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Two-drug regimens with dolutegravir plus rilpivirine or lamivudine in HIV-1 treatment-naïve, virologically-suppressed patients: latest evidences from the literature on their efficacy and safety

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Highlights

- As initial treatment, dolutegravir plus lamivudine had high efficacy and safety.
- Switch to dolutegravir plus rilpivirine maintained HIV suppression over 148 weeks.
- Switch to dolutegravir plus lamivudine led to no viral failures through week 48.
- No emergent dolutegravir-resistant virus has been reported in two-drug regimens.
- Dolutegravir-based two-drug regimens were well tolerated on long follow-up.

Abstract

Objectives. In HIV-positive population, a paradigm shift from three-drug regimens to dolutegravir-based two-drug regimens as both initial and switch treatment approach is beginning to take place, virologically supported by the availability of new, potent drugs with high genetic-barrier that allow to overcome, at least in certain conditions, the dogma of three-drug regimens in HIV-effective therapy. Indeed, there is increasing evidence on their excellent and sustained long-term effectiveness and safety, that this manuscripts aims to review.

Methods. This review includes the most recent results on dolutegravir plus rilpivirine or lamivudine two-drug regimens from randomized clinical trials, meta-analyses and real-life studies, including relevant data presented at international conferences up to August 2019.

Results. As initial treatment strategy, dolutegravir plus lamivudine shows high efficacy and safety over 96 weeks in 1441 patients from GEMINI 1&2 phase III non-inferiority trials. In SWORD 1&2 trials, conducted in virologically suppressed patients, switching to once-daily dolutegravir plus rilpivirine maintained efficacy over 148 weeks; similarly, in TANGO trial no confirmed virological withdrawals were observed with dolutegravir/lamivudine through week 48. Consistent results were observed in real-life cohorts. No emergent dolutegravir-resistant virus has ever been reported in a patient in whom dolutegravir was prescribed in the context of such two-drug regimens. Switching to once-daily dolutegravir plus rilpivirine or lamivudine was generally well tolerated, and associated with favorable renal and bone safety.

Conclusions. The results so far available support dolutegravir-based two-drug regimens as excellent treatment options for adults with HIV-1 infection, either naïve or already virologically-suppressed on their current antiretroviral regimen.

Keywords: dual therapies; dolutegravir; treatment simplification; residual viremia; integrase resistance

1. Introduction

Three-drug regimens (3DRs) and two-drug regimens (2DRs) with integrase inhibitors (INIs) are now recommended for both initial and second/third-line combination antiretroviral treatment (cART) by all international guidelines (1-7). In parallel with the widespread use of INIs, in which dolutegravir (DTG) is playing a pivotal role, recently flanked by bictegravir (approved in association with tenofovir alafenamide [TAF] and emtricitabine [FTC]) (4), a paradigm shift from 3DRs to 2DRs is beginning to take place in real-world clinical practice.

The prospect of using 2DRs is the consequence of an epochal change in long-term efficacy and safety of latest-generation antiretrovirals. The possibility of reaching, with only 2 drugs, the same antiviral potency and genetic barrier that were previously achieved with 3 or 4, is actually the critical element that led to consider 2DRs clinically and virologically feasible. The dogma of 3DRs was based upon the characteristics (and limitations) of the first-generation antivirals available in the '90s, paradigmatically demonstrated by the complete control of virus replication in a substantial number of patients treated with zidovudine-lamivudine (AZT-3TC) and indinavir (8). Indeed, their low genetic barrier (as nearly all other drugs available at that time) is a critical weakness that allows the virus to escape antiviral-pressure by developing and selecting resistance mutations. A remarkable evidence, supported also by a mathematical approach (9), confirms that if the virus is subject to a three-drugs pressure (but not of two first-generation drugs) has low chances to escape by developing resistance.

These key studies underlined the need to keep three first-generation drugs in the effective regimen. However, the advent of second-generation drugs (mostly protease inhibitors [PIs] and INIs, but also, albeit at a lower level, nucleos(t)ide reverse transcriptase inhibitors [NRTIs] and non-nucleotide reverse transcriptase inhibitors [NNRTIs]), changes the rules of the game. Their remarkable genetic barrier, mirrored by the difficulty in selecting *in vitro* resistant viral strains (10-14), prompted skilled clinicians to test the efficacy of 2DRs. They were initially based on boosted-

PIs (usually with 3TC, for its potency and effect on viral-fitness reduction), and directed to virologically-suppressed patients with undetectable HIV-RNA, whereby, by definition, the number of replicative cycles is low, and the virus has lower chances to select a resistant, mutated strain. The results have been quite exciting, showing a remarkable long term efficacy (15-19), and opening the way towards treatment of drug-naive patients, in whom preliminary attempts in relatively small but well-conducted trials confirmed antiviral efficacy (20, 21).

Then, the advent of second-generation INIs further pushed 2DRs forward. Since 2015, DTG superseded raltegravir (RAL) as first INI to be prescribed in INI-naïve patients (22, 23). Indeed, above all others, DTG-based regimens are recommended as the better option for either initiating or switching cART (4, 7, 24) thanks to their particular potency and genetic barrier, that brings a rapid viral-suppression (25), a low potential for drug-drug interactions (26), low or no risk for drug resistance development (13), better tolerability (27), lower pill burden and availability as fixed-dose formulations. Such characteristics are particularly relevant in the context of 2DRs, that confirmed the excellent potency and the high genetic barrier of DTG, with no resistance whatsoever detected, also in patients failing first-line therapy (28-33).

Taken all together, these data suggest that the new generation drugs may favor a change of the paradigm of 3DRs, at least in certain conditions and patients. With 2DRs we can now play a new game, in which we can associate an excellent and sustained long term effectiveness, and improved safety profile, and lower costs. DTG currently plays a leading role in this game, supported by increasing evidence from most recent randomized clinical trials (RCTs), meta-analyzes and real-life studies, that this manuscript aims to review.

2. Dolutegravir plus lamivudine two-drug regimens as initial treatment of cART-naïve patients

The availability of consistent data on the excellent efficacy and safety of 2DR strategies with DTG+3TC have led international guidelines to change their recommendations in order to include such possibility as initial treatment strategy (Table 1).

This 2DR benefits from the robust potency, resistance barrier, and tolerability of DTG coupled with 3TC, the only antiretroviral agent that has been in the DHHS guidelines since they were first published. Upon first administration, 2DR with DTG+3TC is characterized by a rapid kinetics of viral load (VL) decay, which includes a steep initial decay, followed by a slower but progressive HIV-RNA reduction, that eventually leads to the achievement of a complete viral suppression in a relatively short time-frame (median 29-57 days, depending on baseline VL) (28, 34-36). Overall, the similar time-to-suppression between DTG+3TC 2DR and 3DR in naïve patients demonstrated a comparable initial antiviral potency, even in patients with baseline VL 100,000-500,000 copies/mL (median time-to-suppression of DTG+3TC:113 days, *vs*. DTG+TDF/FTC 3DR:169 days, difference not significant) (34, 35, 37). This preservation by 2DR of rapid decay-kinetic, even in individuals with high pretreatment VL, is important to effectively prevent viral transmission (38), as well as to reduce the risk of drug-resistance development due to incomplete viral suppression (35, 39, 40).

On the long-term, the virological efficacy of DTG+3TC as initial strategy is now solidly supported by GEMINI 1 and 2, two parallel, fully powered, double-blind, phase III non-inferiority RCTs, that compared this 2DR with a recommended 3DR of DTG+FTC/tenofovir disoproxil fumarate (TDF) (28, 29). A total of 1441 cART-naïve adults were enrolled with the following inclusion criteria: VL 1,000-500,000 copies/mL at screening, no pre-existing major viral resistance mutations, no HBV infection, or HCV infection requiring therapy. The primary endpoint of HIV-RNA<50 copies/mL at week-48 by FDA-snapshot analysis was fulfilled in 91% of patients in DTG+3TC, and 93% of patients in DTG+FTC/TDF arms (28). Non-inferiority was confirmed at week-96, when the proportion of patients with VL<50 copies/mL was 86% and 90%, respectively (29), an efficacy

comparable to previous 96-weeks results for DTG-based 3DRs in RCTs (41-45) (Figure 1, Panel A).

Response rates at 96-weeks were high and similar between arms, even in those 20% of difficult-to-treat participants with baseline VL of 100,000-500,000 copies/mL (Figure 1, Panel B), consistently with the 48-weeks response (36), and with previous results of the ACTG A535 single-arm study (46).

A lower response rate at week-48 and 96 was observed in the (few) patients starting ART with $CD4^{+}$≤200 cells/mm^3 (Figure 1, Panel C). The clinical interpretation of the observed reduced DTG+3TC efficacy in patients with low $CD4^{+}$ value advocates for further (indeed currently ongoing) analyses to fully understand whether the observation is consistent or driven by other independent factors, including the increased drop-off of patients for reasons not driven by virological failure (as it seems to be from a preliminary analysis), and/or the low number of patients enrolled in the two GEMINI studies with such low $CD4^{+}$ lymphocytes count (that make difficult any significant analysis) (28, 29).

It is worth noting that, in a recent meta-analysis, DTG+3TC induced similar increases in $CD4^{+}$ cell count at week-48 compared with 13 3DRs investigated (with the only exception of DTG+TAF/FTC) (47). Mean differences for DTG+3TC vs. 3DRs ranged from -44.49 cells/μL compared with DRV/r+ABC/3TC, to 56.22 cells/μL compared with DTG+TAF/FTC (47). This result supports the beneficial immune recovery effect that patients with all $CD4^{+}$ cells count levels (including the lower ones) could take advantage from 2DR.

In the near future, it is difficult that data on direct comparison between DTG+3TC and other currently recommended 3DRs (or 2DRs) will be extensively available from RCTs. In this regard, it can be noted that a recent meta-analysis provided additional support for the efficacy of DTG+3TC in drug-naïve patients, as this 2DR was found to be significantly better than EFV+TDF/FTC, and similar to all other 12 3DRs analyzed, in terms of viral suppression at 48-weeks (47). This result was consistent in the subgroup of difficult-to-treat patients with baseline HIV-RNA of 100,000-500,000 copies/mL (47).

Taken all together, these data firmly support the use of a 2DR with DTG+3TC as initial cART regimen. This can be relevant also from the economical point of view. While this is not a purpose of this review, it should be remembered that a modeling study recently found that when DTG plus generic 3TC was used as initial therapy or for induction-maintenance by 50% of persons initiating ART in the United States, and 25% of those currently virally suppressed switched to DTG+3TC, cost savings over 5 years could exceed $3 billion (48). Other studies and reviews of the literature can properly address this important point.

3. Dolutegravir-based two drug regimens in virologically suppressed patients

In virologically suppressed patients, de-escalating from 3DR to 2DR using DTG plus either rilpivirine (RPV) or 3TC has shown high rates of maintenance of virological success (49-52). A recent meta-analysis showed that DTG-based 2DR is highly successful in sustaining virological control at 48-weeks in 1670 cART-experienced patients, as only 0.7% experienced viral failure, none developed DTG-resistance, and only 1 had a major RPV-resistance (see below for further details) (53).

2DR with DTG+RPV is currently recommended by latest Italian, DHHS, IAS-USA, EACS, and GeSida guidelines for treatment switch in virologically-suppressed patients (Table 1), while DTG+3TC is recommended by IAS-USA, and at this time considered as alternative option in the Italian guidelines (published before the availability of latest RCTs results) (Table 1).

3.1 Dolutegravir plus rilpivirine in virologically suppressed patients

SWORD-1 and SWORD-2 are currently the largest (and with the longest follow-up) RCTs investigating the efficacy and safety of a 2DR for the maintenance of HIV-1 suppression (30, 33, 54). The trials successfully demonstrated the non-inferiority of switching to a DTG+RPV 2DR vs. continuing a standard 3DR, with a clinical efficacy of 95% at week-48, irrespective of previous cART (30) (Figure 2). This excellent result was consistently reproduced in the patients who

switched to 2DR after week-52 (late-switch group) (54), and sustained up to week-148, when 84% of patients were virologically-suppressed (33). Pooling together early and late switch arms, overall efficacy by FDA snapshot analysis is 94% at week-48 (930/990), and 89% at week-100 (885/990) (Figure 2) (33). It should be noted that the rates of virological suppression at week-96 in patient who switched to a 2DR with atazanavir/ritonavir+3TC in SALT and ATLAS-M RCTs were 69% (99/143) and 77% (103/133) by ITT snapshot analysis, respectively (16, 17). In DUAL-GESIDA study, DRV/r+3TC led to a 48-weeks ITT efficacy of 88.9% (112/126) (18). Even though a comparison cannot be properly made between these two type of studies (i.e. PI-based and DTG-based), the strong perception coming from these data is that the rate of success of DTG+RPV at long-term observation is at minimum similar (if not widely superior) to that achieved by PI-based 2DRs, such as atazanavir and DRV.

Real-life data from cohorts are also available, and deserve attention. While cohorts differ from the pooled SWORD analysis in various characteristics, yet efficacy results in terms of maintenance (or achievement) of viral suppression were consistent with week-48 and week-96 data (Figure 2). This suggests that the indications for this 2DR may go beyond the SWORD inclusion limitations.

In the French Dat'AIDS cohort (55), 152 virologically-controlled patients (since a median of 10 years) were switched to DTG+RPV; 52% had an history of previous failures, though not on DTG- or RPV-based regimens. At week-24, 90.5% of patients had remained free of confirmed therapeutic failure.

In the Spanish DORIVIR study (56), 21.1% of the 104 patients were viremic at the moment of switch to DTG+RPV. At 24-weeks, 95/104 (91.3%) patients had remained under 2DR, and 92/104 had VL<50 copies/mL, leading to an efficacy of 88.4% by ITT analysis.

In the TivEdO Study (57), 57.2% of the 145 patients that switched to DTG+RPV harbored drug-resistant strains at baseline, 81.4% had an history of previous failures, and 14.5% were viremic. At week-96, the proportion of patients with virological suppression by ITT was 95% (138/145). Interestingly, 123/138 (89%) of them had completely undetectable VL, *vs*. 91/124 (73%) virologically-suppressed patients at baseline.

3.2 Dolutegravir plus lamivudine in virologically suppressed patients

In the pilot RCT ASPIRE, the open-label switch to DTG+3TC during virological suppression was non-inferior to continuation of a standard 3-drug cART at 48-weeks (31) (Figure 3), consistently with previous results from the single-arm LAMIDOL trial (51).

TANGO is an ongoing phase III RCT that recently demonstrated the non-inferior 48-weeks efficacy of a switch to DTG/3TC fixed-dose combination *vs*. continuing a TAF-based 3DR (32) (Figure 3). Notably, no confirmed virologic withdrawals were observed with DTG/3TC through week-48 (100% per-protocol efficacy), and no resistance mutations were observed at discontinuation/failure in any arm.

Few real-life cohort studies investigated, to date, the switch to DTG+3TC. Patients included in such studies usually had a more complex therapeutic history of those enrolled in RCTs, yet available efficacy and safety results are consistent.

In a recent prospective, uncontrolled Italian real-life experience, 94 patients switched, while virologically suppressed, to DTG+3TC (50). All had a long cART history, and were on average on their fourth line of therapy; 14.9% were INI-experienced; only patients with no previous resistance mutations to either INI or 3TC were selected. Over a 24-weeks follow-up, no virological failure, nor viral blip over the 50 copies/ml, were observed, and ITT-efficacy was 97% (91/94 patients) (Figure 3).

The DOLULAM pilot study assessed the efficacy of DTG+3TC in 27 highly treatment-experienced patients (58). Lack of INI resistance was a requirement, while some patients carried (because of previous failures) the M184I/V mutation. Despite most of the patients included had negative predictors for response to treatment, ITT efficacy at 104-weeks was 89% (24/27 patients): no virological failures occurred during the first 2 years of 2DR; only 1 patients experienced blips and 2 discontinued (Figure 3).

The efficacy and safety of DTG+RPV and DTG+3TC were recently investigated and compared also in a Italian cohort of 416 virologically-suppressed patients, of whom 44.3% had had at least

one previous viral failure, and 43.8% switched from another 2DR (59). The two regimens were well tolerated, and demonstrated comparable efficacy, with an overall incidence of 2.9 viral-failures per 100 person-years of follow-up in the 3TC-group (N=229), and 1.3 in the RPV-group (N=187).

4. Focus on dolutegravir-based two-drugs regimens activity on residual and low-level HIV-1 viremia

Residual viremia, represented by a measurement <50 copies/mL with positive HIV-RNA PCR signal (so called detectable, not quantifiable viremia), is not a rare phenomenon in HIV-infected patients treated with ART. In real-life cohorts, average steady-state VL was shown to be <3 copies/mL, though the proportion of patients with steadily-controlled viremia during follow-up ranges between 40.6% and 53.3% (60, 61).

The presence of this residual viremia (potentially indicating an ongoing, low-level, viral replication), was shown to anticipate viral rebound in patients on 3DR (60, 62), and it could therefore be perceived as a major issue when starting or switching to a 2DR, as a consequence of a possible incomplete viral suppression (driven by an alleged decrease of pressure over the virus). In this regard, it should be noted that he high potency of DTG+3TC combination highlighted by the rapid HIV-1 RNA decay kinetics during initial treatment (28, 35, 36) supports the ability of this combination to rapidly overcome viral replication, with a potential positive impact also on HIV-1 reservoir size and low-level viremia (63). This suggests that the potential issue of decreased pressure over the virus caused by DTG-based 2DR vs. 3DR may not be real from the virological standpoint. Nevertheless, confirmation is required from clinical studies.

In this frame, the proportion of patients with undetectable VL in GEMINI 1&2 studies was similar across DTG+3TC and DTG+TDF/FTC arms at all analyzed time-points (34). Upon achievement of viral suppression, HIV-RNA rebounds were rare, and usually represented by ‘blips’ between 50 and 200 copies/mL, that occur with similar frequencies in the two arms, regardless of baseline VL values and treatment outcome, as no blips were observed in patients with confirmed virological

withdrawal (64). Overall, these results support the conclusion that that DTG+3TC and 3DR with DTG+FTC/TDF have a comparable effect on virologic control in patients who start a first-line regimen.

In both ASPIRE and TANGO trials, switch to DTG plus 3TC was comparable to 3DR in maintaining viral suppression by standard viral load assays (31, 32). Ultrasensitive VL quantification in a subgroup of 72 patients from ASPIRE trial demonstrated also a non-significant difference in residual viremia, nor at baseline, nor after 24 and 48 weeks since switch (65). This result was confirmed after adjusting for baseline VL, duration of prior cART, and baseline $CD4^+$.

These initial data from clinical trial settings start to be supported also by real-life observations. In a recent real-life randomized study, HIV-1 residual viremia was investigated in virologically suppressed patients randomized to continue a 2DR with DTG plus one NRTI (3TC, N=23; RPV, N=2), or to switch to a cART with elvitegravir/cobicistat/FTC/TAF (N=25) (66). Notably, the proportion of patients with no residual viremia through week-48 was higher in the DTG arm (76%) than in cART (48%), indicating that the switch to a 3DR was not superior in suppressing residual viremia compared to continuing the same 2DR.

5. Focus on dolutegravir-based two-drugs regimens on proinflammatory activity

The activation of the immune system is closely linked to inflammation, and since HIV infection can be considered as a chronic inflammatory disease, concerns raised about the possibility that a lower antiretroviral action in 2DRs *vs*. 3DRs may result in higher systemic inflammatory activity and immune activation. As inflammation/immune activation plays a relevant role in the pathogenesis of non-AIDS comorbidities (67), pilot studies to ascertain the possible effects on pro-inflammatory biomarkers of DTG-based 2DRs versus triple regimens are currently ongoing (68-70) .

Preliminary data from a small study that included patients receiving DTG+RPV showed no deterioration of soluble markers of inflammation, activation or immune response, along with

significant lower levels of IL6 and sCD14, at least after one year of dual therapy (69). Concordantly, in a cohort of 85 virologically-suppressed patients, the switch to DTG+3TC was not associated with an increased risk of immune-activation compared to triple regimens, after a median follow-up of 35 months (68).

Albeit still limited data are available, at this point there is no evidence that a switch to a 2DR with DTG may lead to an increase in systemic inflammatory activity. Yet, further research is strongly warranted to define this aspect, very important from the clinical point of view.

6. Focus on dolutegravir-based two-drugs regimens genetic barrier and efficacy against drug-resistant HIV-1 infections

DTG is characterized by a high affinity to its target, resulting in strong and sustained binding to HIV-integrase, and a high genetic barrier against resistance development *in vitro* (10-14).

In the two large GEMINI 1&2 trials, none of the (few) patients who experienced a confirmed virological withdrawal to DTG+3TC (or DTG+FTC/TDF) had treatment-emergent INI or NRTI resistance mutations (28, 29). Similarly, the few patients that, to date, failed simplified 2DR with DTG, showed extremely limited or no evidences of resistance emergence (30-33). Indeed, after 148 weeks of treatment with DTG+RPV in SWORD 1&2, only 11/990 (1%) patients met the criteria for confirmed virological withdrawal (of whom 3 after week 100); 5 harboured at least one RPV-associated resistance mutation, while no treatment emergent DTG-resistance was detected (33, 54) (Table 2). These results confirm that DTG+RPV 2DR is able to maintain HIV-1 suppression after switch (up to 148 weeks), with no increased risk of resistance development, at least in a RCT setting.

It should be highlighted that treatment-experienced patients need special attention, as those in whom a first-generation INI has failed may have selected a pathway leading to cross-resistance, including DTG (71). In addition, a shorter time of viral suppression before switch may increase the risk of virological failure, as it is well demonstrated in literature (63, 72, 73).

To reduce the risk associated with previously selected resistance mutations on the maintenance of virological-control during 2DR, RCTs investigating 2DR with DTG enrolled only patients with either: a) a long-standing virological suppression (at least 6 months); b) no previous treatment failure, and/or c) no documented previous major resistance. The ASPIRE trial excluded individuals with any history of NRTI genotypic resistance mutations, in light of a recent report showing that a history of M184V resistance was associated with an increased probability of viral blips in those switching to DTG+3TC (74). In TANGO study no confirmed virological withdrawals were observed up to week-48 among participants with baseline M184V/I (that, however, were only 7, i.e. 1%).

Data from RCT are thus too small to allow definite conclusions, yet real-life data are beginning to be available.

In the TivEdO Study (57), 57.2% of patients that switched to DTG+RPV harbored at baseline drug-resistant strains, including 6 with resistance to RPV and 1 with full INI resistance (who was on twice daily DTG): no virological failure was reported.

In DOLULAM (75), M184I/V mutations were observed in 17/27 (63%) patients. Most of the M184V (8/11) were detected in historical RNA-genotypes, while the M184I was exclusively detected in DNA-genotypes, in 7/10 cases as minority variant by ultra-deep sequencing (most probably related to the APOBEC function, that selects several mutations, including M184I, not associated with resistance to 3TC/FTC, therefore not relevant from the virological standpoint). No correlation was found between the duration of the virological-suppression before switch and the proportion of M184I/V variants at the time of initiation of DOLULAM, and no failures occurred in the first two years of dual DTG+3TC (58).

In 10 subject harboring 4-class drug-resistant HIV-1 (M184V in 9/10), enrolled in the PRESTIGIO Registry (76), simplification to high-genetic-barrier 2DRs (9/10 DTG-based) led to an incidence rate of virological failure of 0.58 per 100 person-months of follow-up. During a median follow-up of 16.5 months, only 1 virological failure occurred.

Overall, the large number of patients included in clinical studies, especially the large SWORD-1 & 2 and TANGO RCTs, as well as the increasing number of real life cohorts that included heavily treatment-experienced patients, have shown that virological failure with DTG 2DR is extremely rare, and when it occurs it is not associated with the development of DTG resistance, confirming the efficacy of this strategy, without exposing patients to an increased the risk of selecting for INI resistance mutations.

Some recent data seem not to recommend 2DR with DTG plus 3TC in the presence of M184V mutation. However, the low number of patients with resistance to the NRTI backbone included in RCTs, and the sometimes contradictory results from real-life cohorts indicate that further studies are needed to assess the possible impact of such situation on the long-term effectiveness and durability of second-line DTG-containing 2DRs.

More evidence is also required to assess the risk of selecting resistance to INI by using RAL in first-line regimens, and how that may affect the subsequent simplification to DTG 2DRs.

7. Safety of two drug regimens with dolutegravir plus rilpivirine or lamivudine

One of the key aims of 2DR is to reduce the potential risk of short- and long-term toxicities mainly related to the negative effects of NRTI backbone on renal function and bone mineral density (77, 78), and of PIs on serum lipids level (79, 80). DTG-containing regimens have been increasingly recognized as preferred treatment options especially because of their good efficacy and tolerability (7, 26, 27, 81).

Across all RCTs, adverse events (AE) observed with DTG 2DRs were consistent with the DTG, RPV and 3TC respective labels. In a recent metanalysis, the odds of having drug-related AE were significantly lower (or at least similar) for patients receiving DTG+3TC *vs*. other 13 regimens investigated in RCTs (including TAF-based ones) (47).

The most recent DTG 2DRs RCTs data on longer follow-up are consistent with such result. In the 1441 naïve patients enrolled in GEMINI 1&2 trials, drug-related AEs leading to withdrawal from the study occurred in only 2% of the whole population at week 96, and were significantly fewer in those receiving DTG+3TC compared to DTG+TDF/FTC. Concordantly, among the 990 patients who switched to DTG+RPV in SWORD 1&2 trials, only 8% discontinued 2DR due to AE over 148-weeks of follow-up, and the overall incidence of sAE remained low (33, 54). In TANGO, AEs leading to withdrawal occurred in 4% of patients at 48-weeks since switch to DTG/3TC, and in 1% of those receiving TAF-based cART (32).

7.1 Renal safety

In drug-naïve patients, changes in renal biomarkers (eGFR, creatinine, urine protein/creatinine ratio, urine retinol-binding protein/creatinine ratio, urine and β2-microglobulin/creatinine ratio) significantly favored DTG+3TC over DTG+TDF/FTC at week-96 (29). Positive results on renal safety were also observed in virologically suppressed patients, especially when switched from TDF-containing regimens. The improvement observed for markers of renal tubular function (urine retinol-binding protein and β2 microglobulin to creatinine ratios) were sustained up to week-148 in patients who switched to DTG+RPV from TDF-based 3DR (33, 54), and estimated GFR did not differ significantly at week-100, irrespective of whether participants were taking TDF before switching (54). Switch to DTG/3TC confirmed renal safety at 48-weeks also in comparison with TAF-based regimens (32).

Overall, these results support the maintenance of renal function, and the good renal safety profile of DTG+RPV and DTG/3TC 2DRs.

7.2 Bone safety

Loss of bone mineral density (BMD), increased concentrations of bone turnover biomarkers, and higher rate of osteoporosis and pathological fractures have been observed in HIV-infected patients, due to both the direct effect of the systemic inflammation caused by viral activity, as well as to the use of certain antiviral agents, such as TDF (82-87). In naïve individuals, significantly better profiles of bone turnover biomarkers were observed at week-48 of treatment with DTG+3TC

compared to DTG+TDF/FTC (28), and these were sustained up to week-96 (29). Switch to DTG+RPV or DTG/3TC in SWORD 1&2 and TANGO studies have shown a sustained improvement in markers of bone resorption (type-1 collagen C-telopeptide), and bone formation (osteocalcin, bone-specific alkaline phosphatase) in comparison with baseline and with TDF- or TAF-based 3DRs (32, 33, 54, 88). These positive results were reported in the week-48 analysis, and still sustained 148 weeks after switching in SWORD studies (33).

Preliminary real-life data also supported a positive effect on BMD at 48-weeks in virologically suppressed patients switching to DTG+3TC *vs*. a 3DR with FTC/TAF plus an INI (spine BMD p=0.031; spine T-score p=0.012; and spine Z-score p=0.014) (89).

7.3 Serum lipids levels

In the 1441 naïve subjects enrolled in the GEMINI 1&2 trials, the 2DR arm with DTG+3TC had a higher increase in triglycerides, as well as in total, HDL and LDL cholesterol (for all $p<0.001$), and a greater decrease of total/HDL cholesterol ratio ($p<0.05$), compared to the 3DR arm with DTG+3TC/TDF, at both week-48 (28) and week-96 (29). On the other hand, switching to DTG+RPV or DTG/3TC caused no consistent, reproducible effects on serum lipids, and no clinically relevant changes from baseline were observed in mean total cholesterol, or the total/HDL cholesterol ratio (one of the stronger predictors of cardiovascular risk (90)), even after 148 weeks of follow-up in SWORD 1&2 trials (32, 33).

Taken all together, these results indicate that the clinical relevance of the serum lipid levels alterations in 2DR compared to 3DR remains quite low, yet to be fully confirmed in long-term studies.

7.4 Other toxicities

In real-life observational cohort studies, CNS toxicity-related DTG interruptions were the most frequent (1.7-2.7%) (91, 92), and mainly occurred during the first two years of treatment (91). Within the ICONA cohort, the use of DTG-based first line regimens was associated to a 2.5% risk of stopping DTG due to neuro-psychiatric AEs (NAEs) by two years (93).

In the large SWORD 1&2 trials, NAEs were reported more frequently in the DTG+RPV arm than in the 3DR arm, even though few resulted in withdrawal from either group. In TANGO trial, NAEs such anxiety, insomnia, depression and irritability were recorded in <1% of patients on DTG/3TC dual (32), supporting the hypothesis that these AEs will probably have a negligible effect on the long term efficacy and safety of a DTG-based 2DR switch.

Clinical concerns also exist on the safety of DTG during the periconception period (until 6-8 weeks after conception). Preliminary results from an observational study on women using DTG at the time of conception in Botswana found an higher risk (10/1000) of neural tube defects (NTDs) at birth, compared with women on a non-DTG regimen (1/1000) (36). However, latest results from the Tsepamo Birth Outcomes Surveillance Study showed that the risk in the prevalence of NTDs among women taking DTG is less than originally signalled. Specifically, NTDs occurred in three per 1,000 deliveries among women on DTG from conception (5/1683), compared with one per 1,000 deliveries among women taking other ARV regimens (15/14,792)(94). Latest WHO recommendations on antiretroviral treatment reconfirm the recommendation to use DTG-containing regimens as the preferred option for first-line and second-line ART across all populations (7). Yet, active research and surveillance are ongoing for additional pregnant women in Botswana and other countries where women have been exposed to DTG at the time of conception.

8. Conclusions

On the way of the most recent, and consistent, evidences on the long-term efficacy and safety of DTG-based 2DRs, we are at the dawn of a paradigm shift towards a common use of this dual strategy in both treatment naïve and virologically-suppressed HIV patients. Virological data support the overcome of a dogma of 3DRs as necessary for all patients, driven by the excellent quality of the new drugs, provided with potency and high genetic barrier. Under these conditions, the absolute need of three drugs in all our patients seems to be no longer necessary, thus paving the

road to the practical use of rational, well-designed 2DRs based upon at least one drug with high genetic barrier

Further research is foreseen to support currently available results on various subpopulations not yet fully studied, in order to help in selecting the most suitable patients for 2DRs strategies. Yet, the possibility to prescribe first-line and maintenance 2DRs based on DTG already represents an outstanding tool in terms of potential reduction of AEs, drug-drug interactions and costs, while preserving excellent antiviral efficacy and high genetic-barrier towards resistance development in the large majority of our patients, particularly those naive starting therapy (with viral load <500,000 copies/ml), and those switching therapy after achieving virological-control.

Declarations

Competing Interests: CFP has received honoraria for involvement in advisory boards from Abbvie, Gilead, VIIV, Janssen, Merck and Theratechnologies, and research grants from Abbvie, Gilead, VIIV, Janssen, and Merck. VC acted as a speaker, and received honoraria from VIIV and Merck.

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Author Contribution

All named authors have made substantial contributions to the conception and design of the study, acquisition and analysis of data, writing and reviewing of the manuscript, and have given final approval of the version to be published.

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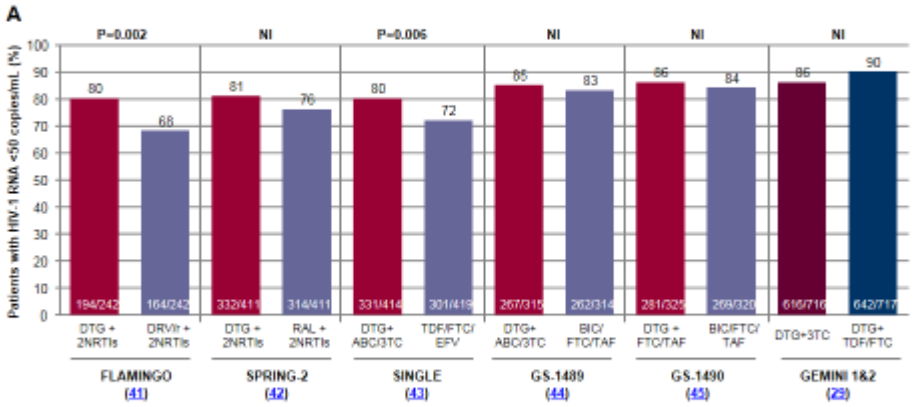
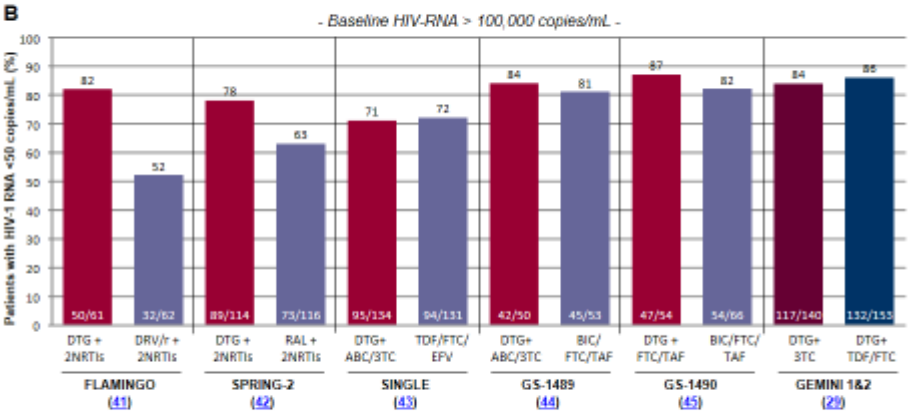
Figure legends

Figure 1. Dolutegravir-based Regimens in Treatment-Naïve Patients, Efficacy by FDA Snapshot Analysis at 96 Weeks. Histograms represent the proportion of patient with HIV-1 RNA below 50 copies/mL after 96 weeks of treatment with dolutegravir-based regimens in randomised clinical trials, including dual therapy with dolutegravir plus lamivudine. **Panel A**, overall efficacy; **Panel B**, efficacy in patients with baseline HIV-1 RNA >100.000 IU/mL; **Panel C**, efficacy in patients with baseline $CD4^+$ T-cell count <200 cells/mm^3. 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; DTG=dolutegravir; EFV=efavirenz; FTC=emtricitabine; NI=noninferior treatment difference; NRTI=nucleos(t)ide reverse transcriptase inhibitor (either ABC/3TC or TDF/FTC in FLAMINGO and SPRING-2); RAL=raltegravir; r=ritonavir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate




B
- Baseline HIV-RNA > 100,000 copies/mL -
Patients with HIV-1 RNA <50 copies/mL (%)
82
52
78
63
71
72
84
81
87
82
84
86
50/61
32/62
89/114
73/116
95/154
94/131
42/50
45/53
47/54
54/66
117/140
132/153
DTG + 2NRTIs
DRV/r + 2NRTIs
DTG + 2NRTIs
RAL + 2NRTIs
DTG+ ABC/3TC
TDF/FTC/ EFV
DTG+ ABC/3TC
BIC/ FTC/TAF
DTG + FTC/TAF
BIC/FTC/ TAF
DTG+ 3TC
DTG+ TDF/FTC
FLAMINGO (41)
SPRING-2 (42)
SINGLE (43)
GS-1489 (44)
GS-1490 (45)
GEMINI 1&2 (29)

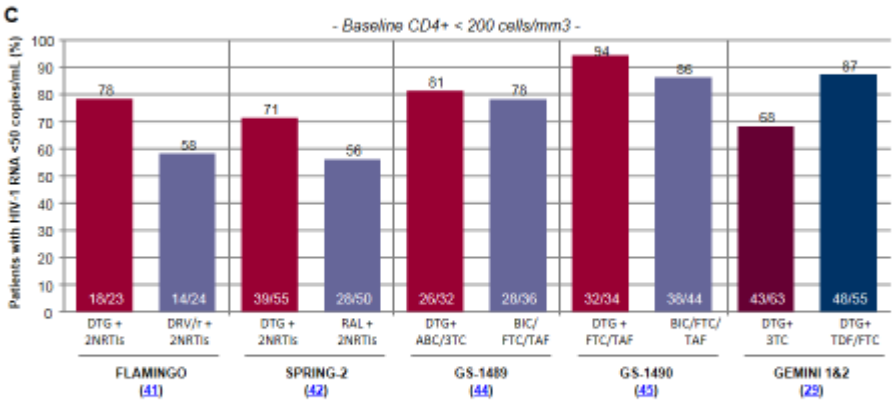

C
- Baseline CD4+ < 200 cells/mm3 -
Patients with HIV-1 RNA <50 copies/mL (%)
78
58
71
56
81
78
94
86
68
87
18/23
14/24
39/55
28/50
26/32
28/36
32/34
38/44
43/63
48/55
DTG + 2NRTIs
DRV/r + 2NRTIs
DTG + 2NRTIs
RAL + 2NRTIs
DTG+ ABC/3TC
BIC/ FTC/TAF
DTG + FTC/TAF
BIC/FTC/ TAF
DTG+ 3TC
DTG+ TDF/FTC
FLAMINGO (41)
SPRING-2 (42)
GS-1489 (44)
GS-1490 (45)
GEMINI 1&2 (29)

Figure 2. Dolutegravir plus Rilpivirine Dual Regimens in Virologically Suppressed Patients - Efficacy in Randomized Clinical Trials and Real-Life Studies. cART, combination antiretroviral treatment; DTG=dolutegravir; NI=noninferior treatment difference; RPV, rilpivirine.

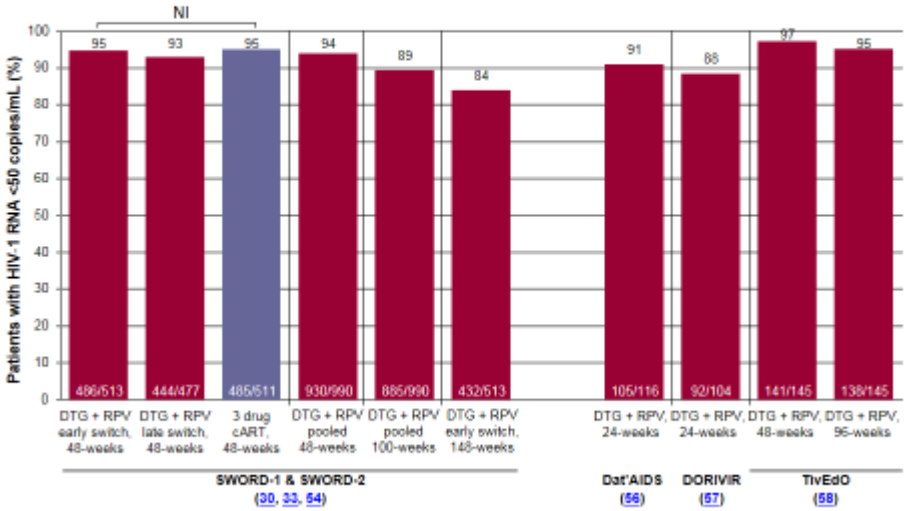
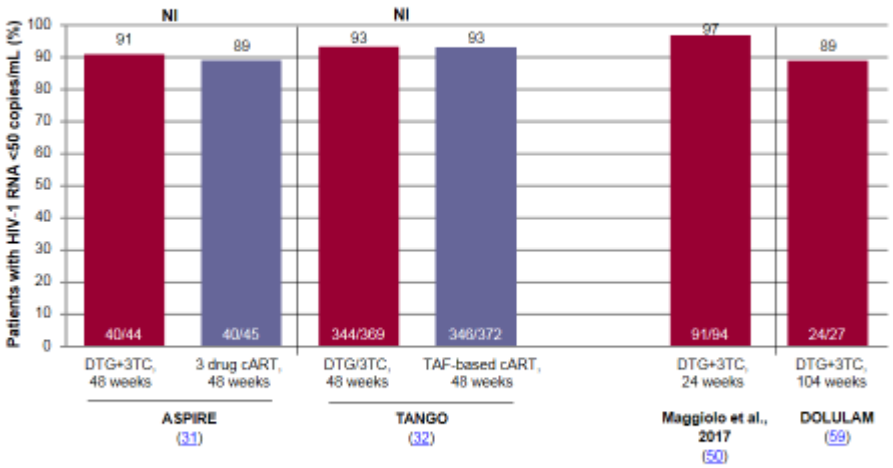


Figure 3. Dolutegravir plus Lamivudine Dual Regimens in Virologically Suppressed Patients - Efficacy in Randomized Clinical Trials and Real Life Cohorts. 3TC, lamivudine; cART, combination antiretroviral treatment; DTG=dolutegravir; NI=noninferior treatment difference; TAF, tenofovir alafenamide



Tables

Table 1. Latest international recommendations for dolutegravir-based two-drug regimens

Regimen	SIMIT 2017-2018 (1, 2)	DHHS 2018 (3)	IAS-USA 2018 (4)	EACS 2018 (5)	GeSida 2018 (6)
cART-naïve patients					
DTG + 3TC	Not recommended*	Alternative [BI][a]	Not yet recommended*	Alternative[a] VL<500,000	
cART-experienced virologically suppressed patients					
DTG + RPV	Recommended [AI]	Recommended [AI][b]	Recommended [AI][$]	Recommended	Recommended [AI]
DTG + 3TC	Alternative [BII][$]	Not yet recommended[$]	Recommended [AII][c]		

[*] Published before the availability of latest results from GEMINI-1 and GEMINI-2 studies (29);

[$] Published before the availability of latest results from TANGO study (32);

[a] When the use of tenofovir disoproxil, tenofovir alafenamide, or abacavir is contraindicated or not desirable; [b] When the use of nucleoside reverse transcriptase inhibitors is not desirable and when resistance to either dolutegravir or rilpivirine is not expected; [c] In patients with no prior virological failure or transmitted drug resistance. 3TC, lamivudine; cART, combination antiretroviral treatment; DTG, dolutegravir; EACS, European AIDS Clinical Society; DHHS, U.S. Department of Health and Human Services; GeSida/PNS, Grupo de Estudio de Sida/Plan Nacional sobre el Sida; IAS, International AIDS Society; RPV, rilpivirine; SIMIT, Società Italiana di Malattie Infettive e Tropicali; VL, viral load. The strength of recommendations is reported as in each guideline.

Table 2. Patients with emergent drug-resistance mutations after confirmed virological withdrawal to dolutegravir-based two-drug regimens in randomized clinical trials

Trial	Treatment experience	Dual treatment	Patients, N	Emergent resistance mutations[a]	
				NNRTI	INSTI
GEMINI-1 and GEMINI-2	Naive	*DTG+3TC, 96-weeks*	-	No emerging resistance found	
ASPIRE	Virologically suppressed	*DTG+3TC, 48 weeks*	-	No emerging resistance found	
SWORD-1 and SWORD-2	Virologically suppressed	*DTG + RPV early and late switch, 100-weeks*	5	K101K/E (N=2) E138E/A (N=1) M230M/L (N=2)	None
TANGO	Virologically suppressed	*DTG/3TC, 48 weeks*	-	No confirmed virologic withdrawals	

[a]Only patients with available baseline and failure resistance testing are reported. 3TC, lamivudine; DTG, dolutegravir; INI, integrase inhibitors; NNRTI, non-nucleotide reverse transcriptase inhibitors; RPV, rilpivirine.