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PERMANYER

AIDS Rev. 2016;18:89-100

Is It Time for Integrase Inhibitors to be the Preferred Regimen for the First-Line Treatment of HIV-1-Infected Naive Patients?

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Abstract

Thanks to the emergence of combination antiretroviral therapy, HIV/AIDS has been transformed into a manageable, chronic condition in just 30 years and the life expectancy of patients living with HIV is now comparable to those without. Recent data (START) support the strategy of starting all HIV-positive patients regardless of CD4 count. However, patients and physicians want more than just viral control: they want better tolerability, convenience, and few drug-drug interactions. Are the guidelines right in recommending an integrase inhibitor-based regimen as the first-line treatment of choice? **(AIDS Rev. 2016;18:89-100)**

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Key words

Integrase inhibitor. Protease inhibitor. Efavirenz. First line antiretroviral therapy.

Introduction

In just 30 years, HIV/AIDS has been transformed into a manageable, chronic condition and the life expectancy of patients living with HIV is now comparable to those without. This is mainly due to the emergence of combination antiretroviral therapy (cART)[1,2]. More than 20 antiretroviral (ARV) drugs are available to treat HIV infection today[3-6]. Patients and physicians want more than just viral control – they want better tolerability, convenience, and few drug-drug interactions. New classes of ARV, integrase inhibitors (INI), are now available as part of cART[7]. With the efficacy and tolerability of this new class of ARV (INIs) and the fact that one of the major goals of ART is the use of effective well-tolerated regimens that require little long-term monitoring, we need to continually re-evaluate what we consider to be the preferred regimen in the light of new data[8].

In daily practice, physicians are preferentially prescribing INIs as third agent of cART for naive HIV-1-infected patients (in one AIDS Reference center for instance, INIs were used as third agents in more than 90% of naive patients in whom treatment was initiated; personal communication). All 2014 international guidelines recommended INIs as part of cART[9-12]. The Spanish guidelines (GESIDA) only have INIs as preferred choice and the recent updated US Department of Health and Human Services (DHHS) and European AIDS Clinical Society (EACS) guidelines have only ritonavir-boosted ritonavir (DRV/r) and INIs as preferred third agent of cART. Efavirenz (EFV) and ritonavir-boosted atazanavir (ATV/r) regimens are now considered as alternatives choices[13-15]. Rilpivirine (RPV) remains recommended as first-line therapy in patients with viral load (VL) < 100,000 copies/ml and CD4 cell count > 200 mm^3 by new EACS guidelines[15].

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In this paper we review available evidence from phase III randomized clinical trials in terms of efficacy, tolerability, drug-drug interactions, adverse events, and risk of drug resistance profile between the most prescribed non-nucleoside reverse transcriptase inhibitor (NNRTI), EFV, and the ritonavir-boosted protease inhibitors atazanavir (ATV or DRV) and INIs.

The end of efavirenz as the gold standard for first-line treatment?

Efavirenz, a NNRTI of HIV-1, has been recommended as a preferred third agent together with two nucleos(t)ides for first-line combination ART for more than 15 years. This choice is based on the virological and pharmacological properties of EFV, such as its high *in vitro* potency, pharmacological forgiveness in regard to missed doses, and simplicity of dosing usually in a fixed-dose combination. Indeed, the availability of a once-daily, single tablet regimen, the first including EFV, represented an important milestone with regard to convenience and potential for improved patient adherence, a factor that is most important in determining the success or failure of any ART regimen[16]. It remained a gold standard for many years as consistent data from multiple randomized clinical studies demonstrated that EFV-containing regimens were "unbeaten" in terms of rates of virological suppression[17-24] and it worked at all baseline viral loads and CD4 counts[25]. In addition the forgiveness of efavirenz due to its long half life was a big advantage over other drugs and even led to two studies where it was taken five days a week (with a week-end off drug) without virological failure in patients with long-term suppressed viral load[17-18]. Accordingly, EFV has been the comparator for clinical trials and is recommended by the World Health Organization in resource-limited settings[25]. Adverse side effects associated with the use of efavirenz, notably its central nervous system (CNS) side effects (neuropsychiatric toxicity in particular), remain a major concern. The association of EFV and suicidality, which came out of the ACTG trials, is concerning but has not been confirmed by cohort data and remains an important area of debate[26-28]. Other negative issues include short- and long-term neuropsychiatric side effects, its low genetic barrier to resistance, and its FDA Category D ranking in pregnancy[29]. Given the availability of new treatment options, the place of EFV as the treatment of choice has been reconsidered and guideline committees are moving it into the alternative category.

Rilpivirine (RPV) has challenged EFV as an alternative NNRTI[30-32]. It too has problems, with the need for sufficient calorie intake and the need to avoid gastroprotective medication such as proton pump inhibitors. The STaR study was a multicenter, international, randomized, open-label phase IIIb 96-week study that evaluated two single-tablet regimens, tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) and TDF/FTC/RPV, in first-line ART in 786 HIV-1 antiretroviral-naive adults. Randomization involved stratification on the basis of baseline HIV-1 RNA (≤ or > 100,000 copies/ml). Overall, the RPV arm was superior to EFV arm in the subgroup with viral load ≤ 100,000 copies/ml and was non-inferior in the subgroup with viral load > 100,000 copies/ml[29]. In patients with pre-ART viral load > 500,000 copies/ml, virologic failure was more common in RPV-treated patients than in EFV-treated patients. The combination TDF/ FTC/RPV was also better tolerated than TDF/FTC/EFV, with significantly fewer nervous system and psychiatric adverse events (p = 0.001) and significantly fewer discontinuations due to adverse events (3 vs. 11%, respectively). Resistance development to TDF/FTC/RPV consisted of NNRTI and NRTI mutations and was more frequent than resistance development to TDF/FTC/EFV through week 96. Emergent resistance after week 48 was infrequent in both arms. Within the TDF/ FTC/RPV arm, resistance development was more frequent in subjects with baseline HIV-1 RNA > 100,000 copies/ml compared to baseline HIV-1 RNA ≤100,000 copies/ml[33]. In the Echo-thrive trial patients with pre-ART viral load > 100,000 copies/ml or CD4 < 200 mm^3 experienced more virologic failure in the RPV arm than in the EFV arm compared to those with pre-ART viral load < 100,000 copies/ml or CD4 > 200 per cubic mm^3[32]. These results explain the place of RPV in new DHHS or EACS guidelines[14,15].

Could EFV side effects be improved by dose reduction? Recently the ENCORE1 study demonstrated at 48 week non-inferiority of EFV 400 vs. 600 mg, with 10% reduction of side effect particularly in neuropsychiatric adverse events[34]. Data was confirmed at 96 weeks[35]. Although this reduction was not as big as was expected, the biggest advantage of the 400 mg dose would be the overall cost reduction in low- and middle-income countries.

Integrase inhibitors versus efavirenz as the first-line agent of choice?

Efavirenz has been compared with INIs (raltegravir, elvitegravir, dolutegravir) in three pivotal phase III

studies: STARTMRK[36-38], Single[39-41], and Study 102[42-44], respectively.

STARTMRK

STARTMRK was a phase III trial in which 566 previously untreated HIV patients without baseline resistance to EFV, TDF or FTC were randomized to raltegravir (RAL) twice daily or EFV once daily, both combined with the TDF/FTC backbone[36-38]. It was the first study to show superiority over EFV (192 weeks). At 48 weeks the main analysis (with non-completion counted as failure) showed that 86.1% of the RAL group and 81.9% of the EFV group achieved virological suppression below 50 copies/ml (Table 1). Efficacy outcomes were comparable between patients with high baseline HIV-1 RNA (> 100,000 copies/ml) and those with baseline viral load ≤ 100,000 copies/ml. As expected, the time to achieve such viral suppression was shorter for patients on RAL than on EFV (log-rank test $p < 0.0001$). Significantly fewer drug-related clinical adverse events occurred in patients on RAL (n = 124, 44.1%) than those on EFV (n = 217, 77.0%; $p < 0.0001$); 2.6 vs. 6% discontinued due to adverse events in the RAL group compare to EFV, respectively (Table 1). Neurotoxicity, such as headache, dizziness, and sleep disorders was more frequently observed in the EFV group than in the RAL group. All CNS-related adverse events were classified as mild in 46 of 74 (62%) RAL recipients, whereas 132 of 167 (79%) EFV recipients experienced neuropsychiatric symptoms (Table 2). Only one patient, who was on EFV, discontinued the trial because of CNS-related adverse events. After 240 weeks, HIV viral load remained < 50 copies/ml in 71% of patients treated with TDF/FTC/RAL and 61% treated with TDF/FTC/EFV.

SINGLE

SINGLE was a phase III randomized controlled trial, directly comparing an INI-based treatment regimen dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) once daily with an EFV-based regimen (TDF/FTC/EFV once daily) in treatment-naive patients[39-41] (Table 1). At week 48, the proportion of participants with an HIV-1 viral load of < 50 copies/ml was significantly higher in the DTG /ABC/3TC group than in the TDF/FTC/EFV group (88 vs. 81%; $p = 0.003$), thus meeting the criterion for superiority. The DTG/ABC/3TC group had a shorter median time to viral suppression than the TDF/FTC/EFV group (28 vs. 84 days; $p < 0.001$), as well as greater increases in $CD4^+$ T-cell count (267 vs. 208 mm^3; $p < 0.001$). Efficacy outcomes were comparable between patients with high baseline viral load (> 100,000 copies/ml) and those with baseline viral load ≤ 100,000 copies/ml. The proportion of participants who discontinued therapy due to adverse events was lower in the DTG/ABC/3TC group than in the TDF/FTC/EFV group (2 vs. 10%); rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common in the TDF/FTC/EFV group, whereas insomnia was reported more frequently in the DTG/ABC/3TC group (Table 2). Superiority was therefore driven by tolerability. DTG/ABC/3TC remained superior at 96 and 144 week time points[40,41].

No participants in the DTG/ABC/3TC group had detectable antiviral resistance; one TDF-associated mutation and four EFV-associated mutations were detected in participants with virologic failure in the TDF/FTC/EFV group (Table 3).

Study 102

Study 102 was a phase III trial comparing the first-generation boosted INI, elvitegravir/cobicistat (EVG/COBI) + TDF/FTC with EFV/TDF/FTC[42-44]. A total of 700 patients were randomly assigned and treated (348 with EVG/COBI/FTC/TDF, 352 with EFV/FTC/TDF). EVG/COBI/FTC/TDF was non-inferior to EFV/FTC/TDF; 87.6 vs. 84.1% of patients had HIV viral load < 50 copies/ml at week 48 (Table 1). Proportions of patients discontinuing drugs for adverse events did not differ substantially (3.7% in the EVG/COBI/FTC/TDF group vs. 5.1% in the EFV/FTC/TDF group). Nausea was more common with EVG/COBI/FTC/TDF than with EFV/FTC/TDF (20.7 vs. 13.7%); dizziness (6.6 vs. 24.4%), abnormal dreams (15.2 vs. 27%), insomnia (8.6 vs. 13.9%), and rash (6.3 vs. 12.2%) were less common in the EVG/COBI/FTC/TDF group (Table 2). Serum creatinine concentration increased more by week 48 in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (median 13 µmol/l, IQR 5-20 vs. 1 µmol/l, –6 to 8; $p < 0.001$). The study showed similar rates of virological suppression and similar rates of viral failure for EVG/COBI at 48 and 96 weeks and 144 weeks[42-44] (Table 2). In the EVG/COBI/FTC/TDF group, eight had resistance mutations (Table 3). These eight patients had NRTI resistance mutations (five had M184V/I only, three had M184V/I and K65R). Seven of the eight patients also had integrase resistance mutations (mainly E92Q). In the EFV/FTC/TDF group, eight developed

Table 1. Summary of all randomized clinical trials in naive patients between integrase inhibitors and efavirenz or protease inhibitors[36-62]

Study characteristics	STARTMRK (RAL)[36-38]	SINGLE (DTG)[39-41]	STUDY 102 (EVG)[42-44]	STUDY 103 (EVG)[58-60]	FLAMINGO (DTG)[48,49]	ACTG 5257 (RAL)[45-47]
Design	Double-blind	Double-blind	Double-blind, double-dummy	Double-blind, double-dummy	Open-label multicenter phase III	Open-label
Duration (years)	5	3	5	5	4	5
comparator	EFV	EFV	EFV	ATV	DRV	DRV/ATV
Nucleotide/nucleoside backbone	TDF + FTC	ABC/3TC	TDF/FTC	TDF/FTC	TDF/FTC or ABC/3TC	FTC/TDF
n, total	563	833	700	708	484	1,809
Female (%)	19	16	11%	10%	13%	24%
Median baseline HIV-1 RNA (log_{10} copies/ml)	5	4.68	4.75	4.8	4.49	4.6
Median baseline CD4 (cells/mm^3)	2O8	338	376	351	395	308
Primary endpoint	Per protocol, non-completer = failure	ITT-FDA Snapshot	ITT-FDA Snapshot	ITT-FDA Snapshot	ITT-FDA Snapshot	ITT (regardless of ART change)
Non-inferiority margin	12%	10%	12%	12%	12%	12%
Week 48 outcome HIV-1 RNA < 50 copies/ml (INI vs. comparator)	86.1 vs. 81.9%	88 vs. 81%	87.6 vs. 84.1%	89.5 vs. 86.8%	90 vs. 83%	92 vs. 88% (DRV) vs. 90% (ATV)
Difference in virological success (95% CI)	4.2 (–1.9 to 10.3)	7% (2-12)	3.6% (–1.6 to 8.8)	3% (–1.9 to 7.8)	7.1% (0.9-13.2)	ATV vs. RAL 3.4 % (–0.7 to 7.4), DRV vs. RAL 5.6% (1.3-9.9), ATV vs. DRV –2.2% (–6.7 to 2.3)
Discontinuation for AE (INI vs. comparator)	2.6 vs. 6.0%	2.4 vs. 10.0%	3.7 vs. 5.1%	3.7 vs. 5.1%	2 vs. 4%	NA
Response rate, baseline HIV-1 RNA < 100,000 copies/ml (INI vs. comparator); difference (95% CI)	92.5 vs. 89.1%; 3.4% (–4.1 to 11.0)	90.4 vs. 82.6% (2-13)	NA	NA	88 vs. 87%	NA
Response rate, baseline HIV-1 RNA > 100,000 copies/ml (INI vs. comparator); difference (95% CI)		82.8 vs. 76.3%	NA	NA	93 vs. 70%	NA
Week 96 outcome HIV-1 RNA < 50 copies/ml (INI vs. comparator)	81 vs. 79%	80 vs. 72%	84.2 vs. 81.5%	83 vs. 82%	80 vs. 68%	94 vs. 89% (DRV) vs. 88% (ATV)
Difference in virological success (95% CI)	2% (–4 to 9)	8 % (2.3-13.8)	2.7% (–2.9 to 8.3)	1.1% (–4.5 to 6.7)	12%	ATV vs. RAL 3.4% (–0.7 to 7.4), DRV vs. RAL 5.6% (1.3-9.9), ATV vs. DRV –2.2% (–6.7 to 2.3)
Week 96 response rate, baseline HIV-1 RNA < 100,000 copies/ml (INI vs. comparator); difference (95% CI)	NA	DTG was superior to EFV	85.7 vs. 80.9%; 4.7% (–2 to 11.5)	84 vs. 84%	80 vs. 73%	NA

(Continue)

Table 1. Summary of all randomized clinical trials in naive patients between integrase inhibitors and efavirenz or protease inhibitors[36-62] *(continued)*

Study characteristics	STARTMRK (RAL)[36-38]	SINGLE (DTG)[39-41]	STUDY 102 (EVG)[42-44]	STUDY 103 (EVG)[58-60]	FLAMINGO (DTG)[48,49]	ACTG 5257 (RAL)[45-47]
Week 96 response rate, baseline HIV-1 RNA > 100,000 copies/ml (INI vs. comparator); difference (95% CI)	NA	DTG was non-inferior TO EFV	81.4 vs. 82.8%; –1.4% (–11.2 to 8.4)	82 vs. 80%	82 vs. 52%	NA
Discontinuation for AE (INI vs. comparator)	3.6 vs. 6.7%	3 vs. 11%	5 vs. 7%	4 vs. 6%	2 vs. 3%	1 vs. 5% (DRV) vs. 16% (ATV)
Long-term outcome (HIV-1 RNA < 50 copies/ml at week 144 or 240); difference in virological success (95% CI)	71.0 vs. 61.3%; 9.5% (1.7-17.3) Difference in patient with VL < 100,000 copies/ml	71 vs. 63%; 8% (2.0-14.6)	82 vs. 78%	81 vs. 79%	NA	94 vs. 90% (DRV) vs. 90% (ATV)
Emergence of resistance (INI vs. comparator)	NA	0 vs. 2%	3 vs. 3%	2 vs. < 1%	None in each arm	3 vs. < 1% (DRV) vs. 1.5% (ATV)
Study conclusions	RAL/FTC/TDF seemed to have superior efficacy compared with EFV/FTC/TDF at week 144 and 240 (RAL was non-inferior at week 48 and 96)	Once-daily DTG was superior to once-daily EFV/FTC/TDF in treatment-naive HIV-1-positive individuals	EVG/COBI was non inferior to EFV/FTC/TDF	Once-daily EVG/FTC/TDF was non-inferior to ATZ/FTC/TDF	Once-daily DTG was superior to once-daily DRV/r in treatment-naive HIV-1-positive individuals	RAL proved superior to both protease inhibitors for the combined virologic/tolerability endpoint, and DRV proved superior to ATV for this endpoint
Main explanation of study conclusion	Result was driven by tolerability. Less CNS toxicity and less discontinuation in RAL arm	Result was driven by tolerability. Less rate of discontinuation due to AEs in DTG arm			Discontinuation for AE and others reasons and virological response in high VL	Superiority of RAL is driven by tolerability particularly jaundice and hyperbilirubinemia in ATV arm

INI: integrase inhibitor; ITT: intent to treat; FDA: Food Drug Administration; TDF: tenofovir; FTC: emtricitabine, EFV: efavirenz; ATV: atazanavir; ABC: abacavir; 3TC: lamivudine; DTG: dolutegravir; RAL: raltegravir; EVG: elvitegravir; COBI: cobicistat; DRV: darunavir; NA: not available; VL: viral load; AE: adverse event.

resistance to one or more components of EFV/ FTC/TDF; the most common resistance profile was the K103N mutation (seven patients, five with K103N, two with K103N, M184V, and K65R).

Thus, INIs offer a real alternative to EFV. They are superior (RAL, DTG) or non-inferior (EVG/COBI) when compared to EFV. These results are driven not only by virological efficacy, but preferentially by tolerability. A particular concern of EFV is its neuropsychiatric toxicity, which can include dizziness that can persist for years, strange dreams, and an increased risk of suicide and attempted suicide (suicidality)[26-28]. Mollan, et al.[28] in a recent meta-analysis of four randomized controlled trials showed an increased rate of suicidality events (suicidal ideation or attempted/completed suicide) associated with EFV compared to other regimens, but only a trend towards a higher rate of completed/attempted suicides, as only 17 events occurred. However, in two large real world databases in the USA, EFV use was not associated with suicidality or the expanded definition of suicide attempt[26]. HIV-infected patients with depression and psychiatric conditions were less likely to be prescribed EFV. A recent D:A:D[27] analysis showed no higher death rates from suicide amongst those receiving EFV. There are likely confounding factors by indication in these observational two studies. In light of conflicting results from randomized controlled trials, this potentially could suggest that in clinical practice, EFV may be less frequently prescribed in those with underlying psychiatric conditions. Reduced dose of EFV leads to fewer side effects[34,35], but there are no long term data on suicidality on this dose. New guidelines recommend thus EFV as an alternative choice[13-15].

Table 2. Summary of most frequent side effects of integrase inhibitors versus comparator in pivotal studies in HIV-infected naive patients[36-60]

	STARTMRK (RAL vs. EFV)[36-38#‡]	Single (DTG vs. EFV)[39-41#]	Study 102 (EVG. vs. EFV)[42-44#]	Study 103 (EVG/ ATV)[58-60#]	Flamingo (DTG vs. DRV)[48,49#]	ACTG 5257 (RAL vs. DRV vs. ATV)[45-47#]
Gastrointestinal	20.3 vs. 28.7%	16 vs. 21%	44 vs. 33%	42 vs. 36%	33 vs. 47%	18.3 vs. 25.7 vs. 25.1%
Neurological	18.1 vs. 49.5%	14 vs. 44%	21 vs. 34%	15 vs. 12%[†]	21 vs. 15%	14.5 vs. 12.6 vs. 25.1%
Psychiatric	18.5 vs 30.9	16 vs. 20%	33 vs. 52%	–	12 vs. 8%	–
Rash	1.1 vs. 8.2%[‡]	3 vs. 14%	6 vs. 12%		4 vs. 6%	–
Jaundice	–	–	–	1 vs. 14%	–	< 1 vs. < 1 vs. 47%[¶]

DTG: dolutegravir; RAL: raltegravir; ATV: atazanavir; EFV: efavirenz; DRV: darunavir; EVG: elvitegravir.
*CNS: neuropsychiatric.
[†]Headaches.
[‡]Moderate to severe.
[#]All grade(more frequent > 5-10%).
[¶]Hyperbilirubunemia.

What about protease inhibitors as the third agent of combined antiretroviral therapy

Ritonavir-boosted protease inhibitor regimens (PI /r) have antiviral potency and a high barrier for development of drug resistance. They are an alternative to NNRTIs for some patients, including those with transmitted resistance to NNRTIs, those unlikely to adhere to therapy, women of childbearing potential, or to avoid the neuropsychiatric disorders associated with EFV[4-6,9-12]. Regimens including ritonavir are generally well tolerated but are associated with metabolic complications such as dyslipidemia, lipodystrophy, insulin resistance, and multiple drug interactions[4-6]. The main limitation of ritonavir-based therapy is the additional pill, prescription burdens, and tolerability profiles of the PI/r. Atazanavir (ATV/r) and darunavir (DRV/r) boosted by ritonavir are the only two PI/r found in recommendations of international guidelines as the third agent of cART in HIV-naive patients[4-6,9-12]. However, recently DHHS and EACS guidelines recommended ATV/r as alternative PI regimen[13-15].

How do integrase inhibitors compare to protease inhibitor-based treatments in treatment-naive patients?

Integrase inhibitors have been compared to PI/r in HIV-infected naive patients in three phase III pivotal studies: ACTG 5257 (RAL vs. ATV/r vs DRV/r), Study 103 (EVG/COBI/TDF/FTC/ vs. ATV/r) and FLAMINGO (DTG vs. DRV/r) (Table 1).

ACTG 5257

ACTG 5257 was an open-label phase III study comparing two boosted PIs to RAL[45-47]. Treatment-naive patients were randomized in equal numbers to ATV/r once daily, RAL twice daily, or DRV/r once daily, all combined with backbone treatment with TDF/FTC once daily. Patients in each study arm were free to switch to one of the two other study arms if they were not satisfied with the tolerability of their initial treatment. Although rates of viral suppression were similar in the three arms when switching was excluded, rates were substantially higher with RAL when switching was considered as treatment failure (80% with RAL, 63% with ATV/r, and 73% with DRV/r at 96 weeks; intent to treat, off-ART = failure snapshot analysis). Raltegravir had a lower rate of switching due to tolerability failure than either of the boosted PIs. In particular, rates of switching due to jaundice/hyperbilirubinemia, which was very common with ATV (47%), and renal toxicity were lower with RAL. The authors of the trial concluded that RAL was superior to both PIs for the predetermined combined virologic/tolerability endpoint[45-47]. Because adverse effects were greater in ATV/r arm than the two others, DHHS and EACS recommended actually ATV/r as an alternative choice[14-15]. Resistance to INIs was detected in

Table 3. Virological failure and resistance in pivotal phase III study of integrase inhibitors[36-62]

	STARTMRK: RAL bid/FTC/TDF vs. EFV/FTC/TDF qd	STUDY 102: EVG/COBI/FTC/TDF qd vs. EFV/FTC/TDF qd	STUDY 103*: EVG/FTC/TDF qd vs. ATV/r/FTC/TDF qd	ACTG 5257: RAL bid vs. ATV/r qd vs. DRV/r qd with FTC/TDF qd	SINGLE: DTG/FTC/TDF qd vs. EFV/FTC/TDF qd	SPRING-2 (96 weeks)†: RAL bid vs. DTG qd with FTC/TDF or ABC/3TC qd	FLAMINGO: DTG vs. DRV/r qd with ABC/3TC or FTC/TDF qd
Protocol-defined virologic failure	27 vs. 39	14 (4) vs. 17 (5)	12 (3) vs. 8 (2)		–	22 (5) vs. 29 (7)	2 (< 1) vs. 2 (< 1)
INI-resistant mutations	4 vs. 0	7 (2%) vs. 0	4 vs. 0		0 (0) vs. 0 (0)	0 (0) vs. 1 (< 1)	0 (0) vs. 0 (0)
NRTI-resistant mutations	4 vs. 2	8 (2) vs. 2 (1)	4 vs. 0		0 (0) vs. 1 (< 1)	0 (0) 4 (< 1)	0 (0) vs. 0 (0)
NNRTI-resistant mutations	0 vs. 3	0 vs. 8 (2)	–		0 (0) 6 (1)	–	0 (0) vs. 0 (0)

INI: integrase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; RAL: raltegravir; FTC: emtricitabine; TDF: tenofovir; EFV: efavirenz; EVG: elvitegravir; COBI: cobicistat; ATV: atazanavir; /r: ritonavir boosted; DRV: darunavir; DTG: dolutegravir; ABC: abacavir; 3TC; lamivudine; qd: once daily; bid: twice daily.
*One participant had INI-resistance mutations T97T/A, E138E/D, V151V/I, and N155H, and NRTI-resistance mutations A62A/V, K65K/R, K70K/E, and M184V; one participant had NRTI-resistance mutation M184M/I; one participant had NRTI-resistance mutation A62A/V; and one participant had NRTI-resistance mutation M184M/V. †Four patients had emergent primary integrase mutations; two had Gln148Arg (Q148R), one had Asn155His (N155H), and one had Thr66Ile (T66I), Glu92Gln (E92Q), and Asn155His; all had phenotypic resistance to elvitegravir and cross-resistance to raltegravir. Three of these patients also developed reverse transcriptase resistance mutations (Met184Val [M184V]) and phenotypic resistance to emtricitabine, and one also developed Lys65Arg (K65R).

10/18 patients in the RAL group and no PI resistance was detected in the ATV/r and DRV/r group (Table 3).

FLAMINGO

FLAMINGO showed superiority of DTG over DRV/r. It is however an open-label phase IIIb trial, which can bring in biases for both patients and physicians, for example in staying on the randomized therapy and ascertainment of side-effect causality. In this study, patients were randomized to DTG or DRV/r, combined with either an ABC/3TC or TDF/FTC backbone according to the physician's choice[48,49]. In total, 484 patients were included in the analysis (242 in each group). At week 48, 90% of patients receiving DTG and 83% of patients receiving DRV/r had HIV-1 RNA < 50 copies/ml, meeting the non-inferiority criteria, and in the secondary analysis DTG was superior (p = 0.025). Treatment difference across high and low baseline HIV-1 RNA strata showed a significantly higher treatment difference in patients with high baseline viral load (p = 0.005; Table 1). Confirmed virological failure occurred in two (< 1%) patients in each group; no treatment-emergent resistance in either group was recorded (Table 3). Discontinuation due to adverse events or stopping criteria was less frequent for DTG (four patients, 2%) than for DRV/r (ten patients, 4%) and contributed to the difference in response rates. The most commonly reported (≥ 10%) adverse events were diarrhea (DTG 17% patients vs. DRV/r 29% patients), nausea (16 vs. 18%), and headache (15 vs. 10%); Table 2). Patients receiving DTG had significantly fewer low-density lipoprotein values of grade 2 or higher (2 vs. 7%; p = 0.0001). Increases in serum creatinine were evident in the DTG group by week 2, but remained stable to week 48. The change from baseline values ranged from −24.8 to 48.6 µmol/l for DTG and from −240.6 to 37.1 µmol/l for DRV/r (Table 4). Changes in serum creatinine for DTG were consistent with previous findings and not regarded as clinically significant[50-52]. DTG inhibits the organic cation transporter 2 (OCT2), similar to other drugs such as trimethoprim or cimetidine[52-57], which decreases tubular secretion of creatinine and therefore increases concentrations of serum creatinine without affecting glomerular filtration (GFR)[53-57]. No patients had grade 3 or 4 creatinine elevations, and no patients in either group discontinued the study because of a renal adverse event.

Study 103

Study 103 was a double-blind phase III trial comparing the first-generation boosted INI, EVG/COBI/TDF/

Table 4. Lipid and renal alterations in pivotal study with integrase inhibitors[36-62]

Third agent in pivotal studies in naive patients	TC (mmol/l) SD or 95% CI	HDL (mmol/l) SD or 95% CI	LDL (mmol/L) SD or 95% CI	TC/LDL SD	Scr (mmol/l) SD or 95% CI	eGFR (ml/min) SD or 95% CI
RAL vs. EFV (STARTMRK)[36-38]	0.55 (1.87)/ 1.82 (1.87)*	0.23 (0.47)/ 0.56 (0.61)*	0.33 (1.37)/ 0.89 (1.61)*	–0.02 (0.06)/– 0.01 (0.08)†	–	–
DTG vs. EFV (SINGLE)[39-41]	0.44 (0.67)/ 0.62 (0.88)*	0.13 (0.23)/ 0.21 (0.28)*	0.22 (0.54)/ 0.34 (0.77)	–0.1 (1)/–0.1 (1)†	10-13 in DTG	–
EVG vs. EFV (STUDY 102)[42-44]	0.25/0.49*	0.13/0.20*	0.26/0.44*	–	13 (5-20)/1 (–6 to 8)*	–14.3 (–24.2 to –4.3)/–3.0 (–11.2 to 8.2)*
EVG vs. ATV (STUDY 103)[58-60]	0.26 (–025 to 0.75)/0.21 (–0.33 to 0.77)†	0.15 (0.00-0.33)/0.13 (–0.05 to 0.28)†	0.28 (–0.11 to 0.65)/0.27 (–0.20 to 0.70)†	–	11 (5-18)/ 7 (1-5)*	–12.7(–21.8 to –4.3)/–9.5 (–17.9 to 0.2)*
DTG vs. DRV (FLAMINGO)[48,49]	0.11 (0.63)/ 0.58 (0.85)*	0.05 (0.23)/0.06 (0.26)†	0.08 (O.51)/ 0.36 (0.64)*	0.0 (1)/0.0 (1)	–24.8 to 48.6/–240.6 to 37.1	–
RAL vs. DRV vs. ATV (ACTG 5257)[45-47]	0.00/0.39/0.34	0.13/0.14/0.11	0.07/0.15/0.09	–	–	–
DTG vs. RAL (SPRING 2)[61,62]	0.18 (0.72)/0.23 (0.74)	0.07 (0.28)/0.07 (0.28)	0.07 (0.54)/0.08 (0.59)	–0.04 (1)/–0.1 (2)	12.3/4.7*	–16.5 (14.17)/ –5.4 (13.88)*

DTG: dolutegravir; RAL: raltegravir; ATV: atazanavir; EFV: efavirenz; DRV: darunavir; TC: total cholesterol; HDL: high density lipoprotein; LDL: light density lipoprotein; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; SD: standard deviation; 95% CI: confidence interval.
*Statistically significant; †non statistically significant.

FTC with ATV/r + TDF/FTC[58-60]. A total of 708 were treated (353 with EVG/COBI/FTC/TDF and 355 with ATV/r + FTC/TDF). The EVG/COBI/FTC/TDF was non-inferior to ATV/r + FTC/TDF for the primary outcome, viral load < 50 copies/ml (316 patients [89.5%] vs. 308 patients [86.8%]; Table 1). Viral suppression was high in both treatment groups, including patients with HIV viral load > 100,000 copies/ml at baseline. Both regimens had favorable safety and tolerability; 13 (3.7%) vs. 18 (5.1%) patients discontinued treatment because of adverse events. Fewer patients receiving EVG/COBI/FTC/TDF had abnormal results in liver function tests than did those receiving ATV/r + FTC/TDF and had smaller median increases in fasting triglyceride concentration (90 vs, 260 µmol/l; p = 0.006). Small median increases in serum creatinine concentration with accompanying decreases in estimated GFR occurred in both study groups by week 2; they generally stabilized by week 8 and did not change up to week 48 (median change 11 vs. 7 µmol/l) (Table 4). Two patients, one in each treatment group, discontinued because of a renal adverse event (increased creatinine concentration and toxic nephropathy), with abnormalities that were reversed after discontinuation of study drugs. The small increase in serum creatinine concentration and accompanying decrease of estimated GFR caused by interaction between COBI and the multidrug and toxin extrusion transporter 1 (MATE 1) supports the need for monitoring of renal function to distinguish between the drug-transporter effect and tenofovir-associated kidney injury, which can present as an increased serum creatinine concentration combined with proximal tubular injury (i.e., glycosuria, proteinuria, and hypophosphatemia)[53-57]. Five in the EVG/COBI/FTC/TDF group developed a resistance mutation versus no patients in the ATV/r + FTC/TDF group (Table 3).

Is there one integrase inhibitor with the best profile for treatment-naive patients?

Only one large trial compared INIs (RAL vs. DTG) in a head-to-head fashion; The SPRING 2 study is a placebo-controlled phase III study[61,62], where treatment-naive patients were randomized to RAL or DTG and, as in the FLAMINGO study, the treating physician could choose to combine them with either the ABC/3TC or TDF/FTC backbone. A total of 411 patients were randomly allocated to receive DTG and 411 to receive

Table 5. Summary of direct comparison between integrase inhibitors (SPRING 2 study)[61,62]

Study characteristics	SPRING 2 (DTG)
Design	Double-blind non-inferiority
Duration (years)	2
Comparator	RAL
Nucleotide/nucleoside backbone	FTC/TDF or ABC/3TC
n, total	411
Female (%)	14%
Median baseline HIV-1 RNA (log_{10} copies/ml)	4.52/4.58
Median baseline CD4 (cells/mm^3)	359/362
Primary endpoint	FDA snapshot analysis
Non-inferiority margin	10%
Week 48 outcome HIV-1 RNA < 50 copies/ml (DTG vs. comparator)	88 vs. 85%
Difference in virological success (95% CI)	2.5% (–2.2 to 7.1)
Discontinuation for AE (DTG vs. comparator)	2 vs. 2%
Response rate, baseline HIV-1 RNA < 100,000 copies/ml (DTG vs. comparator); difference (95% CI)	90 vs. 89%; 0.4% (–4.5 to 5.3)
Response rate, baseline HIV-1 RNA > 100,000 copies/ml (DTG vs. comparator); difference (95% CI)	82 vs. 75%; 7.5% (–3.1 to 18.0)
Week 96 outcome HIV-1 RNA < 50 copies/ml (DTG vs. comparator)	81 vs. 76%
Difference in virological success (95% CI)	4.5% (–1.1 to 10.0)
Week 96 response rate, baseline HIV-1 RNA < 100,000 copies/ml (INI vs. comparator); difference (95% CI)	82 vs. 82%; 0.1% (–6.1 to 6.1)
Week 96 response rate, baseline HIV-1 RNA > 100,000 copies/ml (INI vs. comparator); difference (95% CI)	78 vs. 63%; 15.1% (3.5-26.8)
Result:	RAL was non-inferior to DTG
Discontinuation for AE (INI vs. comparator)	2 vs. 2%
Emergence of resistance (DTG vs. comparator)	0 vs. 5% (INI) and 20% NRTI
Overall AE	

RAL: raltegravir: FTC: emtricitabine; TDF: tenofovir; ABC: abacavir; 3TC: lamivudine; DTG: dolutegravir; INI: integrase inhibitor; AE: adverse event; NRTI: nucleoside reverse transcriptase inhibitor.

RAL and received at least one dose of study drug. At 48 weeks, 361 (88%) patients in the DTG group achieved an HIV-1 viral load < 50 copies/ml compared with 351 (85%) in the RAL group, reaching non-inferiority criteria (Table 5). Investigators reached the same non-inferiority conclusion at week 96, with 332 (81%) of 411 patients in the DTG group and 314 (76%) of 411 patients in the RAL group with HIV viral load < 50 copies/ml. Adverse events were similar between treatment groups. The most common events were nausea (14% patients in the DTG group vs. 13% in the RAL group), headache (12% in each group) and diarrhea (11% in each group) (Table 2). Few patients had drug-related serious adverse events (3 [<1%] vs. 5 [1%]), and few had adverse events leading to discontinuation (2% in each group). Rates of graded laboratory toxic effects were similar. No evidence of clinically significant changes over time in the fasting lipid profile in either group. Patients receiving DTG had small mean increases in serum creatinine that were evident by week 2 and remained stable through week 96; the RAL group showed smaller increases in creatinine that also remained stable (Table 4). No evidence of treatment-emergent resistance in patients with virological failure

Table 6. Comparison of integrase inhibitors taking into account efficacy, tolerability, drug-drug interaction, and resistance profile

	RAL	EVG	DTG	EFV	PI/r
Efficacy	4	4	4	3	3
Tolerability	4	3	4	2	2
Drug-drug interaction*	1	3	2	3	4
Barrier of resistance	1	2	3	1	4

Grade: 1 = low, 2 = moderate, 3 = high, 4 = very high.
RAL: raltegravir; EVG: elvitegravir; DTG: dolutegravir; EFV; efavirenz; PI/r: ritonavir-boosted protease inhibitor.
*The lower the gradation is the better the characteristics.

on DTG, whereas of the patients with virologic failure who received RAL, one (6%) had integrase treatment-emergent resistance and four (21%) had NRTI treatment-emergent resistance.

A direct comparison between EVG/COBI and DTG are needed. Rogatto, et al.[63] performed an indirect efficacy comparison between EVG/COBI/FTC/TDF and DTG/ABC/3TC at week 48 and 96 using the Single study and the Study 102 .The results of this indirect comparison showed a risk difference of HIV viral load < 50 copies/ml between EVG/COBI/FTC/TDF compared with DTG /ABC/3TC of –4% (95% CI: –11 to 3) for the intent to treat (ITT) 48 weeks (p = 0.3) and –5% (95% CI: –13 to 3) for the ITT 96 weeks (p = 0.2). In regards to safety, there was no significant difference between EVG/COBI/FTC/TDF and DTG/ABC/3TC for any adverse event (p = 0.3), serious adverse events (p = 0.13), drug-related adverse events (p = 0.7), or drug-related serious adverse events (p = 0.6).

In order to have better view of different characteristics of INIs, we need to analyze efficacy, tolerability, resistance, and drug-drug interactions, taking into account data of direct comparison in randomized clinical trials of these INIs (Table 6). When looking carefully at efficacy, it is not a matter of concern; INIs are very potent in terms of virological control, irrespective of the baseline viral load and whether they were combined with ABC/3TC or TDF/FTC. Data from the SPRING-2 and FLAMINGO trials showed that DTG and RAL produced similar rates of virological suppression irrespective of the baseline viral load and whether they were combined with ABC/3TC or TDF/FTC[48,49,61,62]. In term of tolerability (Table 2), the global rate of adverse events was equal between the three INIs. Resistance was infrequent with INIs. No treatment-emergent resistance was seen with DTG and few with RAL and EVG/COBI (integrase and nucleoside treatment-emergent resistance). These results suggest that DTG has a higher barrier of resistance than the other two INIs and in fact no acquired resistance to DTG has been seen in any of these naive trials or been reported from real world use.

Conclusion and perspectives

We have reached fantastic efficacy with our new ARV combinations (cART). Increasingly, choices are based on tolerability and ease of use. Despite the high efficacy of EFV, available data on tolerability and long-term toxicities, especially CNS toxicities, suggest that EFV can no longer be considered as the best third agents of cART for the treatment of naive HIV-1-infected patients in countries where INIs are easily available. Rilpivirine in its combined form with FTC/TDF as a single-tablet regimen (Eviplera or Complera) is becoming the preferred NNRTI. However, the concern with RPV/FTC/TDF remains its lower efficacy at high viral loads (viral load > 100,000 copies/ml and CD4 < 200 ml[3]), food restrictions, drug interactions (proton pump inhibitors), and the requirement of strict patient adherence. In the absence of such adherence, treatment with RPV/FTC/TDF may lead to therapeutic failure resulting in resistance not only to NNRTI but to NRTI as well, thereby jeopardizing second lines of treatment. Direct comparisons of RPV/FTC/TDF with INIs in randomized clinical trials have yet to be performed.

As for PI/r, their tolerability, long-term toxicities, and especially the drug-drug interactions now limit their use in cART for naive HIV-infected-patients. They may still be prescribed to naive patients who present late and in which no genotype is available or in case of suspected transmitted mutations, patients with questionable compliance, or patients where potential toxicities of NRTIs or comorbidities (renal failure or high risk of cardiovascular diseases) require NRTI-sparing regimens,

and they are also used during pregnancy. It is possible that their co-formulation with NRTIs in a fixed-dose combination will lead to reconsideration of their role. INIs are becoming the drugs of choice as third agents of cART. Their high efficacy at all levels of viral load, irrespective of the backbone (FTC/TDF or ABC/3TC), combined with their excellent tolerability make them very attractive drugs. Each INI has its own characteristics Raltegravir is well tolerated, has few side effects and drug interactions, but does however currently require twice-daily dosing and has a low barrier of resistance. Elvitegravir is also well tolerated, but its association with cobicistat requires closer monitoring of renal function in the first month of treatment, although the upcoming formulation with tenofovir alafenamide will perhaps limit this[64], and is also associated with a significant number of drug-drug interactions similar to PI/r. It also has a low barrier of resistance. Its advantage at the time being is that it is currently the only INI in fixed-dose combination with TDF/FTC. Dolutegravir is well tolerated with few side effects (10% nevertheless of insomnia[65]) and few drug-drug interactions. The inhibition of OCT2 at the renal level induces an increase in serum creatinine and a reduction of estimated GFR, but not the actual GFR, thus also requiring monitoring of renal function in the early phase of the treatment (first month). It appears to have a better resistance threshold than other INIs, but in naïve patients it is not known if it is as high as a PI/r. Dolutegravir has the advantage of being combined with ABC/3TC as single-tablet regimen.

In the context of the current economic crisis, the high cost of INIs remains a challenge that needs to be addressed. In resource-rich countries there is still an important role for individualization of therapy, where the advantages of new approaches need to be weighed against the potential limitations.

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