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SHORT COMMUNICATION

Stable HIV-1 reservoirs on dolutegravir maintenance monotherapy: the MONODO study

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Objectives

Dolutegravir (DTG) is a highly effective integrase inhibitor with a strong genetic resistance barrier and a potential role in simplified HIV maintenance treatment. We assessed the feasibility of DTG maintenance monotherapy and measured HIV reservoirs on DTG monotherapy.

Methods

An interventional, open-label, single-arm study including eight virologically suppressed HIV-1-infected patients switched to DTG 50 mg once daily for 24 weeks was performed. HIV-1 RNA levels in plasma and cerebrospinal and seminal fluids were measured at baseline and week 24, as well as HIV-1 DNA in peripheral cells and DTG concentrations in these compartments.

Results

HIV-1 RNA remained undetectable in all samples of blood, cerebrospinal fluid and sperm throughout the 24 weeks, except for one cerebrospinal fluid sample with a value of 28 HIV-1 RNA copies/mL at week 24. One patient discontinued the study because of a neurological side effect. There was no change in the mean HIV-1 DNA level between baseline and week 24. Plasma and cerebrospinal fluid DTG concentrations reached therapeutic levels in all patients in these two compartments.

Conclusions

In this small sample of carefully selected patients, HIV-1 reservoirs were well controlled on DTG monotherapy over a period of 24 weeks. Viral suppression was also maintained throughout follow-up.

Keywords: dolutegravir, HIV, HIV reservoirs, maintenance therapy, simplification

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Introduction

Current HIV treatment changes are mainly driven by the need for regimen simplification and toxicity issues. Regimen optimization is also critical to further scaling up of treatment and to support retention in care, particularly in low- and middle-income settings [1]. Dolutegravir (DTG) is a highly effective and well-tolerated integrase inhibitor. The SINGLE, FLAMINGO and SPRING 2 randomized controlled studies have shown the superiority of DTG at week 48 compared with efavirenz and ritonavir-boosted darunavir, as well as its noninferiority to raltegravir in antiretroviral drug combinations among treatment-naïve HIV-1-infected patients [2–4]. DTG was also found to be superior to raltegravir among treatment-experienced patients with resistance to at least two classes of antiretroviral drugs [5]. No resistance to integrase inhibitors or the associated nucleotide backbone has been described in treatment-naïve patients included in these trials. In treatment-experienced patients, initial or subsequent integrase mutations did not result in high-level resistance to DTG, suggesting a high genetic barrier at least similar to that of boosted protease inhibitors [6].

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The aim of our study was to assess the feasibility of treatment simplification with DTG maintenance monotherapy in virologically suppressed patients on combination antiretroviral therapy (cART), and to measure HIV reservoirs by quantifying total HIV-1 DNA in peripheral blood mononuclear cells (PBMCs) and HIV-1 RNA in plasma, cerebrospinal fluid (CSF) and seminal fluid from patients on DTG monotherapy as well as DTG concentrations in these compartments. We also investigated the effect of DTG monotherapy on lipodystrophy features, bone mineral density and immune activation.

Methods

We conducted an interventional, open-label, single-arm study in which participants were switched to DTG monotherapy 50 mg once daily for a duration of 24 weeks (the MONODO study). We included HIV-1-infected patients > 18 years of age who had HIV-1 RNA < 50 HIV-1 RNA copies/mL plasma for at least 6 months on first-line cART. Previous changes of antiretroviral drugs because of toxicity or for simplification were allowed. Eligible participants had no history of previous virological failure on cART or documented drug resistance. All patients provided written informed consent. The study was approved by the research ethics committee of Geneva, Switzerland, and registered on clinicaltrials.gov (NCT02572947).

Participants consented to provide CSF and sperm samples at baseline and week 24, although lumbar puncture was optional at baseline. Study visits were scheduled on a monthly basis with a plasma HIV-1 RNA quantification performed at each visit, as well as an adherence evaluation performed using pill count and validated questionnaires. The following tests were performed at baseline and week 24: determination of HIV-1 RNA in plasma, CSF and seminal fluid using polymerase chain reaction (PCR) with a limit of detection of 20 copies/mL (COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0; Roche Diagnostics, Rotkreuz, Switzerland); total HIV-1 DNA quantification in PBMC samples using digital droplet PCR; measurement of DTG concentrations in plasma, CSF and sperm by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS); dual-energy X-ray absorptiometry (DXA) scans and anthropometric measurements; and biochemistry and measurement of inflammatory and hypercoagulability markers. The primary outcome was the proportion of patients completing 24 weeks of DTG monotherapy without experiencing virological failure, defined as plasma HIV-1 RNA ≥ 200 copies/mL or detectable HIV RNA in CSF. We compared outcome variables between baseline and week 24 using a paired sample *t*-test. We used Wilcoxon's signed rank test for nonparametric data. All statistical analyses were performed using STATA software, version 12 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

Eight patients (five men, two women and one transgender patient) were included in the study from June 2015 to December 2016. The mean age was 47.4 years (median 44.5; range 36–66 years). Mean durations of HIV-1 infection and ART before enrolment were 11.9 years (median 10.5; range 2–26 years) and 9.7 years (median 8.7; range 2.2–19.4 years), respectively. Seventy-five per cent (six of eight) of participants were treated with a combination of tenofovir, emtricitabine and a non-nucleoside reverse transcriptase inhibitor prior to the switch. The mean zenith viral load was 5.4 log copies/mL (median 5.4; range 4.6–7 log copies/mL) and the mean nadir CD4 count was 301 cells/μL (median 305; range 21–555 cells/μL).

Virological outcomes

Seven of eight patients (87.5%) completed the study. Of these, all had undetectable plasma HIV-1 RNA (< 20 copies/mL) throughout the 24 weeks of follow-up (Table 1). Therefore, our intention-to-treat plasma virological success at week 24 was 87.5%.

Mean adherence was 98.6% (median 99.4%; range 94.7–100%). Mean change in CD4 count from baseline to week 24 was 28 cells/μL [95% confidence interval (CI) 100 to 157 cells/μL; $P = 0.6$]. Six patients underwent lumbar puncture at week 24 and one provided a CSF sample at baseline. HIV-1 RNA was undetectable in all samples except one, with a value of 28 HIV-1 RNA copies/mL after 24 weeks of DTG monotherapy. Sperm samples were available for five and four men at baseline and week 24, respectively. HIV-1 RNA in seminal fluid was undetectable in all samples with a detection threshold of 40 or 80 copies/mL according to the sample dilution. We were able to measure total HIV-1 DNA in PBMCs both at baseline and at week 24 in five patients. No significant change was observed in mean HIV-1 DNA level between the two time-points (42.1 HIV-1 DNA copies/10^6 genomic equivalents; 95% CI −127.3 to 211.6 DNA copies/10^6 genomic equivalents; $P = 0.5$) (Table 1).

Table 1 Results by study participant for HIV-1 RNA and dolutegravir (DTG) concentrations in plasma, cerebrospinal fluid and sperm, and total HIV-1 DNA in peripheral blood mononuclear cells

		MONODO patient ID							
		01	02	03	04	05	06	07	08
Plasma HIV-1 RNA (copies/mL)	Baseline	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
	Week 4	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
	Week 8	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
	Week 12	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
	Week 16	< 20	< 20	< 20	< 20	< 20	< 20	< 20	NA*
	Week 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20	NA*
	Week 24	< 20	< 20	< 20	< 20	< 20	< 20	< 20	NA*
CSF HIV-1 RNA (copies/mL)	Baseline	NA†	< 20	NA†	NA†	NA†	NA†	NA†	NA†
	Week 24	< 20	< 20	< 20	28	< 20	NA	< 20	NA*
Seminal fluid HIV-1 RNA (copies/mL)¶	Baseline	< 40	NA‡	NA‡	< 40	< 40	< 40	NA‡	< 80
	Week 24	< 80	NA‡	NA‡	< 40	< 40	< 40	NA‡	NA*
Total HIV-1 DNA in PBMCs	Baseline	NA§	170.9	NA§	205.8	185.6	248.6	67.2	NA§
(DNA copies/10^6 genomic equivalents)††	Week 24	NA§	108.9	NA§	279.1	72.0	483.3	145.5	NA*
DTG concentration at week 24 (ng/mL)	Plasma	367	2088	1707	2104	2834	145	3100	NA*
	CSF	9	10.4	6.1	5.4	10.4	NA	12.6	NA*
	Seminal fluid	0	NA‡	NA‡	84	205	0	NA‡	NA*

ID, identification; NA, not available; CSF, cerebrospinal fluid; PBMCs, peripheral blood mononuclear cells.
*Patient discontinued the study at week 12.
†Lumbar puncture optional at baseline.
‡Female or transgender: no sperm sample possible.
§Missing data.
¶The limit of quantification in seminal fluid is 40 copies/mL because of sample dilution.
††HIV-1 DNA and the single-copy host gene C-C chemokine receptor type 5 (CCR5) were quantified by digital droplet polymerase chain reaction in parallel. Cell counts are displayed as genomic equivalents as defined by two *CCR5* copies per genomic equivalent (cell).

Safety data

One participant discontinued the study because of mild recurrent anxiety and hallucinations. The patient had never used DTG previously. The first episode of symptoms occurred during the first month of treatment and lasted 24 h. The patient recovered spontaneously. At week 12, the patient experienced similar symptoms and asked to withdraw from the study. The DTG plasma concentration at week 12 was measured as being below the 10th percentile (569 ng/mL, 12 h after DTG intake). We suspected that the symptoms were related to illicit drug intake.

For the remaining seven patients, the mean plasma DTG concentration was 1764 ng/mL blood (median 2088; range 145–3100 ng/mL), well above the protein-adjusted 90% inhibitory concentration (IC90) of 64 ng/mL. Measurements were made between 8 and 23.5 h after drug intake. In terms of percentiles, these values were above the 50th percentile for four patients, but below the 10th percentile for three others. We measured the CSF DTG concentration at week 24 for six patients, and the mean value was 9.0 ng/mL (median 9.7; range 5.4–12.6 ng/mL) (Table 2).

Finally, we observed that participants gained weight while on DTG monotherapy, with a mean increase in weight of 4.1 kg (95% CI 1.4–6.9 kg; $P = 0.01$) from baseline to week 24. However, there was no significant change in visceral or subcutaneous adipose tissues from baseline to week 24 as measured by DXA scans. Full results for safety parameters are presented in Table 2.

At the end of the study, five participants remained on DTG monotherapy, one was switched to dual therapy with DTG and emtricitabine and two, including the patient who withdrew from the study, were switched back to cART. All had an undetectable plasma HIV RNA after 48 weeks of follow-up.

Discussion

In this small study, HIV-1 RNA remained undetectable in the plasma, CSF and sperm of selected patients who received DTG monotherapy as maintenance treatment throughout 24 weeks of follow-up. One patient had detectable HIV-1 RNA in the CSF at week 24 with a value of 28 copies/mL. This result was not considered to be a virological failure as this value could not be repeated and was close to the detection limit of the test. Moreover, this patient had undetectable plasma HIV-1 RNA during the entire follow-up and DTG plasma and CSF concentrations at week 24 were 2104 and 5.4 ng/mL, respectively. The patient reported minor side effects of fatigue and anxiety at the end of the study and he was switched back to DTG and emtricitabine without any further problems reported. One patient withdrew from the study at his request

Table 2 Safety parameters, anthropometric measurements, dual-energy X-ray absorptiometry (DXA) scan values and inflammatory markers at baseline and week 24

	Baseline	Week 24	Mean change between baseline and week 24 (95% CI)	*P*-value
Immunological measurement				
CD4 count (cells/μL) [mean (± SD, median)]	800 (± 380, 743)	842 (± 349, 974)	28 (−100, +157)	0.6
Biochemistry measurements				
Creatinine (μmol/L) [mean (± SD, median)]	80.5 (± 16.9, 77.5)	82.6 (± 6.2, 84.0)	7.1 (−4.4, +18.7)	0.2
ALAT (UI/L) [mean (± SD, median)]	34.4 (± 26.2, 21.5)	30.4 (± 13.0, 29.0)	4.7 (−8.1, +17.6)	0.4
Total cholesterol (mmol/L) [mean (± SD, median)]	4.6 (± 0.7, 4.7)	5.2 (± 1.8, 4.9)	0.6 (−1.2, +2.4)	0.4
HDL cholesterol (mmol/L) [mean (± SD, median)]	1.3 (± 1.0, 0.9)	1.2 (± 0.6, 1.2)	−0.2 (−1.0, +0.65)	0.6
Triglycerides (mmol/L) [mean (± SD, median)]	1.4 (± 0.6, 1.3)	2.1 (± 1.6, 1.5)	0.6 (−0.6, +1.9)	0.3
Anthropometric and fat distribution measurements				
Weight (kg) [mean (± SD, median)]	79.2 (± 14.3, 84.7)	85.3 (± 15.4, 87.5)	4.1 (+1.4, +6.9)	0.01
BMI (kg/m^2) [mean (± SD, median)]	27.1 (± 4.6, 26.8)	28.5 (± 4.9, 28.3)	1.1 (+0.1, +2.0)	0.03
Waist/hip ratio [mean (± SD, median)]	0.95 (± 0.09, 0.94)	0.95 (± 0.07, 0.97)	−0.01 (−0.09, +0.07)	0.8
Visceral adipose tissue (cm^2) [mean (± SD, median)]	129.2 (± 76.4, 102.5)	124.1 (± 50.7, 115.5)	−15.7 (−61.9, +30.4)	0.4
Subcutaneous adipose tissue (cm^2) [mean (± SD, median)]	223.4 (± 102.4, 223.4)	277.6 (± 117.4, 243.6)	32.2 (−13.1, +77.4)	0.1
Bone density measurements				
L1-L4 T-score [mean (± SD, median)]	−0.75 (± 0.98, −0.45)	−1.07 (± 1.04, −1.3)	−0.13 (−0.50, +0.24)	0.4
Femoral neck T-score [mean (± SD, median)]	−0.66 (± 0.67, −0.75)	−0.64 (± 0.52, −0.6)	0.17 (−0.11, +0.35)	0.06
Hip T-score [mean (± SD, median)]	0.09 (± 0.39, 0.2)	0.01 (± 0.47, 0.2)	−0.03 (−0.24, +0.19)	0.8
Inflammatory and hypercoagulability markers				
hs-CRP (mg/L) [mean (± SD, median)]	2.5 (± 3.3, 0.9)	7.5 (± 12.6, 1)	5.1 (−6.6, +16.7)	0.3
TNF-α (pg/mL) [mean (± SD, median)]	2.8 (± 1.1, 2.6)	3.6 (± 1.7, 2.9)	0.8 (−0.4, +2.1)	0.2
MCP1/CCL2 (pg/mL) [mean (± SD, median)]	267.4 (± 86.0, 265.0)	242.0 (± 68.1, 273.4)	−20.7 (−78.2, +36.9)	0.4
Insulin (UI/L) [mean (± SD, median)]	11.7 (± 6.6, 10.5)	62.4 (± 129.3, 15.3)	49.5 (−65.7, +164.7)	0.3
D-dimers (μg/L) [mean (± SD, median)]	337.8 (± 296.1, 259.5)	455 (± 477.2, 232)	110.4 (−103.9, +324.8)	0.2

ALAT, alanine transaminase; BMI, bone mineral index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; SD, standard deviation; TNF, tumour necrosis factor; MCP1/CCL2, monocyte chemoattractant protein 1.

because of side effects. Therefore, our intention-to-treat virological success at week 24 was 87.5%.

These results are similar to those reported in observational studies of DTG monotherapy throughout 24 weeks, which ranged from 89% to 97% [7–9]. However, a large randomized controlled trial of DTG maintenance monotherapy showed that, while DTG monotherapy was noninferior to cART at 24 weeks, most virological failures occurred after week 24 and could lead to integrase inhibitor-associated mutations [10]. A meta-analysis of simplified DTG maintenance therapy confirmed these findings and reported that DTG maintenance monotherapy led to a relevant risk of virological failure in 220 participants on this treatment. The proportion who experienced virological failure was 3.2% (95% CI 1.5–6.5%) and 8.9% (95% CI 4.7–16.2%) at weeks 24 and 48, respectively [11]. Moreover, 50% of patients who experienced failure developed resistance to the integrase inhibitor class.

In our study, we quantified total HIV-1 DNA in PBMCs and DTG concentrations in different compartments. Total HIV-1 DNA levels in PBMCs were low at baseline with no significant change during follow-up. Our measurement amplified integrated and unintegrated, and replication competent as well as defective viral DNA. First, it has been shown that total HIV-1 DNA measurement in patients on successful cART for > 6 months mainly reflects integrated HIV-1 DNA, as unintegrated HIV-1 DNA largely vanishes within the first few months on cART [12], and that defective forms facilitate the persistence of HIV reservoirs in the body [13]. Secondly, total HIV-1 DNA is considered as a sensitive and clinically relevant biomarker for the HIV-1 reservoir and low levels of total HIV-1 DNA indicate low risks of disease progression, viral rebound and development of drug resistance [13]. Furthermore, HIV RNA remained under the limit of detection in all samples of seminal fluid. Similar genital shedding and residual viraemia were also observed among patients on simplified maintenance regimens, including DTG monotherapy, compared with those on cART [14]. These data suggest that DTG monotherapy is sufficient to contain the peripheral HIV reservoir on a short-term basis.

Plasma DTG concentrations exceeded the protein-adjusted IC90 of 64 ng/mL for all patients in our study [15,16]. In the CSF, the median DTG concentration at week 24 was 9.7 ng/mlL (range 5.4–12.6 ng/mL). All values exceeded the *in vitro* 50% inhibitory concentration for wild-type HIV (0.2 ng/mL) as described by Letendre

et al. [17], thus suggesting a therapeutic concentration in this compartment.

We also demonstrated that DTG was safe and led to no change in the CD4 cell count, kidney or liver functions, lipid profile, bone mineral density or markers of inflammation and hypercoagulability. DTG is known to be lipid-neutral compared with efavirenz or boosted darunavir [3,4]. We observed no reduction in the level of cardiovascular biomarkers or benefits for bone mineral density as described with raltegravir after switching from a protease inhibitor [18,19], but none of our participants had received this class of drug prior to study enrolment. We found a significant increase in weight, with a mean gain of 4.1 kg in 24 weeks, and body mass index among our participants on DTG monotherapy. Similarly, a retrospective study showed that patients who switched from an efavirenz- to an integrase-based regimen gained an average of 2.9 kg at 18 months compared with 0.9 kg for those who continued on efavirenz ($P = 0.003$); those who switched to DTG gained the most weight (+ 5.3 kg) [20]. The potential correlation with lipodystrophy needs to be evaluated in the long term.

Our study has several limitations. The sample size was small, the study duration was short and it was a single-arm study. In addition, we could not compare DTG maintenance monotherapy with cART. Participants were rigorously selected with no prior documented ART failure, which renders it difficult to generalize our results.

Conclusions

In our study, HIV reservoirs in PBMCs, CSF and sperm remained stable over a period of 24 weeks in selected patients switched to DTG maintenance monotherapy. As virological failures mostly occur after 24 weeks of follow-up, DTG maintenance monotherapy is not a switch strategy option in the long-term. However, DTG remains a good candidate for simplified dual therapy in virologically suppressed patients.

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