Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD)
April 30 2018

Briefing note

Objective

Optimization of current antiretroviral drug regimens is a critical component to support country efforts to achieve the 90/90/90 treatment targets. As of end 2017, more than 50 low- and middle-income countries (LMICs) are including or planning to include dolutegravir (DTG) containing regimens in their national protocols, as the preferred first-line option, particularly the fixed dose combination (FDC) tenofovir/lamivudine/dolutegravir (TLD). This technical note aims to brief countries and regulatory agencies on key clinical and programmatic information about this new FDC.

Information on the drug profile

Efficacy

The efficacy of dolutegravir (DTG) has been demonstrated in several randomized control trials conducted among antiretroviral therapy (ART) naïve (SINGLE, SPRING, FLAMINGO) and experienced patients (STRIIVING)[1-4]. Among the treatment naïve patients, DTG is superior to both efavirenz (EFV) and ritonavir-boosted darunavir, and non-inferior to raltegravir – a twice-daily dosed integrase inhibitor.

Recent systematic reviews and meta-analysis conducted by WHO have showed that DTG-based regimens are better tolerated and tend to be protective against treatment discontinuation due to adverse events (AEs), when compared with EFV600 [5]. Among stable, virologically suppressed patients on non-nucleoside reverse transcription inhibitor (NNRTI) or protease inhibitor-based first-line antiretroviral (ARV) treatments, substitution with a DTG-containing regimen was also well-tolerated and non-inferior in maintaining viral suppression, with high rates of satisfaction compared to those remaining on their existing regimen.

Furthermore, DTG is associated with a more rapid viral suppression and higher genetic resistance barrier, when compared with NNRTIs. It is also effective against HIV-2 (which is naturally resistant to NNRTIs) [6-8]. Pharmacokinetic studies showed that DTG is effective in subpopulations,
including pregnant women and tuberculosis (TB)-coinfection, with a dose increase of DTG to overcome drug-drug interactions with rifampicin in the latter [9,10].

**Safety**

DTG is a very well tolerated drug, with lower overall incidence of AEs (<5%) when compared with EFV [11]. The most common reported AEs associated with DTG are gastrointestinal symptoms (nausea, vomiting), hypersensitivity skin reactions, and central nervous system effects (insomnia, dizziness) which are most often mild and self-limited. Discontinuation rates observed in clinical trials and in programme data are low.

A few European cohorts have detected an increased occurrence of central nervous system side effects in people over 60 years of age, those using abacavir (ABC) and women [12-14]. However, channelling and other confounding factors are likely to be the reasons for these findings. An increased occurrence of immune reconstitution inflammatory syndrome (IRIS), cardiovascular events and suicidal ideation was initially suspected, but recent analysis has not detected significant differences when compared with other standard regimens [15].

Despite limited data from clinical trials on DTG use in pregnant women and TB coinfected subpopulations (who are usually excluded from these studies), growing data from observational and programme cohorts have not detected differences in terms of expected outcomes.

**Simplification**

DTG as a stand-alone generic formulation has been available in low- and middle-income countries (LMIC) since late 2017. Fixed dose combinations (FDC) of DTG were recently tentatively approved by the US Food and Drug Administration (FDA), and approved by the European Medicines Agency (EMA) in the beginning of 2018. Dose adjustment (50 mg twice daily) is required only in TB patients taking concomitant rifampicin.

**Harmonization**

Considering the drug profile, DTG is strategically placed to be a harmonized ARV drug option that can be used across different subpopulations (i.e. adults, adolescents, TB, pregnancy, PWID (people who inject drugs), HIV-2 infection). Pharmacokinetics modelling and preliminary data from ongoing studies support the use of TLD in adolescents > 30 kg.

For children, DTG has been approved for those over 6 years of age and > 30 kg (by US FDA) or >15 kg (by EMA); ongoing studies are underway to assess use and dosing among children as young as 4 weeks old, including children receiving TB co-treatment.

**Cost**

The prices of DTG formulations are expected to be 10–15% less expensive than current EFV formulations in LMIC (current median price: US$ 75 per person per year). With generic competition and increased purchase volumes, further price reductions are expected. While paediatric generic formulations of DTG to be used in children are still under development, the innovator product is
being registered in a number of countries, and is expected to be made available at access price to enable early access for the paediatric population [34].

Clinical evidence of DTG use during pregnancy

There is increasing evidence from several cohort studies of DTG safety when ART was started during pregnancy. However, information on DTG safety in women who started ART before pregnancy is limited and further studies are still needed.

- **Antiviral Pregnancy Registry (APR) [16]**: As of January 2017, pregnancy outcomes and birth defects were analysed from 142 pregnancies with reported exposure to DTG during pregnancy. There were 128 live births reported (3 terminations, 11 miscarriages, no stillbirths). Only 4 (3.0%) reported birth defects, which is similar to the expected rate of birth defects in the general population.

- **European Pregnancy and Paediatric HIV Cohort Collaboration (EPPIC) [17]**: As of July 2017, 101 pregnancies with exposure to DTG had been identified with 84 birth outcomes. Rates of preterm delivery and “small for gestational age” were similar to outcomes reported from women on alternative regimens (standard of care in the United Kingdom of Great Britain and Northern Ireland).

- **IMPAACT P1026s [10]**: DTG pharmacokinetics in pregnant and postpartum women with HIV was evaluated, with establishment of intensive steady-state 24-hour PK profiles after DTG 50 mg once daily in 29 women during second trimester, third trimester and postpartum. DTG exposure was lower in pregnancy compared to postpartum, although trough concentrations were above DTG EC90. The study also showed that DTG readily crosses the placenta, and that elimination in infants is prolonged, with half-life over twice that of adult controls. All of the 29 infants born from the 29 women in the study were HIV negative.

- **Tsepamo Study (Botswana) [18]**: Since August 2014 the Tsepamo Study has performed ongoing birth surveillance to evaluate the safety of ART in pregnancy. Recent analysis compared women who started either TDF/FTC/EFV (4593 delivered from August 2014 to August 2016) or TDF/FTC + DTG (845 delivered from November 2016 to April 2017) during pregnancy. The analysis found no significant differences in: total and severe adverse birth outcomes, preterm, very preterm birth, small for gestational age, very small for gestational age, stillbirth, and neonatal death. Adjusted risk ratios (aRR) for DTG-based regimens with EFV-based regimens as reference were respectively (for the above outcomes): aRR 1.0 (95% CI: 0.9–1.1); aRR 1.0 (95% CI: 0.8–1.2); aRR 1.0 (95% CI: 0.8–1.1); aRR 1.2 (95% CI: 0.8–1.7); aRR 1.0 (95% CI: 0.9–1.2); aRR 0.9 (95% CI: 0.7–1.2); aRR 0.9 (95% CI: 0.6–1.5); and aRR 1.0 (95% CI: 0.5–1.9). Information on pregnancy safety in women with preconception exposure to DTG are still limited.
Clinical evidence of DTG use during TB treatment

Co-administration of DTG with rifampicin decreases DTG plasma concentrations. However, PK modelling data has shown that DTG can be used with dose adjustment. Recently reported studies outlined below provide clinical data to support the best dosing approaches (twice daily DTG 50 mg when used with rifampin). An ongoing study is assessing the effectiveness of 50 mg twice daily versus 100 mg once daily dosing of DTG to overcome the rifampin drug-drug interaction.

- **INSPIRING [19]:** Interim week-24 results from this ongoing study show that DTG 50 mg twice daily is effective and well-tolerated in HIV/TB coinfected adults receiving rifampin-based TB therapy. Rates of IRIS were low. There were no new toxicity signals for DTG and no discontinuations due to liver events.

- **RADIO:** PK of DTG 50 mg and 100 mg once daily with rifampicin. (Results expected in May 2018.)

Estimated number of patients in LMIC taking DTG-based ARV regimens

By the end of 2017, approximately 300 000 people living with HIV were using DTG in high-income settings [35]. Among LMIC, Botswana, Brazil and Kenya have implemented a programmatic transition to DTG, with 80 000, 60 000 and 13 000 patients respectively using DTG until December 2017. However, more than 50 countries have informed WHO that they plan to shift to DTG-based regimens, primarily as a TLD combination, in 2018/2019, representing 40% of the current HIV global burden [20].

TLD use and clinical outcomes from programmatic data in selected countries

- **Brazil:** Since January 2017, Brazil has recommended a DTG-based regimen in first-line for ART-naïve patients. The use of DTG as a third-line option to replace raltegravir has been recommended since 2016. Currently, more than 50 000 people living with HIV are taking the regimen of TDF/3TC + DTG in first-line (and another 30 000 are using DTG-containing regimens in third-line). Approximately 8000 new patients are initiating TDF/3TC+DTG-containing regimens per month. A national online pharmacovigilance system to record DTG-associated AEs has been implemented since April 2017 with support from WHO. Preliminary results, as of December 2017, are reassuring: they reveal that approximately 2% of people on DTG reported an AE, and nearly all AEs (89%) were rated as mild. A total of 149 individuals were switched to another regimen due to AEs during this period. The reactions reported in Brazil are similar to the reactions recorded in clinical trials; they include gastro-intestinal symptoms, skin reactions, and insomnia. No IRIS was reported. From 3 months of treatment, the proportion of people living with HIV treated with a DTG-based regimen with undetectable viral load (<50 copies/mL) were more than 81%, reaching
88% at 10–11 months of treatment. At 12 months of ART initiation, 88% of DTG-based treated individuals presented a viral load <50 copies/mL, compared to 83% with EFV-based regimens. Suppression was also faster among those on DTG-based regimens compared to EFV-based regimens – 81% of individuals who started with a DTG-based regimen presented a viral load below 50 copies/mL after 3 months of treatment, compared to 61% for those on an EFV-based regimen.

- Botswana: Botswana introduced DTG-based first-line ART for all adults, including pregnant women, in May 2016. Approximately 60 000 people living with HIV are currently receiving a DTG-based regimen including TDF/3TC in Botswana: 50 000 on first-line treatment and 10 000 treatment switches. Unlike Brazil, the Botswana programme is using DTG in people with TB receiving rifampin treatment and among pregnant and breastfeeding women. Overall, more than 90% of people living with HIV on a TDF/3TC+ DTG have achieved full virologic suppression on DTG by 6 months, with less than 1% reporting AEs, usually gastrointestinal disturbance. Preliminary data reveals that approximately 300 people living with HIV have completed TB treatment while taking a double-dose DTG-based regimen. No difference in AE incidence has been observed with the increased dose of DTG. Of 53 DTG failures detected, only 3 patients were found to have integrase mutations (<0.75%).

- Kenya: Approximately 13 000 patients are receiving DTG in combination with TDF/3TC in Kenya. In 2017, among people on DTG regimens, 88.7% were virally suppressed. In 2018, among people on DTG, 90% were suppressed.

Cost-effectiveness of transition to DTG-containing regimens

Data on the cost-effectiveness of DTG as an option for first-line ART is still emerging. A review of studies evaluating the cost-effectiveness of DTG as a first-line therapy option revealed a total of 12 studies.

Three studies evaluated DTG as options for both first-line and second-line [21-23]. The studies used a variety of economic models to evaluate DTG against the current recommended therapy. Two studies evaluated the cost-effectiveness of DTG in LMIC [24,25].

The remaining studies were from Canada [21], France [29,30], Italy [22], Slovakia [23], Slovenia [31], Spain [28] and the United States of America [26,27]. Three studies looked at both clinical outcomes in addition to economic outcomes [24–26]. Outcomes measured included incremental cost-effectiveness, quality of life indices and total costs.

Two papers [32,33] discussed the cost-impact and cost-savings of DTG as a first-line option. All the studies concluded that using DTG-based regimens is highly cost-effective compared to the current standard of care (either at the level of a national treatment policy or compared to current WHO guidelines); has lower total costs; offers significant cost-savings; has lower rates of treatment failure and transition to second-line therapy; and improves clinical outcomes overall.
WHO prequalification requirements

For TLD tablets, the WHO Prequalification programme requests a single-dose, crossover bioequivalence study comparing the proposed 3-FDC to the same dose of the individual reference products (comparators) – i.e. Tivicay® (DTG) 50 mg tablets of GlaxoSmithKline; Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline, and Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences. These data ensure that the FDC delivers the TLD at the same rate, and to the same extent, as the loose combination of monocomponent products used clinically up to now.


Clinical evidence for the triple TLD combination

The 3 individual components of the FDC of TLD – tenofovir disoproxil (TDF) + lamivudine (3TC) + DTG – were developed by 2 different innovator companies: TDF by Gilead; 3TC and DTG by ViiV. For this reason, there are not many studies published with this specific FDC combination – innovator companies rarely sponsor clinical trials using products from competitors.

Nevertheless, there is very abundant clinical evidence for all 3 of the components in various combinations. WHO therefore considers that there is sufficient clinical data for this triple combination. The concern regarding a lack of clinical data appears to stem from inappropriately giving credence only to studies that use the "exact" combination.

WHO ARV guidelines regard 3TC (ViiV) and FTC (emtricitabine, Gilead) as interchangeable. The guidelines also regard TDF (Gilead) and ABC (abacavir, ViiV) as very similar in efficacy, with somewhat different AE profiles. There are many published trials using TDF+FTC or ABC+3TC and permutations thereof with DTG.

Current regulatory status of TLD

The US FDA gave tentative approval to Mylan for this FDC in 2017. The "tentative" is due to the fact that 2 of the 3 drugs are still under patent. (3TC is not.) https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209670Orig1s000TAltr.pdf.

Current guideline status of TLD

The FDC appears on the current 29 May 2017 WHO Expression of Interest for HIV products, section 3.4.
The 3 drugs also appear in the current 2016 WHO HIV consolidated ARV guidelines, as a first-line "alternative" regimen (Table 4.2, page 99).  


- The European AIDS Clinical Society Guidelines (2017) contain all 3 TLD components in their “recommended regimens” category.


**Conclusion**

WHO does not see a basis for requiring "exact combination" studies as the only permissible clinical evidence for this FDC, as we consider that there is sufficient published evidence for all components.
References:


15. Hill AM, Mitchell N, Hughes S, Pozniak AL. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for


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