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Is Antiretroviral Two-Drug Regimen the New Standard for HIV Treatment in Naive Patients?

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Abstract

The use of a combination antiretroviral therapy (cART) has changed dramatically the prognosis and the life expectancy of people living with HIV. The current treatment guidelines continue the convention of preferred cART based on combining a dual nucleoside reverse-transcriptase inhibitor (NRTI) backbone with a third "anchor" agent, such as a ritonavir (r)- or cobicistat (c)-boosted protease inhibitor (PI), a non-NRTI (NNRTI), or an integrase inhibitor (INI) boosted or unboosted. However, due to toxicities of NRTIs, sparing NRTI regimen has been studied for a long time with moderate success due to low efficacy (especially in patients with high viral load and low CD4) compare to standard triple therapy. New strategy with lamivudine (3TC) plus a boosted PI or INI showed promise results and indicated that modern two-drug regimens might now, in fact, become a reliable treatment for HIV-infected naïve patients. This article discusses recent data from dual therapy studies in naïve HIV-infected patients and the challenges behind this strategy.

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Key words

Antiretroviral therapy. Naïve human immunodeficiency virus-infected patients. Dual therapy. 3TC. Protease inhibitor. Integrase inhibitor.

Introduction

The use of a combination antiretroviral therapy (cART) in the treatment of people living with human immunodeficiency virus (PLWHIV) infection has reduced dramatically disease progression and death rates[1]. Until now, triple therapy (TT) is considered as the goal standard of HIV treatment in naïve patients as shown in several randomized clinical studies[2-6] and reflected in major international guidelines[7-11]. Life expectancy of PLWHIV has increased and tends to reach that of the general population[12]. With a longer

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life expectancy than before, PLWHIV are at an increased risk of developing non-acquired immune deficiency syndrome (AIDS) comorbidities such as cardiovascular, kidney, bone diseases, and cancers[13-15]. To mitigate the detrimental effect of comorbidities, a global transition to antiretroviral drugs with lower toxicity and decreased exposure is needed urgently, along with adoption of comprehensive interdisciplinary management of comorbidities[13-15]. Strategies to attenuate the persistent inflammatory state during cART might also help stabilized or ameliorate the consequences of the increasing age in PLWHIV. Innovative developments in antiretroviral therapy, including long-acting agents, new delivery modalities (injectable, nanoparticles), and novel paradigms, such as immunotherapy or dual therapy (DT), should be exploited to provide a better quality of life for PLWHIV[13-22]. The current treatment guidelines continue the convention of preferred cART based on combining a dual nucleoside RT inhibitor (NRTI) backbone with a third "anchor" agent, such as a ritonavir (r)- or cobicistat (c)-boosted protease inhibitor (PI/r or c), a non-NRTI (NNRTI), or an integrase inhibitor (INI) boosted or unboosted[7-11]. The toxicities associated with long-term use of NRTIs have led to the assessment of mono or DT approaches that do not include an NRTI component[23-29]. Non-inferiority or a higher risk of treatment failure (TTF) was observed in early NRTI-sparing studies compared with current standard TT regimens, especially on subclass of patients with low CD4 cell count and a high viral load (VL)[23-31]. The Global Anti-Retroviral Design Encompassing Lopinavir (GARDEL)/r and lamivudine versus LPV/r-based standard therapy comparing a DT regimen of lamivudine (3TC) plus boosted lopinavir by ritonavir (LPV/r) to standard TT in naïve patients show non-inferiority along with better tolerability at 48 and 96 weeks (W)[32,33]. This study has given renewed hope for DT. This trend has increased with the arrival of new generation of INI such as dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB)[34,35]. The DT strategy has been applied as initial therapy in antiretroviral-naive patients or as a switch strategy in those patients who have become virologically suppressed on standard regimens[21,22]. In the current guidelines, until further data are available, initial two-drug regimens are reserved for special situations (e.g. comorbidities, pre-treatment VL [< 100,000 copies/mL], and CD4 cell counts [> 200/mm^3]) when individuals cannot take abacavir (ABC), tenofovir alafenamide, or tenofovir disoproxil fumarate (TDF)[7-11].

In this article, we will first provide a brief history on DT attempts and then discuss recent data from DT studies in naïve HIV-infected patients and the challenges and perspectives behind this strategy.

The history of DT in naïve HIV-infected patients

The use of cART began in the mid-1990s, in which two NRTIs were combined with a third agent from a different therapeutic class. Two major trials published in 1998 comparing TT with indinavir (IDV) + zidovudine (AZT) + lamivudine (3TC) to either 3TC + IDV or AZT + 3TC or IDV monotherapy[30,31] after an induction period of 12 or 24 weeks showed the superiority of TT. At that time, these two studies were already pointing to the problem of efficacy in patients with low CD4 cell counts and high VL in the DT or monotherapy arm[30,31]. Then, TT continues to be until now the goal standard[7-11]. The toxicities associated with long-term use of NRTIs[13-20] have led to the assessment of mono or DT approaches that do not include an NRTI component in naïve and experiences patients[21-26]. Several combinations excluding NRTI were tried in naïve patients[29,36-38]. In ACTG 5142[38] (n = 753), time to viral failure (VF) was similar in the LPV/r + efavirenz (EFV) arm when compared with the TT arms; however, resistance (any mutation [excluding minor protease mutations] and NNRTI-associated mutations) and Grades 3 and 4 laboratory events were more common with LPV/r + EFV. Among patients with HIV-1 RNA levels of 100,000 copies/mL or more at screening, the EFV group had a longer time to VF than either the LPV/r group (p = 0.01) or the NRTI-sparing group (p = 0.02). Later, maraviroc (MVC) was combined to PI/r[27-29,36]. LPV/r or atazanavir/r (ATV/r) combined with MVC studies[28,29], showed good virologic suppression; however, in the ATV/r study, the Grades 3 and 4 elevations in bilirubin levels in patients treated with ATV/r + MVC (36.7%) versus ATV/r + TDF/emtricitabine (FTC) (19.7%) were of concern[28,29]. In the MIDAS study darunavir (DRV/r + MVC; n = 24), the rate of VF was high, especially in patients with higher baseline VL; the virus was not suppressed at 48 W in 16.7% of patients (4/24), despite reported perfect adherence to therapy[29]. The A4001095 (MODERN; n = 812) was designed to assess therapy with DRV/r + TDF/FTC and DRV/r + once-daily MVC and utilized 150 mg MVC with DRV/r 800/100 mg once daily. This study was terminated early due to inferior efficacy in the MVC arm[27].

With the improved potency, tolerability, and durability of newer drugs such as INI, raltegravir (RAL) was combined with a boosted PI. RAL was combined to either ATV/r[23], LPV/r[26], or DRV/r[29,38,39]. In the ATV study (SPARTAN), high rate of hyperbilirubinemia leads to early termination of the study[23]. RAL combined to LPV/r in the PROGRESS study (n = 206) was non-inferior to LPV/r + TDF/FTC and was also well tolerated, but the study not powered and had low number of patients with VL > 100,000 copies/mL[26]. DRV the only PI actually recommended in guidelines[7-11] was combined with RAL in three studies[39-41]. In two of them, RADAR study[39] and ACTG A 5262[40] showed poorer results in terms of virologic suppression. The NEAT 001 study[41], a large (n = 805) non-inferiority randomized open-label study comparing the efficacy and safety of DRV/r in combination with either TDF/FTC or RAL, utilized time to TTF (virologic or clinical) as the primary endpoint. Per Kaplan–Meier methodology, therapy failure occurred in an estimated 17.4% of patients in the RAL arm and 13.7% in the TDF/FTC arm after 96 W (adjusted difference, 3.7% [95% CI, −1.1-8.6]), falling within a pre-specified non-inferiority margin of 9%. In subgroup analyses, patients with CD4 counts < 200 cells/mm^3 had substantially higher rate of TTF using RAL therapy compared with TDF/FTC therapy (Table 1, more data in supplementary file). The reasons for less than optimal treatment response in the non-NRTI arm in this subset of patients are not completely understood.

Whereas PIs seemed to be a good companion for INIs as a result of the protective effect of their high resistance barrier, the poor gastrointestinal tolerability of LPV/r and the frequent hyperbilirubinemia with ATV were major drawbacks. In the NEAT 001 study, where DRV/r was combined with RAL, patients with low CD4 cell count (< 200 cells/mm^3) and high VL (> 100,000 copies/mL) remain challenging[41].

3TC is a potent inhibitor of the RT enzymes of HIV-1 and is active against hepatitis B virus (HBV). The unique chemical structure of 3TC, which is characterized by excellent antiviral activity with little toxicity, strongly contributes to its clinical success[42]. 3TC has been part of most nucleoside backbones recommended so far[7-11]. The good results obtained with DT (3TC plus LPV/r) in the GARDEL study[32,33], whether for low or high VL and the good tolerance observe, have revived the DT strategy, especially with the advent of new INI such as DTG[34,35,43-45] which have an excellent tolerance, a good barrier of resistance, and low pill burden.

Successful DT for naïve HIV-infected patients

Until now, the successful DT in naïve patients used 3TC combined either with a boosted PI[32,46] or the second generation of INI, DTG[43-45].

3TC plus a boosted PI

3TC has been combined with either LPV/r or DRV/r[32,46].

The GARDEL study[32] (n = 426) is a Phase 3, multicenter, randomized, controlled, open-label, non-inferiority trial in antiretroviral therapy-naive adults (age ≥ 18 years) with documented HIV-1 RNA VL of at least 1000 copies/mL, comparing 3TC plus boosted LPV/r to standard TT (lopinavir/r-based therapy) in naïve patients show non-inferiority along with better tolerability at 48 and 96 W[32,33]. Between December 10, 2010, and May 15, 2012, patients were randomly assigned (1:1) to DT (DT, n = 217) or TT (n = 209) by sealed envelopes, in blocks of four, stratified by baseline VL (< 100,000 vs. ≥ 100,000 copies/mL). At W48, 88.3% in the DT group and 83.7% in the TT group had viral response <50 copies/mL (difference 4.6%, 95% CI −2.2-11.8; p = 0.171). Patients with baseline VL of at least 100,000 copies/mL showed similar results (87.2 vs. 77.9%, respectively; difference 9.3%, 95% CI −2.8 to 21.5; p = 0.145). The 48 W trial demonstrated non-inferiority for the DT with a VL <50 copies/mL as the primary outcome. These results were confirmed at 96 W[31]. On the one hand, the authors described more toxicity related discontinuations and total adverse side effects in the TT arm at W48 which supports the hypothesis that DT is less toxic, but, on the other hand, serious adverse events (SAEs), i.e., a case of death due to bacterial sepsis were only reported for the DT group[30] (Table 1). Li et al. performed the same design study in Chinese naive HIV-infected patients (n = 198) but compared 3TC + TDF plus EFV to 3TC plus LPV/r[47]. They found similar results after 48 W and concluded that DT of LPV/r plus 3TC is effective, safe, and comparable to the first-line triple-therapy regimen containing 3TC/TDF plus EFV in China, even in patients with high baseline VL[47] (supplementary file).

The ANDES[46] was a randomized, open-label, Phase IV study, designed to compare DT with DRV/r (800/100 mg) fixed-dose combination (FDC), plus 3TC (300 mg), to TT with DRV/r (800/100 mg) plus 3TC/TDF (300/300 mg), FDC in treatment-naïve HIV-1-infected patients. Primary endpoint: proportion of patients with

Table 1. Successful dual therapy in HIV-infected naïve patients

Year of publication	Study name and authors	Duration	Study design	DT versus TT	Virological response	Main/median CD4 increase (cells/mm^3)	Results
2014-2015	GARDEL, Cahn et al.[32]	48 W	Phase III Multicenter Randomized (1:1) Controlled Open label Non-inferiority n = 426	DT: LPV/r (400/100 mg BID) + 3TC (150 mg BID) versus TT: LPV/r (400/100 mg BID) based regimen+3TC or FTC+1 NRTI in FDC	VL < 50 copies/mL after 48 W DT: 88.3% versus TT: 83.7% (p = 0.171) If baseline VL ≥ 100,000 copies/mL: DT: 87.2% versus TT: 77.9% (p = 0.145)	W48: DT: 227 versus TT: 217	Non-inferior at W48 regardless of baseline viral load
2018	ANDES, Figueroa et al.[47]	48 W	Phase IV Multicenter Randomized 1:1 Open label n = 145	DT: DRV/r (800/100 mg QD in a FDC) + 3TC (300 mg QD) (n = 75) versus TT: DRV/r (800/100 mg QD) + 3TC/TDF (300/300 mg in a FDC QD) (n = 70)	VL < 50 copies/mL after 48 W: DT: 93% versus TT 94% (95% CI: −1.0% [−7.5; 5.6%]) If baseline VL > 100,000 copies/ml: DT 91% versus TT 92% Per-protocol analysis: DT 100% versus TT 99%	W48: DT: 246 versus TT: 200 (p = 0.20)	Non-inferiority even in patients with VL ≥ 100,000 copies/mL
2014	NEAT 001/ ANRS 143, Raffi et al.[42]	96 W	Phase III Multicenter Randomized Open label Parallel group Non-inferiority n=805	DT: RAL (400 mg BID) + DRV/r (800/100 mg QD) (n = 401) versus TT: TDF/FTC (245/200 mg QD in FDC) + DRV/r (800/100 mg QD) (n = 404)	TTF after 96 W: DT 17.4% versus TT 13.7% If baseline VL<100,000 copies/mL: DT: 7.4% versus TT 7.3% If baseline VL≥100,000 copies/mL: DT 36.8% versus TT 27.3% (p = 0.1) If baseline CD4<200/mm^3: DT 43.2% versus TT 20.9% (p = 0.010)	W96: DT 267 versus TT 266	Non-inferiority was met for composite primary end point; however, TT was superior in patients with CD4 < 200/mm^3
2017	PADDLE, Cahn et al.[45]	48 W	Phase IV Single arm Open label Pilot study n = 20	DTG (50 mg QD) + 3TC (300 mg QD)	VL < 50 copies/mL after 48 W: 90% (18/20)	W48: 267	High efficacy However, only four patients with VL > 100,000 copies/mL
2019	ACTG A5353, Nyaku et al.[46]	48 W	Phase II Single arm Pilot study n = 120	DTG (50 mg QD) + 3TC (300 mg QD)	VL < 50 copies/mL after 48 W: 85% If baseline VL ≤ 100,000 copies/mL: 78%) versus 88% (p = 0.18) if baseline > 100,000 copies/mL	NA	Virologic efficacy with study entry VL up to 500.000 copies/mL

(Continue)

Table 1. Successful dual therapy in HIV-infected naive patients *(Continued)*

Year of publication	Study name and authors	Duration	Study design	DT versus TT	Virological response	Main/median CD4 increase (cells/mm^3)	Results
2018	GEMINI 1/ and 2, Cahn et al.[44]	48 W	Phase IV Multicenter RCT Double-blind Parallel group Non-inferiority studies n = 1433	DT: DTG (50 mg QD) +3TC (300 mg QD) (n = 719) versus TT: DTG (50 mg QD) + TDF (300 mg)/FTC (200 mg) (n = 722)	VL < 50 copies/mL after 48 W): 91% versus TT 94% If baseline VL > 100,000 copies/mL: DT 92% versus TT 90% If baseline CD4 ≤ 200 cells/mm^3: DT 79% versus TT 93%	NA/NA	Non-inferiority. However, there was a significant difference when results were stratified by baseline CD4 count above versus below 200 cells/mm^3

DT: dual therapy, TT: triple therapy, W: week, FDC: fixed-dose combination, VL: viral load; NRTI: nucleoside reverse-transcriptase inhibitor, 3TC: lamivudine, FTC: emtricitabine, TDF: tenofovir disoproxil fumarate, DRV/r: darunavir/ritonavir, LPV/r: lopinavir/ritonavir, DTG: dolutegravir, RAL: raltegravir, BID: twice a day, TTF: time to treatment failure, NA: not applicable.

VL < 50 copies/mL at W48 (FDA snapshot – ITT analysis). Of 182 patients screened, 145 were randomized to receive DT (n = 75) or TT (n = 70). At W48, 93% of patients on DT and 94% on TT achieved VL < 50 copies/mL, difference (95% CI): −1.0% (−7.5; 5.6%). Patients with baseline VL > 100,000 copies/mL showed 91% in DT arm and 92% response in TT arm. One patient presented VF at W48 (TT arm). Per-protocol analysis: 100% were responders in DT arm and 99% in TT arm. Median CD4+ cell count change between baseline and W48 was similar in both arms[46].

3TC plus INI

The pilot antiretroviral design with DTG lamivudine (PADDLE) is a pilot study involving HIV-1-infected patients naive to ARV treatment (n = 20). Participants were enrolled in Argentina between September 24, 2014, and February 28, 2015. PADDLE evaluated DTG and 3TC as a DT regimen and showed that 90% (n = 18/20) of patients were virologically suppressed at 48 W[44], and 100% of patients (n = 18) who were included in the extension phase maintained virologic suppression at 96 W[48]. To extend the findings of PADDLE, 3TC was paired with DTG in patients with HIV-1 RNA < 500,000 copies/mL in the Phase II 52 W ACTG A5353 pilot study (n = 120)[45]. At W48, 102 of the 120 participants (85%; 95% CI 77%-91%) had virological success. Virological success was similar between screening HIV-1 RNA groups. Six (5%) participants had virological non-success and one additional participant experienced VF while on study but off-study treatment. No new drug resistance mutations were observed after 24 W (3 VF and in one patient R263K and M184V). Six (5%) participants had study-related Grade 3 or higher AE and none discontinued study treatment[45]. These proof-of-concept studies provide the rationale for two Phase III trials, GEMINI-1 and GEMINI-2 which compare DTG/3TC with DTG plus TDF/FTC in treatment-naive patients. GEMINI 1 and 2 (44, Table 1, supplementary file) are identically designed studies. Both are large, international Phase 3 studies and each randomized just over 700 treatment-naive participants to either DTG + 3TC or DTG + TDF/FTC. The primary endpoint was the proportion of participants with plasma VL < 50 copies/mL at W48 (using ITT or snapshot analysis). GEMINI 1 and 2 randomized 719 and 722 treatment-naive participants respectively with screening VL < 500,000 copies/mL. Baseline characteristics included median CD4 and VL of 432 cells/mm^3 (range: 19-1497), with 10% < 200 cells/mm^3 and 4.4 log copies/mL (range: 1.6-6.4)

respectively, with 20% > 100,000 copies/mL and 9% < 200 CD4 cells/mm^3. Approximately 2% of participants in each arm were later reported as having VL above entry criteria threshold of 500,000 copies/mL (explained by fluctuations between screening and baseline). At W48, VL was < 50 copies/mL in the DT versus TT in 90% (320/356) versus 93% (332/358) in GEMINI 1 and 93% (335/360) versus 94% (337/359) in GEMINI 2. This resulted in adjusted between-arm differences that were slightly lower in the DT arm, though with a 95% CI that was well within the predefined margin of –10%: –2.6 (95% CI: –6.7 to +1.5) and –0.7 (–4.3 to +2.9), in GEMINI 1 and 2, respectively. Although the adjusted treatment differences favored the TT arm, non-inferiority was also easily met in the combined analysis: –1.7 (–4.4 to +1.1). Virologic non-response (VL ≥ 50 copies/mL at W48) in DT versus TT arm was 4% versus 2% in GEMINI 1 and 2% versus 2% in GEMINI 2. Virologic responses by pre-specified criteria of VL above versus below 100,000 copies/mL were broadly similar, with no suggestion that DT was less effective (Table 1, supplementary file). However, there was a significant difference when results were stratified by baseline CD4 count above versus below 200 cells/mm^3. While each arm reported 93% viral suppression to < 50 copies/mL at W48 when CD4 count was > 200 cells/mm^3, this dropped to only 79% of the participants who started with CD4 counts < 200 cells/mm^3 in the DT arm (snapshot analysis). This difference was unrelated to efficacy or TTF (lost of follow-up, protocol violation, withdrew to start HCV treatment, etc…)[43].

Challenges

Does DT reduce adverse events or side effects?

In the NEAT 001[41], the differences in SAEs were numerically higher in the RAL arm, but differences were not statistically significant. There were 89 versus 75 SAEs (in 73 vs. 61 patients; incidence rate 10.2 versus 8.3/100 patient-years (PY), p = 0.17) (Table 2). Changes in fasting lipids were more significant in the RAL group (Table 2), but there was no significant difference in TC/HDL-c ratio (p = 0.7). Grade 3/4 ALT increases in 3.0 versus 1.0% of the RAL versus TDF/FTC arms, respectively. Creatinine clearance measured by eGFR at week 96 increased by 0.9 ml/min/1.73 m^2 in the RAL group compared to dropping by –3.8 ml/min/1.73 m^2 in the TDF/FTC arm (p = 0.02) with the drop occurring in the first 4 weeks of treatment. Bone markers were in favor of RAL arm[41] (Table 2).

In the GARDEL study, AEs leading to discontinuations were more common in the TT group (n = 10 [4.9%]) than in the DT group (n = 1 [0.4%]; difference 4.5%, 95% CI –8.1-–0.9; p = 0.011). Sixty-five AEs in the DT group and 88 in the TT group were possibly or probably drug related (p = 0.007). The most common AEs were hyperlipidemia, diarrhea, and nausea. Changes in TC, LDL-c, and HDL-c were higher in DT compared to TT (32% DT vs. 26% TT for TC; 25% DT vs. 16% TT for LDL-c, and 33% DT vs. 28% TT for HDL-c). Increase in triglycerides was higher in TT compared to DT (55% DT vs. 92% TT) (Table 2). In TT arm, LDL-C and TC elevations were lower among patients receiving TDF compared to those treated with ZDV or ABC. No data on bone and kidney safety were available[32,33].

In the safety analysis of Gemini 1 and 2, similar numbers of participants in the DT group (15 [2%]) and TT group (16 [2%]) had AEs that led to permanent discontinuation of study drug (Table 2). Similar proportions of SAEs were observed in the DT group (50 [7%]) and TT group (55 [8%]), with no single disorder reported as an SAE in more than 1% of participants in either group. Changes in renal biomarkers were generally favorable in the DT group compared with the TT group. Increases in bone turnover biomarkers were observed in both treatment groups at week 48. The magnitudes of the increases were smaller in the DT group than in the TT group. Changes in lipid parameters at W48 varied between parameters and treatment groups. TC, LDL-c, and total triglycerides increased from baseline to W48 in the DT group and decreased in the TT group, with the differences between groups being significant for each. A significantly greater increase was observed in HDL-c in the DT group than in the TT group. Small decreases in TC/HDL-c ratio were observed, but the decrease in the TT group was significantly greater than in the DT group[43] (Table 2).

Globally AEs leading to discontinuations were less in DT versus TT in major studies[32,41,43]. Changes in bone serum marker or bone mineral density and renal function or urinary markers were in favor of DT. Lipid changes were more favorable in conventional TT arm probably due to tenofovir lipid-lowering effect (Table 2).

What about resistance at failure

In the NEAT 001 study[41], no resistance was detected in 13/15 patients with VF and genotypic results in the TDF/FTC arm compared to five major mutations in 28/36 patient with results with RAL. This included one case of K65R and five patients with N155H and 4/5 of

Table 2. Comparison of adverse events of dual therapy versus triple therapy

Studies	Lipids	Bone	Kidney	Central nervous system	Liver	AEs and AEs leading to discontinuation
Neat 001/ANRS: RAL+DRV/r) versus TDF/FTC+DRV/r[42]	DT versus TT at W96: statistically significant increases TC+0.9 versus+ 0.5 mmol/L ($p < 0.001$) HDL-c+0.2 versus+ 0.1 mmol/L ($p < 0.001$) LDL-c+0.5 versus+ 0.4 mmol/L ($p = 0.02$)	DT versus TT at W96: change in BMD: femoral neck−1.74 versus−5.99 ($p = 0.025$) Hip: −1.57 versus−3.86 ($p = 0.0032$) Lumbar spine: -0.43 versus -2.8 ($p = 0.0054$) A raltegravir-based regimen was associated with significantly less loss of bone mineral density than a standard regimen containing tenofovir disoproxil fumarate	DT versus TT at W96 e GFR (ml/min/1.73m^2): +0.9 versus−3.8 ($p = 0.02$)	No difference	DT versus TT at W96: Grades 3-4 ALT increase: 3 versus 1% ($p = 0.036$)	Incidence rates of AEs (100-PY) were similar between arms (DT vs. TT): W96: AE: 3.9 versus 4.2 p? SAE: 10.2 versus 8.3 P = 0.17 AEs leading to discontinuation for treatment-limiting AE W96 DT: 1.5% versus 2.6% in TT
GARDEL: 3TC+LPV/r versus 2 NRTI+ LPV/r[32,33]	DT versus TT at W48 TC 157 versus 154 mg/dl Trig: 142 versus 139 mg/dl LDL-c: 94 versus 91 mg/dl HDL: 36/35 mg/dl Changes in TC, LDL-c, and HDL-c were higher in DT compared to TT (32% DT versus 26% TT for TC; 25% DT versus 16% TT for LDL-c and 33% DT versus 28% TT for HDL-c). Increase in TG was higher in TT compared to DT (55% DT versus 92% TT W96: Hyperlipidemia: DT (n = 165): 22% TT (n = 141): 21%	No data	No data	No data	No data	At W48: total number of patients with Grades 2-3 AEs (possibly or probably drug related) DT versus TT: 20 versus 24% ($p = 0.43$) AEs leading to discontinuation DT versus TT: 0.4 versus 4.9% ($p = 0.01$) W96: total number of patients with Grades 2-3 AEs (possibly or probably drug related) DT: 63/165 (38%) TT: 65/141 (46%) AEs leading to discontinuation toxicity/tolerability DT: 0.61% TT: 2.84%

(Continue)

Table 2. Comparison of adverse events of dual therapy versus triple therapy *(Continued)*

Studies	Lipids	Bone	Kidney	Central nervous system	Liver	AEs and AEs leading to discontinuation
Gemini 1 et 2: FTC/TDF+DTG versus 3TC+DTG[44]	DT versus TT at W48 (mmol/l) TC (↑0.32/↓0.25, P<0.001) HDL-c (↑0.15/↓0.02, P<0.001) LDL-c (↑0.17/↓0.14, P<0.002) TG: ↑0.03/↓0.08, P<0.0457) Ratio TC/HDL-c: ↓0.12/↓024, P = 0.0182)	DT versus TT at W48 serum phosphatase. Alkaline: 1.22/4.07 (p < 0.001) Serum osteocalcin: 0.60/6.12 (p < 0.001)	DT versus TT at W48 creatinine: + 10.4 micromol/l versus 13.5 (p < 0.001) eGFR (ml/min/1.73m^2): −12.1/−15.5 (p = 0.001) Urine markers: Protein creatinine ratio: 0.87 g/mol/1.03 g/mol (p < 0.001) RBP: 0.93/1.11 (p < 0.0001) B2 microglobulin: 0.92/1.31 (p < 0.04)	At W48 Suicidal ideation 2% versus 2% 76% in DT versus 56% in TT had A previous history of depression or suicidal behavior or other psychiatric events		Similar proportions of SAE were observed in the two-drug regimen group (50 [7%]) and three-drug regimen group (55 [8%]), with no single disorder reported as a serious adverse event in more than 1% of participants in either group AEs leading to discontinuation (2% DT vs. 2% TT)
ANDES: 3TC+DRV/r versus FTC/TDF+DRV/r[47]	DT versus TT: TC: 19% versus 4% (p = 0.01) LDL-c: 14% versus 6% (ns) TG: 25% versus 14% (ns)	No data	No data	More neurological complaints: DT 0% versus 4.3% in TT		Total AEs: DT 13.3% (11 AEs/10 patients) versus 22.9% (21 AEs/16 patients) in TT GI side effects: 6.7% in DT versus 12.9% in TT

GI: gastrointestinal, TT: triple therapy, DT: dual therapy, TC: total cholesterol, TG: triglyceride, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, RBP: retinol-binding protein, DTG: dolutegravir, LPV/r: lopinavir/ritonavir, DRV/r: darunavir/ritonavir, TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, AEs: adverse events, SAE: severe adverse event.

these patients had baseline VL "considerably higher than 500,000 copies/ml[39]." At 143 W, no resistance-associated mutation (RAM) was observed in the TDF/FTC plus DRV/r arm and 18 in the RAL arm. The frequency of INI mutations at failure was significantly associated with baseline VL: 7.1% for a VL of < 100,000 copies/mL, 25.0% for a VL of ≥ 100,000 copies/mL and < 500,000 copies/mL, and 53.8% for a VL of ≥ 500,000 copies/mL (p = 0.007). Of note, 4/15 participants with IN RAM had a VL < 200 copies/mL at the time of testing (Table 3).

In the GARDEL study, 10 patients (4.7%) in the DT group and 12 (5.9%) in the TT group (difference –1.3 [95% CI–6.1%-3.5; p = 0.720]) met criteria for VF. Seven VFs were confirmed at W24 (one in the DT group and six in the TT group) and 15 at W48 (nine in the DT group and six in the TT group). In two patients in the DT group, the M184V mutation was present at virologic failure (Table 3). None of the amplified samples at virologic failure in the TT group showed any resistance mutations. Mutations associated with PI were not identified in either arm[32].

In Gemini 1 and 2 studies, 10 (< 1%) participants overall (six in the DT group and four in the TT group) met pre-specified criteria for confirmed virological withdrawal through W48. Genotypic testing of the HIV-1 RT, protease-RT, and INI genes was successful for baseline and virological withdrawal samples from 9/10 patients. For those with successfully amplified and sequenced samples, none had emergence of mutations conferring resistance to INIs or NRTIs (Table 3)[43].

In summary, in patient failing with DT treatment (3TC plus PI/r or INI), globally, no major resistances were detected[32,43].

Patients harboring prior M184V/I mutation at initiation

The frequency of M184V/I has shown more variability across studies (ranging from 0.3% to 4.3%)[49,50]. Recently, Margot et al. showed a frequency of 0.1%[51]. The overall rare observation of these mutations in ART-naive patients is probably a consequence of the reduced fitness of viruses harboring these mutations[47], resulting in reduced transmission rates and/or a higher rates of reversion to wild type in the absence of drug pressure. Indeed, M184V/I was found at higher frequencies in acutely/recently infected ART-naive patients than in chronically infected ART-naive patients (8.2% and 2.5%, respectively)[49-51], and M184V/I was reported to have a particularly high reversion rate in the absence of drug pressure[51]. None of the randomized clinical trial on DT (3TC with either PI/r or INI) in naïve HIV-infected patients included patient with the M184V/I or any other resistance[32,43-46]. The previous study with TT in naive or experimented HIV-infected patients with M184I/V mutations showed good success on suppression of HIV replication confirming the residual activity of 3TC despite these resistances[51,52]. However, Johnson et al. recently showed that a considerable proportion of transmitted HIV-1 drug resistance is undetected by conventional genotyping and that minority mutations can have clinical consequences. Seven (78%) of the nine participants with minority resistance mutations in their study experienced virologic failure. One participant who experienced failure within 2 months had both the K103N and the M184V mutations, which confer resistance to two drugs in the regimen, EFV and 3TC, respectively[53]. Recent maintenance DT studies (3TC + DTG or 3TC plus PI/r) do not show any impact of the M184I/V[54,55]. In addition, recently, ***in vitro*** culture selection experiments have shown that the presence of the M184V or K65R mutation prevented the selection of DTG resistance mutation. These data support the hypothesis that selection of M184V by 3TC results in residual antiviral activity that can be effective in controlling viral replication in combination with other antiviral agents even with DT[56]. Actually, guidelines recommend standard genotype at HIV diagnosis ("baseline genotype") to detect transmitted drug resistance. However, Hyle et al. showed that with INI-based first-line regimens (TT) in the US, baseline genotype offers minimal clinical benefit and is not cost effective[57]. The impact and cost-effectiveness of baseline genotype in INI DT base regimen remain to be demonstrated.

HIV-1 subtypes non-B and HIV-2

There is strong evidence suggesting differences in the patterns and mechanisms of drug resistance between HIV-1 subtype B, which dominates in the United States, Western Europe, and Australia, and non-B infections that are most prevalent in countries of Africa and Asia[58]. Garrido et al. in their study showed that major INI resistance mutations at positions 66, 92, 143, 148, and 155 were not detected; however, the mean number of polymorphic sites was greater in non-B than in B variants (2.17 vs. 1.59; p < 0.001)[58]. Recently, Rogers et al. used molecular modeling to explore the structural impact of integrase polymorphisms on the integrase reaction mechanism and INI susceptibility[59]. Their data showed that among all non-B subtype sequences, 17 naturally occurring integrase polymorphism positions with 18 polymorphisms were observed[59]. These data togeth-

Table 3. Resistance mutation at failure in major dual therapy studies

	Neat001/ANRS* (42)	GARDEL (32-33)	Gemini 1-2 (44)	ANDES (47)
Comparator	RAL + DRV/r versus TDF + FTC + DRV/r	3TC + LPV/r versus 2NRTI + LPV/r	3TC + DTG FTC/FTC + DTG	3TC + DRV/r versus TDF/FTC + DRV/r
Resistance (n)	18/0 at W96	W48: 2/0 W96: 4/3	0/0 at W48	0/0 at W48
Type of resistance	15/55 (27.3%) participants had viruses with IN RAMs (12 N155H alone, 1 N155H + Q148R, 1 F121Y and 1 Y143C), 2/53 (3.8%) with nucleotide analog RT inhibitor RAMs (K65R, M41L) and 1/57 (1.8%) with primary protease RAM (L76V)	W48: 2 M184V/ none W96: 4 M184V/3 M184V	None resistance to INI, PI or NRTI	None
Comments	More mutations in raltegravir arm	VF: 10/12	6 VF/4 VF no mutation in each arm	1 VF in TT

3TC: lamivudine; TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, LPV/r: lopinavir boosted by ritonavir, DRV/r: darunavir/ritonavir, DTG: dolutegravir, VF: virological failure, NRTI: nucleoside reverse-transcriptor inhibitor, INI: integrase inhibitor, PI: protease inhibitor, RAM: resistance-associated mutation; TT: triple therapy, *143 weeks data.

er showed that HIV-1 subtype non-B harbors more polymorphism naturally than HIV-1 B subtypes. The clinical implication of those polymorphisms remains to be proven and a caution before treating those patients with DT with DTG is necessary.

ART for HIV-2 lags far behind HIV-1 therapeutics, due to the fact that the drugs have been designed using HIV-1 enzyme structures. Protein variability in HIV-2 explains the poor lack of binding and inhibitory effect of some of these agents. In this regard, HIV-2 is non-susceptible to NNRTIs and fusion inhibitors[60]. Moreover, several PIs show weak or no inhibitory activity against HIV-2. The treatment of HIV-2-infected individuals generally follows the rules of HIV-1 with a few special considerations. The optimal treatment strategy for HIV-2 infection remains unclear. Recently, two randomized clinical studies using INSTIS (RAL- or elvitegravir-based regimen) in naive HIV-2 showed an good efficacy in terms of virological suppression with modest gain in CD4 cell count[61,62]. Requena et al. confirmed those results in a real-world experience[60]; however, virological failure under INI-based therapy was recognized in 15 HIV-2-infected individuals, 2 being (11.1%) drug naive and 13 (50%) treatment experienced. A total of 12 individuals developed INSTI-associated resistance mutations. These data showed that there was frequent selection of drug resistance mutations in HIV-2 individuals that failed virologically, despite low VL values[60]. It supports the overall lower barrier to resistance in HIV-2 compared with HIV-1 for currently available antiretrovirals. Awaiting study of DT (either 3TC plus PIs or INIs) in HIV-2-infected patient, caution should be taking before using the DT approach for HIV-2 naive patients even in the absence of resistance in baseline genotype.

HBV coinfection

HBV and HIV both pose significant public health challenges in the developing world. Globally, approximately 10% of HIV-infected individuals are also chronic carriers of HBV[63] as a consequence of shared modes of transmission. Despite its high efficacy, 3TC is not recommended for use as HBV monotherapy in HIV/HBV coinfected patients due to the risk of the emergence of resistance mutations in HBV. The genetic barrier to the development of lamivudine resistance is low, as mutations in tyrosine-methionine-aspartate-aspartate motif of HBV emerge frequently. When HIV/HBV-coinfected patients receive 3TC as the only active drug for HBV, the resistance rates to lamivudine may reach 40% after 2 years and 90% after 4 years in these patients[64]. In area of hyperendemicity for HBV, DT with 3TC with an anchor drug (either PI/r or INI) will be difficult to implement. The disadvantages of DT in this case are currently likely to outweigh advantages in low- and middle-income settings.

Cost

Little is known on the impact of DT on the global cost for the management of HIV-infected naïve patient. Gatel et al. performed a cost/efficacy analysis of preferred Spanish AIDS study group regimens and the DT with LPV/r + 3TC for initial ART in HIV-infected adults. They found that the cost of initiating treatment ranges from 5138 euros for DT to 12,059 euros for TDF/FTC + RAL. DT was the most efficient regimen in the most favorable (5503 euros per responder) and most unfavorable (6169 euros per responder) scenarios[65]. Another study looking at the economic impact on the US health costs if treatment with DTG/3TC proves to be effective modeled 5-year savings of $550-$800 million based on 50% uptake of DT for new patients starting ART[66].

Inflammation

ART reduces dramatically systemic inflammation and immune activation, but not to levels synchronous with HIV-uninfected populations[67]. At present, there are no data of inflammation on DT in naïve HIV-infected patient. Orkin et al. evaluated in experience HIV-infected patients the effect of switching from three- or four-drug current ARV regimen to a DT (DTG plus RPV) on inflammation. No consistent pattern of change from baseline was observed in the pooled analysis of inflammation (hCRP, IL6), hypercoagulability (D-Dimer), and macrophage activation (sCD163) biomarkers and also for monocyte activation (sCD14), endothelial dysfunction (sVCAM-1), and fatty acid metabolism (FABP2) biomarkers[68].

Transmission of HIV

One of the best achievements of cART is the reduction of the transmission of HIV in serodiscordant couples[69,70]. Detection of HIV RNA in the genital tract is correlated with sexual transmission and is best predicted by the degree of plasma viremia[71]. Although there is a near-linear relationship between blood and genital HIV RNA, episodic genital HIV RNA expression occurs in some individuals with suppressed viremia possibly due to genital viral compartmentalization with poor drug penetration[72] or stimulation of virus replication by sexually transmitted infections and genital inflammation. While HAART effectively reduces plasma viremia, it remains unclear how effectively antiretroviral drugs reach mucosal surfaces, such as those of the genital tract. Mkhize et al. have shown that 5% of HAART-compliant women had any detectable HIV in their genital secretions[73]. Other studies reported between 2% and 20%[74-76]. However, there is no evidence that such shedding leads to new infections in the context of suppressed viremia. Gianella et al. investigated genital HIV RNA shedding with DTG plus 3TC. In this pilot study of 51 PLWHIV, the frequency of genital HIV RNA shedding while virologically suppressed in blood was similar between those who were on standard three-drug ART and those who were on DTG+3TC as initial or maintenance therapy[77].

Others challenges (not specific for DT but for INIs)

Child-bearing patients and pregnancy

Because the most promising DT regimens are those that associate 3TC with the INIs[41], the impact of the INI on outcome of children of women exposed to such drugs during pregnancy or pre-conceptional period will be important to know especially in low resources countries most affected by HIV that has large number women of childbearing age. Actually, the impact of newer INIs on pregnancy outcomes has not been well described. A recent systematic review of DTG in HIV-positive pregnant women did not show evidence for increased risks of stillbirth, preterm birth, small for gestational age, or congenital anomalies, compared to historical control studies of ARV-treated pregnant women[78]. However, none of the studies included in this analysis was a randomized clinical trial comparing outcomes for women taking DTG compared with other antiretrovirals in pregnancy. The Tsepamo study in Botswana examined women treated with various ARV regimens during pregnancy since 2014 and has acquired information on 88,755 births, nearly 22,000 of them to women living with HIV[78,79]. Unexpectedly, by July 2018, a higher rate of neural tube defects (NTDs) in infants born to women who were on DTG at the time of conception (0.67 %; n = 4, of 596) compared with women taking EFV at the time of conception and women taking any non-DTG-containing ART regimen. No statistically significant difference in NTD prevalence was found between women who started DTG during pregnancy (i.e. after conception) and women who initiated non-DTG-containing regimens during pregnancy. Recently, in the last Conference of Retrovirus and Opportunistic Infection 2019 in Seattle, authors reported (data of their cohort and pharmacovigilance database) the absence of increases NTD with INI including DTG even in periconceptional period. The main limitations of these

data are limited number of exposed patients on INIs (especially DTG)[80-82]. Awaiting more data on 2019 of the Tsepamo study, the U.S. Department of Health and Human Services has recommended that women with HIV who are of childbearing potential and currently taking DTG either be used effective contraception or be switched to a non-DTG-containing regimen. It remains to be seen if this problem of NTD due to exposure to DTG during periconceptional period will be confirmed definitely and also will spare others new INIs such as elvitegravir, BIC, or CAB[83].

Tuberculosis

Tuberculosis remains the leading cause of death among people living with HIV, accounting for around one in three AIDS-related deaths. Concurrent treatment of TB and HIV remains a challenge as it is compounded by drug interactions, overlapping toxicities, and immune reconstitution inflammatory syndrome[84]. As aforementioned for pregnancy, promise DT will use INIs[43]. Previous pharmacokinetics showed that DTG 50 mg twice daily is safe in coinfected HIV patients with rifampin or rifabutin treatment[85]. INSPIRING is a Phase IIIb, non-comparative, active control, randomized, open-label study in HIV-1-infected DTG-based ART-naive adults with drug-sensitive TB showed good results in terms of viral suppression and safety at 24 W[86]. Two studies showed that BIC[87] and CAB[88] coadministered with RIF significantly decreased their exposures. Another study[89] found that rifabutin modestly reduced oral CAB exposure, but concentrations remained above those linked to durable HIV suppression in a Phase 2 trial. Further study is needed to see how to manage interactions between rifamycins compound with new INIs. These interactions will complicate the use of integrase either in dual or TT in case of TB.

Conclusions and perspectives

Despite efforts to move toward sustained HIV remission or even eradication, lifelong ART is currently still the only option for patients to regain and maintain their health. Until now, TT remains the gold standard and with this, life expectancy of HIV-infected patients has been reported to approach that of the general population; however, other reports continue to find that morbidity and mortality rates remain elevated when compared with HIV-negative people due to immunodeficiency, immunosenescence, inflammation, aging, and long-term drug side effects, especially due to long-term use of NRTIs[13-15]. Sparing NRTI regimen has been studied for a long despite with moderate success due to low efficacy (especially in patients with high VL and low CD4) compare to standard therapy. New strategy with 3TC plus a boosted PI[32,46] or INI[43] showed promise results (high efficacy even in patient with higher VL comprise between 100,000 and 500,000 copies/ml). These results show that modern two-drug regimens might, in fact, become reliable treatment options for HIV-infected naïve patients. However, some challenges remain. For example, in the Gemini 1-2 studies, in those with baseline CD4 counts of < 200 cells/mL, lower responses according to snapshot criteria (HIV-1 RNA < 50 copies/mL at W48) were seen in the two-drug regimen group compared with the three-drug regimen group, but reasons for non-responses were mostly unrelated to virologic failure, which implies caution to interpreting outcomes in this crucial population[43]. The feasibility of a two-drug sparing regimen with 3TC in low-resource countries is, however, limited due to high numbers of HBV coinfection, which are insufficiently covered with 3TC monotherapy. Furthermore, a two-drug regimen requires antiviral coverage by both antiretroviral compounds that are confirmed through baseline genotypic resistance testing and this technique is usually not available or affordable in the global context. The most promising regimen for use in DT for naïve patients include 3TC and INIs. At present, only DTG has been evaluated as DT in RCT[43]. More data are needed in specific populations such as pregnant women (DTG periconceptional exposure is suspected to induce NTD) and coinfection with tuberculosis (drug-drug interactions) HIV-1 non-B subtype and HIV-2.

Supplementary data

Supplementary data are available at AIDS Reviews journal online (http://www.aidsreviews.com). These data are provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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