Erasmus MC
Universitair Medisch Centrum Rotterdam

Switching from combination antiretroviral therapy to DOlutegravir MONOtherapy in virologically suppressed HIV-1 infected adults:

A randomized multicenter, non-inferiority clinical trial

(DOMONO)

Ingeborg E. A. Wijting, PhD-student
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Disclosure of speaker's interest

Potentially relevant company relationships in connection with event	Company name
Speakers fee	Gilead Sciences

Introduction

cART is the standard. But is this still needed anno 2016?

Duo- or monotherapy:

Reduced toxicity, reduced costs, smaller pills.

PI maintenance monotherapy

- Meta-analysis (N=2303)[1]:
  - Viral suppression -8,3% [CI -11.9 tot -4.8%]

- PROTEA-study[2]:
  - Multivariate analysis W48:

    non-inferiority in subset with favorable virological/CD4 criteria.

[1] *Arribas et al, HIV Med 2015*

[2] *Antinori et al, J Int AIDS Soc 2014*

Study question

Is DTG monotherapy non-inferior to cART in maintaining viral suppression in HIV-1 infected patients on cART?

Methods DOMONO

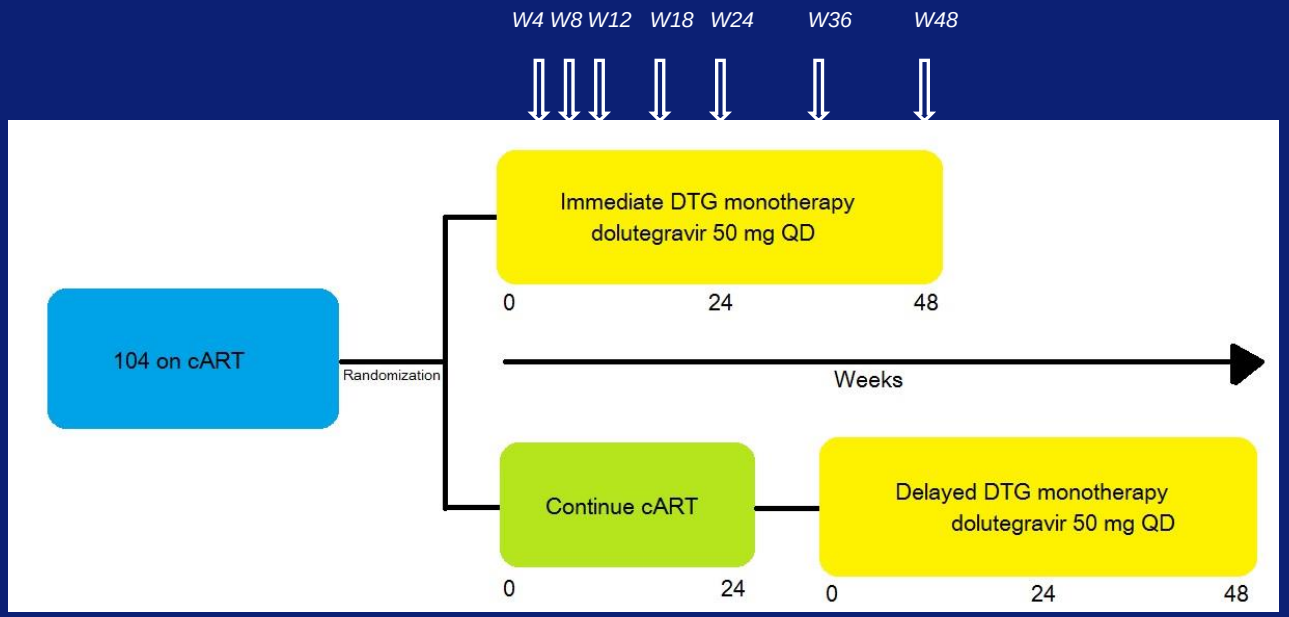
Randomized open label multicenter clinical trial.

Dolutegravir monotherapy 50 mg for 48 weeks.

If HIV-RNA becomes detectable (any level >20c/ml) the patient is instructed to take DTG with a meal.

Key inclusion:

- HIV-RNA < $1,0^{E}5$
- CD4-nadir ≥ 200
- HIV-RNA <50 ≥24W
- Never failed
- No resistance
- HBV immune
- >95% estimated compliance



Methods DOMONO

- ***Primary endpoint:***

  HIV-RNA <200 c/mL on W24 DTG versus cART

  OT analysis: Excludes pts that discontinued for AE while suppressed

- ***Secondary endpoints (virological):***
  - HIV-RNA <50 on W24 in DTG versus con-cART
  - HIV-RNA <200 and <50 at W12 in all patients (immediate + delayed switch)
  - HIV-RNA <200 and <50 at W24 in all patients (immediate + delayed switch)
  - HIV-RNA <200 and <50 at W48 in all patients (immediate + delayed switch)

- ***Secondary endpoints (other):***
  - Renal markers
  - Bone mineral density in TDF subset (N=89)
  - Immune activation
  - HIV DNA reservoir

Methods DOMONO

- Sample size N=104 to show non-inferiority of DTG versus con-cART:
  - Pa=Pb=0.95 δ=-0.12 1-β=0.80 α=0.025

- → ± 2 virological failures in each group of N=52

+- 1700 patients
screened for eligibility

360 fulfilled in/excl criteria

104 randomized

DTG monotherapy **DOLUMONO** N=51

Continued - cART **Con-cART** N=53

170 opted out of study participation
Agreed to have their data used
= Concurrent control group for week 48 results

Results - baseline

	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)
TDF, N(%)	44 (86)	45 (85)
Median (Q1,Q3) time on cART, months	35 (24-61)	43 (25-68)
Median (Q1,Q3) HIV-RNA zenith	21.500 (7.555-64.800)	27.800 (5.200-55.900)
Median (Q1,Q3) CD4 T-cell nadir	320 (250-490)	380 (285-515)

Results primary endpoint:

Week 24 <200 c/ml DOLUMONO versus cART

1/51 patients in DOLUMONO discontinued DTG at W12 (with HIV-RNA <50c/ml) for disturbed sleep.

DOLUMONO N = 49/50 (98%)

Con-cART N = 53/53 (100%)

} *Delta 2% Exact 95% C.I. +12% to -5%* (*)

→ DOLUMONO non-inferior to cART

** Wang et al, Annals of statistics, 2010*

Results secondary endpoint 4 and 5:

Week 24 <200 and <50 c/ml ENTIRE STUDY population on DOLUMONO

- In DOLUMONO, 50 reached W24.
- In Con-cART, 46 switched to DOLUMONO, of whom 39 reached W24.
- In total: 89 patients switched to DOLUMONO and reached W24.

Reason for not switching:

N=1 Moved away from Rotterdam N=1 Withdrew informed consent

N=3 Physician decision N=2 Other

HIV-RNA <200 c/ml in 87/89 (98%, 95% C.I.* 92%-100%)

HIV-RNA <50 c/ml in 83/89 (93%, 95% C.I.* 86%-97%)

** 95% CI according to Agresti and Coull*

Virological failure

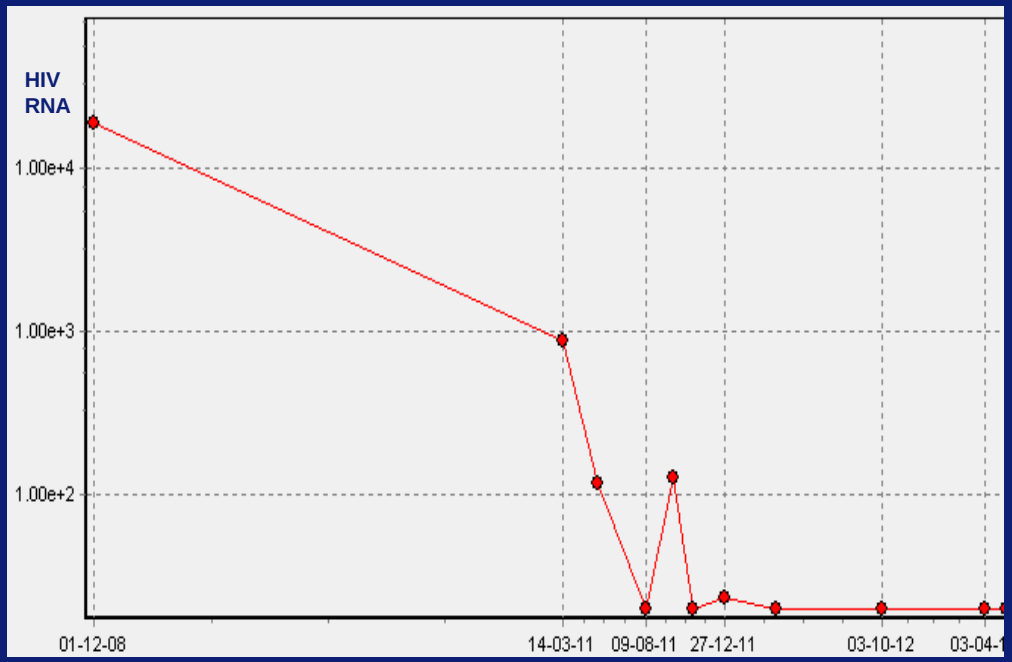
The single patient with virologic failure in the DOLUMONO group:

- Had a CD4-T-cell nadir of 290 and a peak HIV-RNA of 18.500 c/ml
- Was on cART for 4 years (RPV/FTC/TDF) when switched to DTG
- HIV-RNA at W4 on DTG monotherapy: 50.100 c/ml (71.600 c/ml at W5)
- 100% compliance by pill-count + DTG plasma levels of 1.3mg/L

- IN sequence at failure: no known IN mutations
- IN changes observed: V/I32I, L/S45L, T112A
- Phenotypic resistance testing is ongoing
- Restarted RPV/TDF/FTC and is <50c/ml again

→ No loss of future treatment options

NVP/FTC/TDF => RPV/FTC/TDF => DTG => RPV/FTC/TDF



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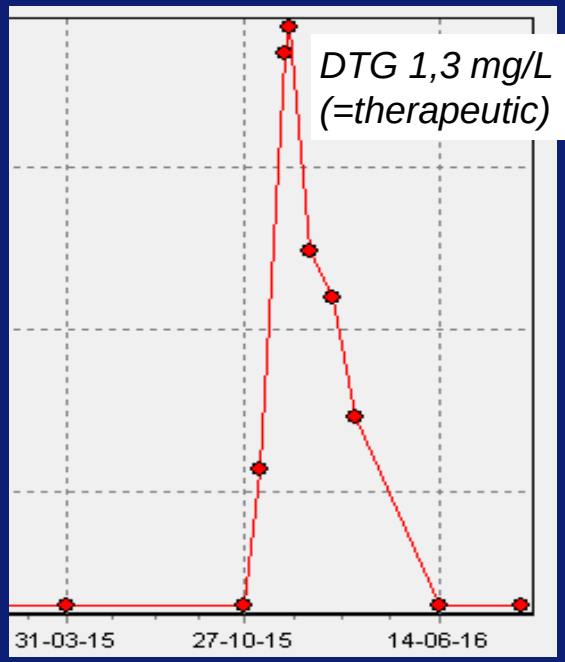

DTG 1,3 mg/L (=therapeutic)

Conclusions

In patients selected on virological, immunological and good compliance criteria switching to dolutegravir monotherapy is a promising treatment option.

However:

2 of 89 patiens had VF at week 24

Longer follow-up needed for more definite conclusions!

→ Week 48 results of DTG monotherapy of all 96 patients

→ Week 48 results of cART of 170 concurrent control patients

Erasmus MC:

B Rijnders

C Rokx, C Boucher, J van Kampen, D de Vries – Sluijs, K Schurink, H Bax, M Derksen, E Andrinopoulou, S Diepstraten-Pas, M van der Ende, E van Gorp, J Nouwen, A Verbon

UMCG:

W Bierman

P van der Meulen

104 brave and motivated patients !

Questions

Methods DOMONO

Why 200 c/ml instead of 50 c/ml as primary endpoint?

1. Clinical significance of 200c/ml > 50c/ml
2. Statistical reason:

   Few endpoints => Exact statistics(*) => larger C.I.

   Likely scenarios with 200c/ml and 5% virol. failures and groups of N=52

DTG	cART	delta	95% C.I.
1/52	0/52	2%	-5% to +12%
2/52	1/52	2%	-7% to +12%
3/52	2/52	2%	-9% to +12%

Impact of a single patient with 80c/ml at week 24 in the DTG group

DTG	cART	delta	95% C.I.
2/52	0/52	4%	-4% to +15%
3/52	1/52	4%	-5% to +14%
4/52	2/52	4%	-5% to +16%

(*) Wang et al. Ann of statistics 2010

Virological failures

Remember:

6/89 patients had VL >50 c/ml at w24

- 2 of them VL >200c/ml
- 4 of them had VL between 50 and 200 c/ml at w24
  - Week 36 follow-up is available for these 4
    - 2 had VL <50 at week 36 again
    - 2 had had virological failure at week 30 (>200c/ml)

Virological failures

The patient with virological failure in the Con-cART group:

- Had nadir CD4 of 220 and peak HIV-RNA of 7.420 c/ml
- Was on cART for 9 years and on EFV/TDF/FTC when he switched to DTG
- HIV-RNA after 12 wks of DTG monotherapy: 387 (678c/ml at week 13)
- 90% compliance by pill-count in the 4 weeks preceding failure
- Had therapeutic DTG plasma levels of 2.0mg/L

- Integrase sequencing not succesfull
- Restarted EFV/TDF/FTC 4 weeks ago; HIV-RNA 13-10-2016 99 c/ml

→ Loss of future treatment options unlikely

Virological failures

Patient 1:

3510 c/ml at week 30

100% compliance, DTG plasma levels OK

IN sequence at failure: no known IN mutations

AA changes observed: A10D, D11E, N17S, L45Q, I50M, T111K, A112T, T124S, I135V, K/R211K, I220L

Phenotypic resistance pending

Resuppressed <50c/ml after restart Eviplera

=> No loss of future treatment options

Virological failures

Patient 2:

1560c/ml at week 30

100% compliance, DTG plasma levels OK

IN sequence: 230R

Phenotypic resistance pending

Resuppressed after restart of Eviplera

230R:

Mutations that do not confer reduced susceptibility when present alone:

H114Y, L74M, R20K, A128T, E138K, and S230R (*)

Stanford website: DTG susceptible, RAL/EVG low-level resistance

=> Possibly some loss of future INI treatment options

(*) Goethals O et al. J Virol 2008