI –2.2 to 7.1) [14]. At week 96, 332 (81%) of 411 patients in the dolutegravir group and 314 (76%) of 411 patients in the raltegravir group had HIV-1 RNA less than 50 copies per mL (adjusted difference 4.5%, 95% CI –1.1% to 10.0%) [15]. These results confirm non-inferiority of DTG 50mg once daily compared with raltegravir 400 mg twice daily.

SINGLE was another randomized, double-blind, phase 3 study in naïve HIV-infected patients. Were enrolled 833 patients received dolutegravir 50

mg plus abacavir-lamivudine once daily (DTG-ABC-3TC group) or efavirenz-tenofovir-disoproxilfumarate (DF) - emtricitabine combination, once daily (EFV-TDF-FTC group). At week 48, the proportion of patients with HIV-1 RNA level less than 50 copies/ml was significantly higher in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (88% vs. 81%, $P=0.003$) and the authors concluded that DTG plus abacavir-lamivudine was more effective through 48 weeks than the regimen with efavirenz-tenofovir DF-emtricitabine [16].

Based on the conclusion that DTG is non-inferior to an integrase inhibitor (raltegravir and superior to a non-nucleoside reverse transcriptase inhibitor (efavirenz), FLAMINGO study demonstrated that dolutegravir 50 mg once-daily in combination with NRTIs was superior to darunavir 800 mg plus ritonavir 100 mg once-daily in naive HIV-infected patients. Were enrolled 484 patients, 242 in each group. At week 48, 217 (90%) patients receiving dolutegravir and 200 (83%) patients receiving darunavir plus ritonavir had HIV-1 RNA of less than 50 copies/mL (adjusted difference 7.1%, 95% CI 0.9–13.2), which proves that dolutegravir was superior to darunavir plus ritonavir ($p=0.025$) [17].

In SAILING study, ART-experienced, INI-naïve 715 patients were randomly assigned (1:1) to once-daily dolutegravir 50 mg (354 patients) or twice-daily raltegravir 400 mg (361 patients) in combination with investigator-selected background therapy. At week 48, 251 (71%) patients on dolutegravir had HIV-1 RNA less than 50 copies/mL versus 230 (64%) patients on raltegravir (adjusted difference 7.4%, 95% CI 0.7 to 14.2) This demonstrates the superiority of dolutegravir compared with raltegravir in these patients ($p=0.03$) [18].

In a single-arm, open-label, phase III VIKING study were included highly treatment-experienced patients with HIV-1 resistant to most ART drugs and to raltegravir (RAL). 183 patients received DTG 50 mg BID and 69% of them achieved HIV-1 RNA less than 50 copies/mL at week 24. Authors of this study concluded that dolutegravir (DTG), would be efficacious in INI-resistant patients at the 50 mg twice daily (BID) dose.

The conclusions of these studies show that DTG 50mg once daily is an effective antiviral drug

in naive HIV infected patients and DTG 50mg twice daily may be effective in experiencing patients with resistance to raltegravir.

Resistance

ART-naïve clinical trials no additional resistance to integrase inhibitors was detected since week 48 in patient receiving dolutegravir [14-17].

In SAILING study (ART-experienced, INI-naïve patients) only 4 patients in the dolutegravir group had phenotypic resistance of integrase inhibitor by week 48, in comparison with raltegravir group (4 [1%] of 354 vs 17 [5%] of 361 patients, $p=0.003$; adjusted difference -3.7% , 95% CI -6.1 to -1.2 , $p=0.003$) [18]. Two DTG subjects had HIV-1 with K substitutions at position R263 at the time of virological failure, with (fold change) FC in IC50 <2 to DTG and RAL and a further two subjects on DTG were found to have additional mutations [18-19].

In Viking study was demonstrate that resistance was limited and high level DTG resistance requires multiple RAL resistance mutations. During 24 weeks of treatment with DTG 50 mg twice daily, integrase resistance emergence occurred in $<15\%$ of all subjects, and these mutations were previously described RAL-associated [20]. Another authors [21] reported in a recent study the emergence of an R $\rightarrow$ K substitution at position 262 (R262K) in HIV-1 subtype B patient with H51Y substitution in integrase.

Hardy I. et al. concluded in his article that five mutations (A49P, L68FL, T97A, E138K and L234V) were implicated in dolutegravir resistance in one treatment-experienced patient with major N155H raltegravir mutation [22] and Hightower et al. demonstrated that the highest genetic barrier of DTG may be attributed to its significantly slower rate of dissociation from the integrase enzyme in viruses that are either wild type or contain the N155, Q148 or Y143 mutations [23].

Table IV - Dissociation $t_{1/2}$ ratio for DTG, RAL and EVG by *ini*-related mutation [23]

$t_{1/2}$ (h) at 37°C	DTG	RAL	EVG
WT	71	8.8	2.7
E92Q	17	3.3	0.4
E138K	84	11	3.7
G140S	20	4.4	1.1
Y143C	60	2	2.1
Y143H	44	2.5	1.6
Y143R	42	1.1	1.7
Q148H	5.2	0.2	0.2
Q148K	11	0.3	ND
Q148R	9.2	0.4	ND
N155H	9.6	0.6	0.4
E92Q /N155H	3.9	0.3	ND
E138K/ Q148R	3.6	0.2	ND
G140S/ Q148H	3.3	0.2	ND

WT = wild-type, ND = not determined

After analyzing the literature we conclude that DTG has a high barrier to resistance and is generally active against raltegravir-resistant mutants Y143R, Q148K, N155H, and G140S/Q148H [24].

Safety. Adverse events

Common side effects of DTG included insomnia and headache in low percent (incidence $\geq 2\%$). Serious side effects included allergic reactions and abnormal liver function in patients who were co-infected with hepatitis B or C [4,5]

In SPRING study, the adverse events at week 96 was similar in DTG and raltegravir group patients and no evidence of changes in the lipid profile or in serum creatinine were observed. [15] (Table V).

Table V - The common adverse events in SPRING study [15]

AE	DTG (n = 411)	RAL (n = 411)
Nausea	15%	14%
Nasopharyngitis	13%	14%
Diarrhea	14%	13%
Headache	14%	13%

In SINGLE study, drug-related adverse events were reported more frequently in efavirenz/tenofovir - emtricitabine group patients than patients who received dolutegravir plus abacavir - lamivudine (66% vs. 43%) and the most frequent adverse events were diarrhea, nasopharyngitis, nausea, headache, fatigue, rash and neuropsychiatric events [16]. Psychiatric and nervous system disorders (most frequent in patients who received efavirenz - tenofovir - emtricitabine) were usually causes of discontinuation [16].

FLAMINGO study discontinuation due to drug-related adverse events was less frequent for dolutegravir (2%) than for darunavir (DRV) plus ritonavir (RTV) (4%) [17]. In the following table it can be seen the most common adverse events [17], (Table VI).

Table VI - The common adverse events in FLAMINGO study [17].

AE	DTG (n = 242)	DRV plus RTV (n = 242)
Diarrhea	17%	29%
Nausea	16%	18%
Headache	15%	10%
Nasopharyngitis	9%	8%
Upper respiratory tract infection	5%	10%
Insomnia	7%	6%
Cough	5%	7%
Vomiting	6%	6%
Fatigue	6%	5%
Pyrexia	5%	6%
Dizziness	6%	5%
Rash	4%	6%
Back pain	4%	5%
Pharyngitis	3%	5%
Bronchitis	2%	5%
Sinusitis	2%	5%
Depression	5%	2%
Arthralgia	2%	5%

In SAILING study was reported adverse events in $\geq 5\%$ of patients in either group [18] (Table VII)

Table VII - The common adverse events in SAILING study [18]

AE	DTG (n = 357)	RAL (n = 362)
Diarrhea	20%	18%
Upper respiratory tract infection	11%	8%
Headache	9%	9%
Nausea	8%	8%
Cough	9%	7%
Influenza	7%	7%
Nasopharyngitis	6%	6%
Urinary tract infection	7%	5%
Vomiting	6%	6%
Fatigue	4%	7%
Rash	5%	5%
Arthralgia	3%	5%
Upper abdominal pain	5%	1%
Alanine aminotransferase (IU/L)	3%	2%
Cholesterol (mmol/L)	2%	4%
Creatinine ($\mu\text{mol/L}$)	<1%	<1%
Hyperglycaemia (mmol/L)	1%	2%
Lipase (U/L)	1%	2%
Total bilirubin ($\mu\text{mol/L}$)	6%	4%
Creatine phosphokinase	2%	1%

Drug-related grade 2–4 adverse events were seen in the similar percentages in the DTG group (28 patients, 8%) and raltegravir group (32 patients, 9%) and drug-related serious adverse events only in fewer cases (2 patients, 1% in DTG group and 4 patients, 1% in raltegravir group), which demonstrates a good tolerability [18].

Drug-drug interaction

No dose adjustment required in the most treatment regimens. Treatment-naïve or treatment-experienced INSTI-naïve when co-administration

with potent UGT1A/CYP3A inducers (efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin): recommended increase dose to 50 mg PO BID [5,9] (Table VIII).

Table VIII - Impact of ARVS on DTG exposure [5,9]

Co-administered drug	DTG C _{trough} C ₂₄ Geometric mean	Recommendation
Protease inhibitors DRV/r 600/100 mg BID ATV/r 300/100 mg QD LPV/r 400/100 mg BID	↓38% ↑121% ↓6%	No DTG dose adjustment required No DTG dose adjustment required No DTG dose adjustment required
NNRTIs RPV 25 mg QD EFV 600 mg QD ETR 200 mg BID	↑22% ↓75% ↓88%	No DTG dose adjustment required DTG 50 mg BID should be given DTG should not be given with ETR without co-administration of ATV/r, DRV/r or LPV/r
NRTIs TDF 300 mg QD	↓8%	No DTG dose adjustment required

C_{trough}, trough concentration

DRV/r – darunavir/ritonavir, ATV/r – atazanavir/ritonavir, LPV/r – lopinavir/ritonavir, NNRTI - non-nucleoside reverse transcriptase inhibitor, RPV – rilpivirine, EFV – efavirenz, ETR – etravirine, NRTI - nucleoside reverse transcriptase inhibitor.

DTG should be administered 2 hours before or 6 hours after medications containing polyvalent cations and after supplements containing iron or calcium [5,9] (Table IX).

Table IX - Impact of medications containing polyvalent cations and acid-lowering agents on DTG exposure [5,9]

Co-administered drug	DTG C _{trough} C ₂₄ Geometric mean	Recommendation
Medications containing polyvalent cations Magnesium oral/aluminium-containing antacid Calcium supplements Iron supplements Multivitamins containing calcium or iron	↓30% ↓39% ↓56% ↓32%	DTG should be administered 2 hours before or 6 hours DTG should be administered 2 hours before or 6 hours DTG should be administered 2 hours before or 6 hours DTG should be administered 2 hours before or 6 hours
Other acid-lowering agents Omeprazole	↓5%	No significant effect observed

In Tuberculosis recommended increase dose to 50 mg PO BID only in presence of rifampin [5,9] (Table X). No DTG dose adjustment required in patient with chronic hepatitis C in treatment with telaprevir or boceprevir and based on their metabolic pathways, drug interactions are not anticipated with

DTG and simeprevir or sofosbuvir [25-27].

Table. X - Impact of drugs used to treat Tb and Hcv on DTG exposure [5,9,25]

Co-administered drug	DTG Cror C24 Geometric mean	Recommendation
Anti-TB drug Rifampin 600 mg QD Rifabutin 300 mg QD	↓72% ↓30%	DTG 50 mg BID should be given No DTG dose adjustment required
Anti-HCV drug TVR 750 mg every 8 hours BCV 800 mg every 8 hours	↑37% ↑8%	No DTG dose adjustment required No DTG dose adjustment required

Conclusions

DOLUTEGRAVIR the new generation of Integrase Inhibitors is an effective and safe ART drug in naive and ART-experienced HIV infected patient. As was shown in clinical studies it has potential advantages in comparison to first-generation INSTI's, including un-boosted daily dosing, limited cross resistance with other integrase inhibitors (raltegravir and elvitegravir) and a high barrier to resistance [28]. Based on these findings, dolutegravir is expected to be an excellent new treatment option especially for naïve patients with HIV but also for experienced patients.

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