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(Supplementary Data)

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

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

Dual therapies with boosted protease inhibitors

Year of publication and duration of the study	Study name and authors	Duration	Study design and primary end point	Dual therapy versus TT	Virological response	Main/median CD4 increase (cells/mm^3)	Results	Inclusion criteria and baseline characteristics
2014-2015 December 10, 2010, and May 15, 2012	GARDEL, Cahn et al.[32,33]	48 W 96 W	Phase III Multicenter Randomized (1:1) Controlled Open label Non-inferiority n = 426 Primary end point: non-inferiority of LPV/r + 3TC at W 48: % HIV RNA < 50 copies/mL by intention to treat, snapshot analysis (lower limit of the 95% CI for the difference = −12%, 85% power)	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 FDC of 2NRTI: ZDV/3TC = 54% TDF/FTC = 37% ABC/3TC = 9% (W 48: n = 217 in DT and n = 209 in TT) (W 96: n = 153 in DT and n = 123 in TT)	VL < 50 copies/mL after 48 W DT: 88.3% (n = 189/198) versus TT: 83.7% (n = 169/175) (p = 0.171) (difference 4.6% [95% CI −2.2; 11.8%]) If baseline VL ≥ 100.000 copies/mL: DT: 87.2% (n = 82/94) versus TT: 77.9% (n = 67/86) (p = 0.145) difference 9.3%, (CI 95%: −2.8% to+21.5%) VL < 50 copies/mL after 96 W DT: 90.3% versus TT: 84.4% p = 0.165 Difference 5.9%, (95% CI – −2.3%; 14.1%) If baseline VL ≥ 100.000 copies/mL: DT: 90.7% versus TT: 84.4% (p = 0.163) Difference 6.3%, (CI 95%: −3.8% to+23.7%)	W48: DT: 227 versus TT: 217 W96: DT: 300 versus TT: 310	Non-inferior at W48 and W96 regardless of baseline VL	Eligibility criteria: ≥ 18 years ARV-naïve VL > 1000 copies/mL Any CD4 cell count HBsAg negative Not pregnant and use of contraceptive methods No PI/NRTI resistance Baseline characteristics: Median CD4: 325 cells/mm^3 CD4 ≤ 100/mm^3: 12 (6%) in DT and TT arm CD4 > 100 mm^3 to ≤ 200 mm^3: 33 (15%) in DT; 26 (13%) in TT CD4 > 200/mm^3: 25% in DT; 19% in TT VL ≥ 100.000 copies/mL: 94 (44%) in DT; 86 (43%) in TT VL < 100.000 copies/mL: 120 (56%) in DT; 116 (57%) in TT
2018 March 1, 2015 September 30, 2015	Li et al.[48]	48 W	China Randomized Open label Non-inferiority n = 198 Primary end point: virological response rate, defined as proportion of participants with plasma VL < 50 copies/mL at W48	DT: LPV/r (400/100 mg BID) + 3TC (300 mg QD) (n = 100) versus TT 3TC (300 mg) + TDF (300 mg) + EFV (600 mg) QD (n = 98)	VL < 50 copies/mL after 48 W DT: 92% (n = 92/100) versus TT: 89.8% (n = 88/98) p = 0.629 Difference 2.2% (95% CI: −6.7%-11.2%) If baseline VL > 100.000 copies/mL DT: 92.8% (13/14) versus TT: 100% (9/9)	W48: DT: 203 versus TT: 175 (p = 0.114)	Non-inferiority even in patients with VL > 100.000 copies/ml	Eligibility criteria: HIV-naïve patients All patients with VL > 1000 copies/mL and CD4 cell counts over 200/mm^3 No HBV or HCV coinfection No active AIDS-associated opportunistic diseases within 30 days Baseline characteristics Median CD4: 344.8 cells/mm^3 in DT; 346.9 cells/mm^3 in TT CD4 > 200- ≤ 350: 58 (58%) in DT; 57 (58.2%) in TT CD4 > 350 cells/mm^3- ≤ 500 cells/mm^3: 35 (35%) in DT; 34 (34.7%) in TT CD4 > 500/mm^3: 7 (7%) in DT; 7 (7.1%) in TT VL > 100.000 copies/mL: 14 (14%) in DT; 9 (9.2%) in TT VL ≤ 100.000 copies/mL: 86 (86%) in DT; 89 (90.8%) in TT
2018	ANDES, Figueroa et al.[47]	48 W	Phase IV Multicenter Randomized 1:1 Open label n = 145 Primary endpoint: non-inferiority of DRV/r + 3TC at W48: % HIV RNA < 50 copies/mL by intention to treat, snapshot analysis	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 48W: 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	Eligibility criteria: ≥ 18 years ARV naïve VL > 1000 copies/mL Any CD4 cell count HBsAg negative No NRTI or PI resistance Baseline characteristics VL (log10 copies/mL) median: DT: 4.6 (4.1-5.1); TT: 4.5 (3.9-5.0) > 100.000 copies/mL: 27% (20/75) in DT arm; 22% (15/70) in TT arm Median CD4 counts/mm^3: 419 (250-564) in DT; 366.5 (275-544) in TT

Dual therapies with integrase inhibitors

Year of publication	Study name and authors	Duration	Characteristics of study	Dual treatment versus triple treatment	Virological response	Main/median CD4 increase (cells/mm^3)	Results	inclusion criteria and baseline characteristics
2014	NEAT 001/ANRS 143, Raffi et al.[42]	123 W	Phase III Multicenter Randomized Open-label Parallel group Non-inferiority n = 805 Primary end point: TTF (virologic or clinical)	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)	VL < 50 copies/mL after 48 W: DT 94% (376/401) versus TT 96% (388/404) VL < 50 copies/mL after 96 W: DT: 89% (356/401) versus TT: 93% (374/404) TTF after 96 W: DT 17.4% versus TT 13.7% ITT analysis (adjusted difference, 3.7% (95% CI,−1.1-8.6) 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) If baseline CD4 ≥ 200/mm^3: DT 13.7% versus TT 12.3%	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	Eligibility criteria: ≥ 18 years ARV naïve VL ≥ 1000 copies/mL CD4 < 500/mm^3 HBsAg negative Creatinine clearance > 60 ml/min No resistance mutation Baseline characteristics ≥ 100.000 copies/mL: 36% in DT and 32% in TT CD4 < 200/mm^3: 15% in DT and 16% in TT Median CD4 counts/mm^3: 340 in DT; 325 in TT
2017 Between September 24, 2014, and February 28, 2015	PADDLE, Cahn et al.[45,49]	48 W 96 W	Phase IV Single arm Open label Pilot study n = 20 Primary endpoint was the proportion of patients with HIV-1 RNA < 50 copies/mL in an intention to treat -exposed analysis at 48W (the FDA snapshot algorithm)	DTG (50 mg QD) + 3TC (300 mg QD)	VL < 50 copies/mL after 48 W: 90% (18/20) VL < 50 copies/mL after 96 W: 100% (18/18)	W48: 267	High efficacy However, only four patients with VL > 100.000 copies/mL	Eligibility criteria ≥ 18 years VL ≤ 100.000 copies/mL CD4 ≥ 200 cells/mm^3 AgHBs negative No IAS-USA defined resistance Baseline characteristics: VL: though as per protocol, all patients had VL ≤ 100.000 copies/mL at screening as required by inclusion criteria, four patients had ≥ 100.000 copies/mL at baseline median CD4: 507/mm^3
2019 Between November 8, 2015, and September 13, 2016	ACTG A5353, Nyaku et al.[46]	52 W	Phase II Single arm Pilot study n = 120 Primary endpoint was to estimate virologic success, defined as HIV-1 RNA < 50 copies/mL on DTG plus 3TC (FDA Snapshot) at W24. Participants with HIV-1 RNA ≥ 50 copies/mL at W24 or who discontinued or changed study treatment earlier and either had HIV-1 RNA ≥ 50 copies/mL or did not have HIV-1 RNA data were counted as virologic non-successes	DTG (50 mg QD) + 3TC (300 mg QD)	VL < 50 copies/mL after 24 W: 90% (n = 108/120) (95% CI of 83%, 95%) If baseline VL ≤ 100.000 copies/mL (n = 83): 90% (75/83) versus 89% (33/37) if baseline VL > 100.000 copies/mL VL < 50 copies/mL after 48 W: 85% (102/120) (95% CI of 77%, 91%) If baseline VL ≤ 100.000 copies/mL: 78% (29/37) versus 88% (73/83) (p = 0.18) if baseline > 100000 copies/mL	NA	Virologic efficacy with study entry VL up to 500.000 copies/mL	Eligibility criteria: VL < 500.000 copies/mL No RT, integrase or major protease resistance mutation AgHBs negative No active/anticipated HCV treatment No CD4 restriction Baseline characteristics CD4 < 200/mm^3: 14% VL > 100.000 copies/mL: 30% (37/120) VL ≤ 100.000 copies/mL
2018 Participant screening commenced on July 21, 2016, for GEMINI-1, and July 18, 2016, for GEMINI-2. screening ended on March 28, 2017, for GEMINI-1 and March 31, 2017, for GEMINI-2	GEMINI 1/and 2, Cahn et al.[44]	48 W	Phase IV Multicenter RCT Double- blind Parallel group Non-inferiority studies n = 1433 The primary endpoint of each GEMINI study was to show the non-inferior virological efficacy of the two-drug regimen compared with the three-drug regimen, with the primary endpoint being the proportion of participants with plasma HIV-1 RNA of < 50 copies/mL at W48 using the FDA snapshot algorithm in the intention-to-treat-exposed population	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): If baseline VL ≤ 100.000 copies/mL: DT 91% versus TT 94% If baseline VL > 100.000 copies/mL: DT 92% (n = 129/140) versus TT 90% (n = 138/153) If baseline CD4 > 200 cells/mm^3: DT 93% (n = 605/653) versus TT 93% (n = 618/662) If baseline CD4 ≤ 200 cells/mm^3: DT 79% (50/63) versus TT 93% (n = 51/55)	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	Eligibility criteria: Naïve or ≤ 10 days of priori ART VL < 500.000 copies/mL No HBV or HCV infection Baseline characteristics: Median VL: 4.4 log copies/mL and VL > 100.000 copies/mL: 20% in each arm Median CD4: 432 cells/mm^3 (range 19-1407) (10% < 200 cells/mm^3) 2% of participants in each arm with VL > 500.000 copies/mL

DT: dual therapy, TT: triple therapy, W: week, FDC: fixed-dose combination, VL: viral load, NRTI: nucleoside reverse transcriptase, ARV: antiretroviral; 3TC: lamivudine, FTC: emtricitabine, ZDV: zidovudine, TDF: tenofovir disoproxil fumarate, ABC: abacavir, DRV/r: darunavir/ritonavir, LPV/r: lopinavir/ritonavir, DTG: dolutegravir, RAL: raltegravir, HBV: hepatitis B virus, HCV: hepatitis C virus, QD: once day; BID: twice a day, TTF: time to treatment failure, VF: virological failure, RCT: randomized clinical trial, NA: not applicable.