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AIDS Rev. 2021;23:126-132

Dolutegravir in Mexico for special populations: A cost analysis perspective

Marco Banda[1], Cristina Herrera[1], Cristhian Reynaga[1], Sigfrido Rangel[1], Josue del Angel[1], Angel Reyes[1], and Prudente Isidoro[2]

[1]GlaxoSmithKline, Mexico; [2]ViiV Healthcare, Uruguay

Abstract

Integrase strand-transfer inhibitors (INSTI) are the latest class of antiretrovirals registered in Mexico. They include raltegravir (RAL), elvitegravir/cobicistat (EVG/c), dolutegravir (DTG) and bictegravir (BIC). Along with international guidelines, Mexico adopted the use of INSTI about two years ago as initial antiretroviral therapy (ART). This is partially due to the increase in the pre-treatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI), mainly efavirenz (EFV). Furthermore, INSTI depict greater efficacy, safety and less drug-drug interactions than NNRTI and protease inhibitors (PI). DTG is a second generation INSTI with a high barrier to resistance. It is recommended in international and national guidelines in a wide variety of clinical scenarios for persons living with HIV (PLWHIV), including treatment-naïve, first-line NNRTI treatment failure, simplification switch in suppressed patients, pregnancy, women with childbearing potential, adolescents and children over 6 years of age. DTG is mostly metabolized by the liver UDP-glucuronosyltransferase, and exhibits low drug-drug interactions overall; on the other hand, it has an extremely low renal elimination, therefore may be used in PLWHIV with advanced kidney disease without dose modification. Tuberculosis is a common coinfection in Mexico that requires rifampin-based anti-tuberculosis therapy, which requires increasing DTG to double dosing (50 mg BID). In Mexico, DTG-based regimens are likely to be cost-effective in many scenarios, given its acquisition costs and the particularities of the HIV population and associated clinical conditions, including a relatively high proportion of the following: i) new HIV diagnoses presenting at AIDS stage; ii) high rate of tuberculosis coinfection; iii) frequent first-line NNRTI treatment failures; and iv) relatively high proportion of infected children and adolescents. ***(AIDS Rev. 2021;23:126-132)***

Corresponding author: Marco Banda, marco.i.banda@gsk.com

Key words

HIV. Mexico. Dolutegravir. Cost.

Introduction

Mexico has a population of roughly 127 million people. Mexico City is the capital of the country and its largest urban area. It is also the largest city in North America with an estimated population of 9 million inhabitants, and 20 million in its metropolitan area[1].

AIDS was first reported in Mexico in 1983. Since then, 313,969 people have been diagnosed with HIV up to

Correspoding author:
Marco Banda
E-mail: marco.i.banda@gsk.com

Received in original form: 26-11-2020
Accepted in final form: 12-05-2021
DOI: 10.24875/AIDSRev.M21000042

November 20th, 2019, of which 109,927 deaths ocurred. Of the estimated 187,873 people living with HIV in Mexico nowadays, AIDS-defining conditions still occur in almost 40% of diagnosed adults in Mexico. During 2019 a total of 13,876 new diagnoses of HIV had been reported, which means there are 2 new HIV diagnoses per hour. [2,3].

The use of antiretroviral drugs in Mexico began in 1997, but it was not until 2003 that it became a public health policy of free and universal access. Since then it became possible to prescribe treatment to those that did not have social security coverage. Until December 1st, 2020, seven in ten people have been diagnosed, six in ten people are under antiretroviral treatment (ART), and six in ten people have reached viral suppression[4]. AIDS-related conditions continue to be the leading cause of death among people living with HIV (PLWHIV) despite achievements in ART access; in 2018, HIV mortality rate in 2018 was 4 per 100,000 habitants[5].

Figure 1 shows estimates of the percentage of PLWHIV in Mexico 2019-2020 that remain undiagnosed, those on ART, and the proportion with undetectable viremia. Thus, there is still a gap to reach the World Health Organization (WHO) goal of 90-90-90. Overall, one third of Mexicans with HIV infection have detectable viremia and therefore do not fully benefit from ART, so this is keeping alive the transmission of HIV across the country[2,6].

Since 2007, five integrase strand-transfer inhibitors (INSTI) have been developed: raltegravir (RAL), elvitegravir cobicistat (EVG/c), dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB).

Booster-free INSTIs have favorable pharmacokinetic and pharmacodynamic properties, which contribute to their efficacy, safety, tolerability and ease of use with less drug-drug interactions[7].

International and national guidelines (Department of Health and Human Services [DHHS], European AIDS Clinical Society [EACS], WHO and Centro Nacional para la Prevención y el Control del VIH y el Sida [CENSIDA]) recommend booster-free INSTIs as one of preferred first-and second-line regimens in adults, adolescents and children (Pediatric European Network for Treatment of AIDS [PENTA], WHO, DHHS and CENSIDA). INSTIs are also recommended in switch strategies such as simplification, except for RAL, toxicity and drug-drug interactions, evaluating CYP3A4 vs. UGT 1A1 competing for metabolic pathways, reductions and treatment optimization[8-12]. CAB is the newest INSTI recently approved by the EMA and FDA as an injectable long-acting strategy for virologically suppressed patients, but it has not yet been included in all the guidelines[13-15].

The prevalence of primary drug resistance to NNRTI in Mexico has surpassed the critical threshold recommended by WHO above 10%, there is a very low prevalence of INSTI-resistant viruses in treatment-naive individuals[16-18]. As a consequence, CENSIDA guidelines were updated two years ago to recommend INSTI as preferred first-line therapy[12].

For patients with antiretroviral drug resistance different to INSTIs, the use of DTG and RAL as part of an optimized antiretroviral regimen has shown to be effective[19]. Nowadays DTG is the only INSTI that has demonstrated efficacy in clinical trials in patients with resistance mutations for RAL and EVG[20].

Table 1 summarizes the main features of the different INSTIs.

Dolutegravir as the preferred INSTI in naïve and stable switch patients

The first approved second generation INSTI was DTG. This drug has demonstrated efficacy, safety and better tolerability for PLWHIV compared with other classes of antiretrovirals. In the **SINGLE**, **FLAMINGO** and **ARIA** trials, DTG was superior to NNRTI and PIs respectively, while in **SPRING-2**, **DTG** was non-inferior to RAL in naïve treatment patients[21-24].

For virologically suppressed patients, DTG maintains viral suppression after switch from NNRTI, PIs and INSTI, in the **STRIVIING** and **NEAT 022** trials with other improvements after the switch, including quality of life and lipid profile[25,26].

Despite the overall good tolerance of DTG, neuropsychiatric manifestations have been occasionally reported as an INSTI-class effect, such as sleep disturbances, changes in mood, headache, etc. More recently, weight gain has been noticed in patients treated with INSTIs, and this should be monitored in PLWHIV[27,28].

Dolutegravir for ART failures

Mexican ART guidelines recommend, for first-line NNRTI failure, a regimen based on boosted darunavir (DRV) or lopinavir (LPV) plus a two-NRTI backbone. When full activity of at least one NRTI is proven by genotype resistance test, a regimen based on DTG plus 2 NRTI is also recommended[12], based on findings from the **DAWNING** study[29] that reported DTG was superior to LPV/r in terms of efficacy and tolerability in patients experiencing first-line failure to NNRTI-based regimens.

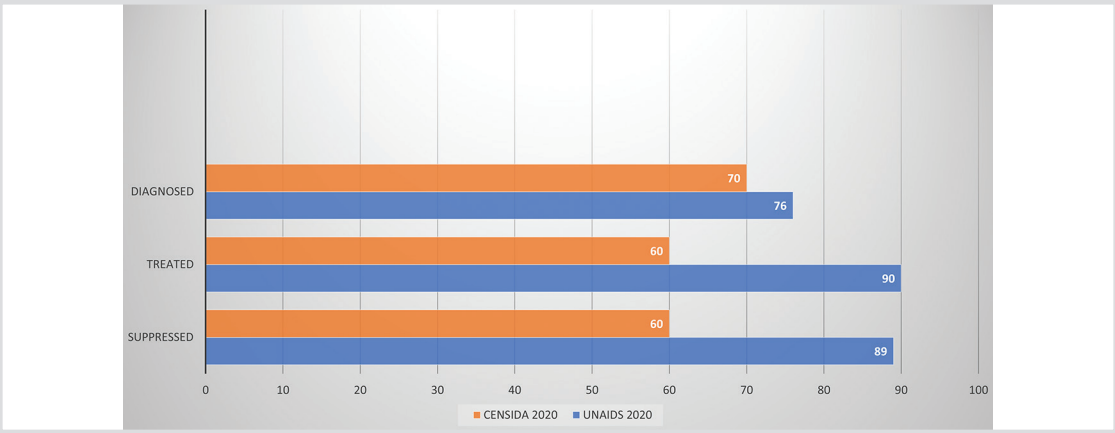

Figure 1. *Antiretroviral therapy in Mexico and WHO goals.*[1,2]

Table 1. Main characteristics of distinct HIV integrase inhibitors[58-63]

	First generation INSTI		Second generation INSTI		
	Raltegravir	**Elvitegravir**	**Dolutegravir**	**Bictegravir**	**Cabotegravir**
Oral administration	yes	yes	yes	yes	yes
Long acting administration	no	no	no	no	yes
Co-formulation	no	yes	yes	yes	no
Drug-drug interactions	few	many	few	few	few
Barrier to resistance	low	low	high	high	high
Approved for drug-naive	yes	yes	yes	yes	no
Approved for tx-experienced	yes	no	yes	no	no
Approved for simplification	no	yes	yes	yes	yes

In the **SAILING** trial[30], DTG showed to be superior to RAL in treatment-experienced patients that had failed to NNRTI or PI-based therapies. Subsequently, in the **VIKING** studies[20] good performance of DTG was demonstrated in patients that had failed first-generation INSTI. This was expected due to the higher barrier to resistance than first-generation INSTIs such as RAL and EVG[31] and importantly, DTG maintained activity in most individuals with prior RAL or EVG failure[32,33]. This relevant finding has been confirmed in a recent study conducted in Mexico on a large group of multi-drug, treatment-experienced individuals failing on RAL[34].

In HIV patients with prior multiple ART failures, the **TRIO** trial demonstrated good virologic outcomes using RAL, etravirine and DRV/ritonavir[19]. On the other hand, the **SAILING** trial showed that DTG was virologically superior to RAL in heavily treatment-experienced patients[30] where some received DTG plus etravirine and DRV/r, opening the possibility of having more optimized options for this type of patient with higher barrier to resistance regimens. Table 2 summarizes the main findings of major registration studies conducted with DTG compared with other ART agents and in different patient populations.

Two drug regimens with dolutegravir

Three-drug regimen combination has been standard HIV care since 1997. However, given the

Table 2. Main trials with dolutegravir in persons living with HIV

Study	HIV population	Comparison	Main result (<50 c/ml HIV- RNA)	Interpretation	References
SINGLE	Drug-naive	DTG/ABC/3TC vs efavirenz/TDF/FTC	71% vs 63% (w144)	Superior	21
SPRING-2	Drug-naive	DTG + 2 NRTI vs raltegravir + 2 NRTI	81% vs 76% (w96)	Non-inferior	24
FLAMINGO	Drug-naive	DTG + 2 NRTI vs darunavir/r + 2 NRTI	80% vs 68% (w96)	Superior	22
ARIA	Drug-naive women	DTG/ABC/3TC vs ATV/R+ TDF/FTC	82% vs 71% (w48)	Superior	23
DAWNING	NNRTI failures	DTG + 2NRTI vs LPV/R + 2 NRTI	84% vs 70% (w48)	Superior	29
SAILING	PI or NNRTI failures	DTG bid (It is QD) + OBR vs raltegravir + OBR	71% vs 64% (w48)	Superior	30
VIKING	RAL or EVG failures	Open DTG bid + OBR	69% (w24)	Effective	20
STRIIVING	Switching	DTG/ABC/3TC vs CAR	85% vs 88% (w24)	Non-inferior	25
NEAT 022	Switching	DTG + 2NRTI vs PI/r + 2 NRTI	93.1% vs 95.2%(w96)	Non-inferior	26
GEMINI 1 & 2	Drug-naïve	DTG + 3TC vs DTG+TDF/FTC	82% vs 84% (w144)	Non-inferior	40-42
TANGO	ART suppressed	DTG + 3TC vs continuing TAF-based triple regimen	99.7% vs 99.5% (w48)	Non-inferior	43
SWORD 1 & 2	ART suppressed	DTG + rilpivirine vs continuing same ART	95% vs 95% (w48)	Non-inferior	37

TDF: Tenofovir; DTG: dolutegravir; ABC: abacavir; 3TC: lamivudine; FTC: emtricitabine; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitors.

well-demonstrated activity of some of the most recent antiretrovirals, the question of whether a two-drug regimen would be enough in certain patient populations has experienced a revival. The issue is particularly relevant, taking into consideration drug costs and toxicities, both in the long and short term[35].

Due to its efficacy, safety, and high barrier to resistance, DTG demonstrated in several patient populations, including hard-to-suppress groups such as those with very high viral load, very low CD4 counts and/or harboring multi-drug resistant viral strains[36], and several studies have explored two drug combinations based on DTG during the last couple of years.

The **SWORD** studies 1 and 2 assessed the efficacy and safety of switching to DTG plus rilpivirine from a three-drug regimen in virologically suppressed patients, and non-inferiority was demonstrated at 48 weeks[37]. Since then a co-formulation of DTG plus rilpivirine given as one pill once daily (Juluca®), has been recommended by EACS as simplification therapy for virologically suppressed patients using triple ART regimens[9].

Lamivudine (3TC) in combination with DTG acts at two different targets in the viral lifecycle in the same way as a three-drug regimen. Intracellular 3TC PK tail matches the plasma PK tail of DTG with a favorable safety profile and no significant drug-drug interactions (DDI)[38,39]. A co-formulation of DTG/3TC has been tested in different scenarios. **GEMINI 1** and **2** studies examined DTG+3TC efficacy and safety as first-line therapy in drug-naïve individuals, and viral

suppression was demonstrated with efficacy rates of 91, 86 and 82 at years one, two and three, being non-inferior to DTG plus tenofovir/emtricitabine combination[40-42]. In the **TANGO** study, DTG/3TC was tested as switch strategy in virologically suppressed patients, resulting as non-inferior to continuing the prior tenofovir alafenamide (TAF)-based three drug regimens at 96 weeks[43].

Dolutegravir in pediatric populations

Children and adolescents with HIV infection represent a special patient population. Several reasons account for this, but mostly that drug adherence may be particularly challenging in this group and that weight and age-adjusted dosage should be ensured[44].

WHO recommends DTG-based therapy as preferred first-line regimen for children living with HIV older than six years and weighing more than 15 kg and is widely available for children weighing at least 20 kg who can take 50 mg film-coated adult tablets (in countries where 10 and 25 mg pediatric presentations are not available)[10]. As alternatives, LPV/r- or RAL-based therapies should be considered. For children 6-12 years old, Mexican antiretroviral guidelines recommend DTG as preferred therapy over PI or NNRTI[12]. However, the National Drug basket only includes PI (LPV/r and DRV/r) for use in children, although 10 and 25 mg pediatric presentations of DTG are already available in Mexico[45].

Dolutegravir in women

There are few clinical trials that exclusively include women, such as the **ARIA** study, in which DTG proved to be superior to ATV/r in efficacy and safety[23]. Furthermore, pregnant women are excluded from clinical trials, which generates knowledge gaps in this population. Accordingly, the **Tsepamo** study, that evaluates the outcomes of newborns of mothers living with HIV exposed to antiretrovirals throughout Botswana hospitals, has reported a decrease from 0.9% to 0.3% in the prevalence of neural tube defects associated with the use of DTG in the periconception period[46,47]. These data have caused a change in the recommendations of guidelines that now propose that women make an informed decision, knowing the risks and benefits[8,10]. Finally, for pregnant women between 14 to 28 weeks[48] or more than 28 weeks[49], the **IMPAACT 2010** and **DOLPHIN-2** trials showed DTG-containing regimen ART superior virologic efficacy compared with an EFV-based regimen with less adverse events rate.

Dolutegravir in HIV patients with tuberculosis coinfection

Efavirenz and RAL are used in clinical practice for HIV treatment with tuberculosis coinfection. However, the prevalence of primary NNRTI resistance in Mexico surpasses the critical threshold of over 10%[16,17] and RAL failed to demonstrate non-inferiority when compared to efavirenz[50]. The **INSPIRING** trial demonstrated DTG was effective and well tolerated in HIV patients receiving rifampicin-based tuberculosis treatment[51].

Dolutegravir and its influence in cost analysis and budget impact in Mexico

Interestingly, a recent cost analysis in patients with failure to a first NNRTI regimen, comparing DTG+TDF/FTC with either LPV/r + TDF/FTC or DRV/r +TDF/FTC, has demonstrated that there would be a significant annual saving of $618,000 with the DTG regimen. The cost analysis considers the proportion of patients achieving viral suppression and discontinuation due to adverse events, an analysis duration of five years and a DTG annual uptake of 10% (from 30% in the first year to 70% in the last year)[52].

Based on prior evidence from an Italian study that demonstrated the cost-effectiveness of DTG over RAL[53], an investigation conducted in Mexico among heavily pretreated patients, showed significant savings for DTG vs RAL, both combined with boosted DRV plus etravirine. Annual mean savings of $1,292 were reported per patient, which nationwide represented $439,000[54].

In pediatric regimens a pharmacoeconomic analysis has demonstrated that the use of DTG 10 or 25 mg (according to body weight) would provide significant annual mean savings (ranging from $61 to $664 per patient) compared to LPV/r after the 46% off discount proposed for DTG, assuming a displacement of 30% in the first year to 70% on the last year. Nationwide estimated savings would range from $14,000 to $219,000 annually[55].

Regarding tuberculosis in Mexico, where the prevalence of coinfection is 9%, significant annual savings using DTG in comparison to RAL ($1,664 per patient) were shown and when DTG is compared with EFV, represents an annual investment per patient of US$ 999. These figures translate to a budget impact saving of $922,000 versus RAL, and average annual investment versus EFV of $603,000 US dollars[56].

Conclusions

Although the continuum of HIV care in Mexico has improved over time[57], the 90-90-90 targets established by UNAIDS not only have not been reached yet (70-60-60), but also there is the possibility for the goals to worsen after the COVID-19 pandemic. This represents a public health problem that needs innovative strategies, immediate linkage and rapid treatment initiation programs. Recently a fourth 90 regarding quality of life was added to the WHO goals.

INSTI-based regimens have had a great impact on the last two 90 goals. Due to their efficacy and safety, they contribute to maintain viral suppression with a better tolerability profile than the older families impacting directly on quality of life. After several years of using NNRTI globally, the prevalence of pre-treatment resistance mutations exceeds what was recommended by the WHO (10%) in different parts of Latin America including Mexico (roughly 13%)[16,17] so INSTI-based regimens became the preferred first- and second-line regimens in the international and national guidelines several years ago[8-12].

DTG has been evaluated in several randomized clinical trials, including diverse clinical profiles like treatment-naïve[21-24], switch in the virologically suppressed[25,26], first, second, third and more lines of failures[20-30], where it has showed non-inferiority or superiority compared with the different standards of care at the time. DTG is suitable for pregnant women[48,49] and women with childbearing potential[46,47]. Furthermore, this drug is easy to use and convenient for treating HIV infection in children and adolescents. In Mexico, the high rate of tuberculosis in PLWHIV underlines the convenience of using ART regimens that allow treatments with rifampin.

Mexico adopted the use of DTG about two years ago and it was included in the preferred regimens. Although the cost of antiretroviral treatment in the country is absorbed by the government, cost-optimization strategies are necessary as DTG showed to be cost effective in many scenarios for PLWHIV.

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