Dolutegravir as Maintenance Monotherapy for HIV-1: a Randomized Clinical Trial

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Hypothesis

Dolutegravir (DTG) monotherapy is non-inferior to cART in maintaining viral suppression in HIV-1 infected patients.

Introduction

The use of an antiretroviral drug with a high genetic barrier against resistance may allow for a step-down to monotherapy after induction therapy with cART has led to an undetectable plasma viral load and adequate immune reconstitution.

Simplification of cART to duotherapy or monotherapy has multiple advantages (e.g. costs, toxicity, pill-burden, pill-size).

DTG has a high genetic resistance barrier and development of integrase (IN) resistance in IN-naïve patients has been exceedingly rare. DTG may therefore be a good candidate to be used as monotherapy for maintenance of viral suppression in HIV-1 infected individuals .

Methods

Design:
Randomized open label multicenter non-inferiority clinical trial.

2 groups:

DOLUMONO: direct switch to DTG monotherapy

Con-cART: continue cART for 24 weeks, followed by DTG monotherapy

Sample size/power:
N=104, Pa=Pb=0.95 δ=-0.12 1-β=0.80 α=0.05

Inclusion criteria:
- On cART and HIV-RNA <50 c/ml for >6 months with good compliance
- HIV-RNA-zenith <100.000 c/ml
- CD4 T-cell nadir >200 cells/mm^3
- No baseline resistance, no previous virological failure
- HBV-immune or willing to be vaccinated before start of DTG monotherapy

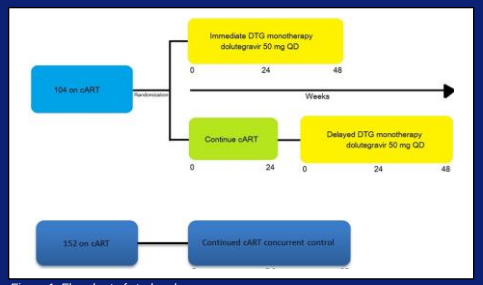

Figure 1. Flowchart of study scheme

Study endpoints:

For analysis of the primary endpoint, virological failure (VF) was defined as a confirmed viral load >200 c/ml

Primary:

Comparison of the proportion of patients in the OT-population with HIV-RNA <200 c/ml at W24.

Secondary:

Proportions HIV-RNA <200 c/ml and <50 c/ml in the entire population on DOLUMONO at W24 and W48.

Post-hoc analysis:
Comparison of HIV-RNA <200 c/ml in entire population on DOLUMONO with the 'Concurrent controls' group. This group consists of 152 patients on cART who fulfilled all inclusion criteria and exclusion criteria, but who did not participate in the study but agreed to have their data used.

OT = On Treatment analysis. This excludes patients who discontinued DTG monotherapy for adverse events at a time that HIV RNA was <200c/ml.

Predefined study stopping rules:
Any new IN-resistance associated mutations are detected in ≥ 2 patients during the study
Discontinuation of DTG for treatment failure in ≥ 20 patients at any time of the study

This trial was registered at www.clinicaltrials.gov under NCT02401828

Results

Study population:

	DOLUMONO (N=51)	Con-cART (N=53)
Male sex, N(%)	47 (92)	48 (91)
Age, median (Q1,Q3)	46 (37,56)	45 (40,51)
Transmission route, MSM N(%)	41 (80)	41 (77)
Ethnicity, Caucasian, N(%)	42 (82)	44 (83)
On TDF before switch, N(%)	44 (86)	45 (85)
Median (Q1,Q3) time on cART, months	35 (24,61)	43 (25,68)
Median (Q1,Q3) HIV-RNA zenith	29.300 (14.800-76.900)	44.877 (16.100-63.100)
Median (Q1,Q3) CD4 T-cell nadir	320 (250-490)	380 (285-515)

Table 1. Baseline characteristics

Primary endpoint:

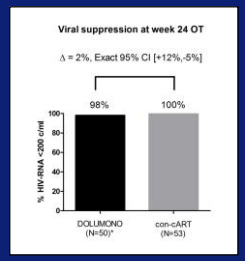

*Figure 2. Percentages of viral suppression at week 24: on treatment analysis. * 1/51 patients discontinued DOLUMONO at week 12 (HIV-RNA < 200 c/ml) for disturbed sleep.*

Secondary endpoint:

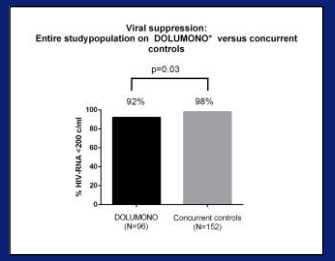

*Figure 3. Percentages of viral suppression in entire study population: On-treatment analysis. * 7/53 patients in con-cART did not switch to DOLUMONO for varying reasons.*

- When 77/96 had reached W48 of DOLUMONO, VF had developed in 8 patients (figure 3).
- IN genotyping was successful in 6/8 patients: IN-resistance associated mutations were found in 3/6 (table 2).
- As per predefined stopping rule, the study was discontinued prematurely.
- In all participants, cART was reinitiated and HIV-RNA was < 50 c/ml within 12 weeks in all patients.

	Moment of failure on DOLUMONO	HIV-RNA-zenith (c/ml)	CD4-T-cell-nadir (cells/mm^3)	cART before DOLUMONO	Time on cART before DOLUMONO (years)	HIV-RNA at failure on DOLUMONO (c/ml)	DTG-plasma level at failure (mg/mL)	Adherence (according to clinician)	IN sequence at failure
Failure 1	W4	18.500	290	TDF/FTC/RPV	4	71.600	1.29 (+14h)	>95%	No RAM's
Failure 2	W12	7.420	220	TDF/FTC/EFV	8Y10M	678	2.00 (+19h)	>95%	Not succesful
Failure 3	W30	17.500	280	TDF/FTC/RPV	4Y4M	3.510	2.59 (+16h)	>95%	No RAM's
Failure 4	W30	99.270	330	TDF/FTC/RPV	2	1.570	2.96 (+22h)	>95%	**S230R**
Failure 5	W36	56.300	210	TDF/TFC/DTG	6Y1M	1.440	1.00 (+24h)	>95%	Not succesful
Failure 6	W48	67.000	230	TDF/FTC/RPV	5Y9M	4.990	1.44 (+24h)	>95%	No RAM's
Failure 7	W60	34.600	240	TDF/FTC/NVP	14Y1M	3.470	0.70 (+13h)	>95%*	**R263K**
Failure 8	W72	20.100	380	TDF/FTC/NVP	1Y9M	4.180	2.15 (+9h)	>95%	**N155H**

*Table 2. Overview of characteristics of the patients with virological failure. TDF=Tenofovir Disoproxil Fumarate, FTC=Emtricitabine, RPV=Rilpivirine, EFV=Efavirenz, DTG=Dolutegravir, NVP=Nevirapine, RAM=Resistance Associated Mutation. * Probably suboptimal gastrointestinal uptake of DTG during 10 days due to gastro-enteritis.*

Conclusions

- **Whereas DTG monotherapy was non-inferior to cART at week 24, VF continued to occur after week 24 and led to IN-resistance associated mutations in 3 patients.**
- **The genetic barrier against resistance of DTG is insufficient to allow for maintenance monotherapy.**
- **Future studies about maintenance therapy with DTG should evaluate DTG + 3TC rather than DTG monotherapy.**