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

A randomized multicenter, non-inferiority clinical trial

(DOMONO)

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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*

Methods DOMONO

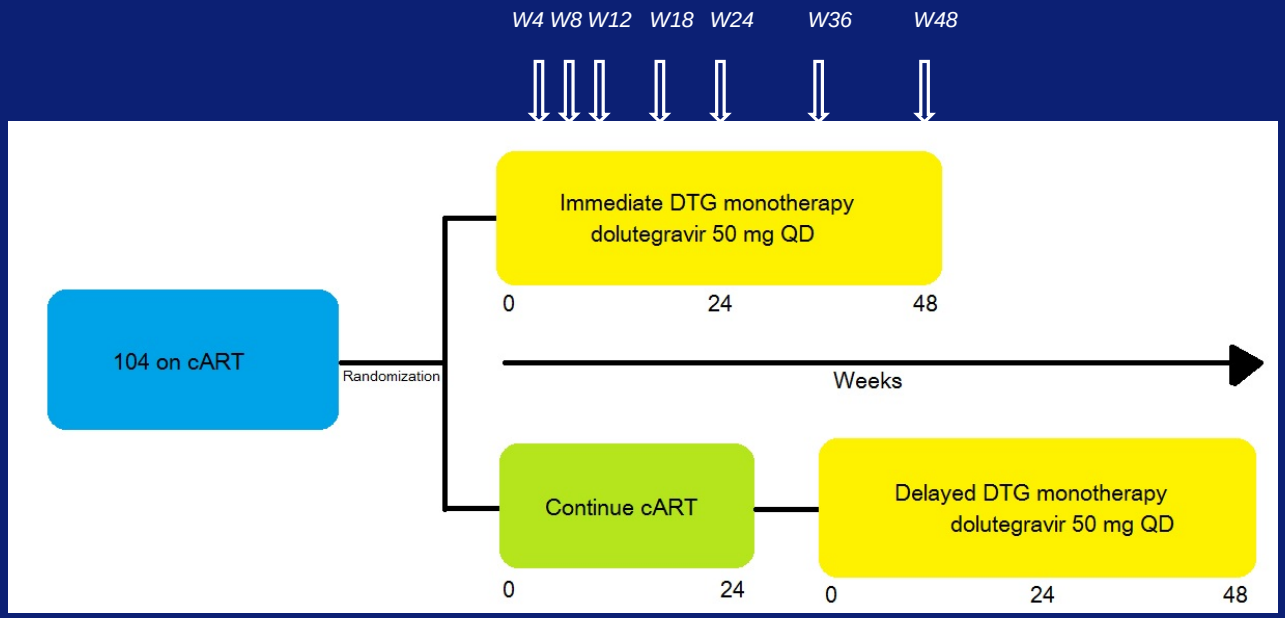
Randomized open label multicenter

Dolutegravir monotherapy 50 mg for 48 weeks with or without a meal.

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

+- 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.

DTG N=49/50 (98%)

cART N=…/53 (…%)

} *Results will be presented at HIV Glasgow**

** Oral presentation Wednesday 26-10, 14.00h and poster.*

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 35 reached W24.
- In total: 85 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 83/85 (98%, 95% C.I.* 91%-99%)

HIV-RNA <50 c/ml in 79/85 (93%, 95% C.I.* 85%-97%)

** 95% CI according to Agresti and Coull*

Virological failures

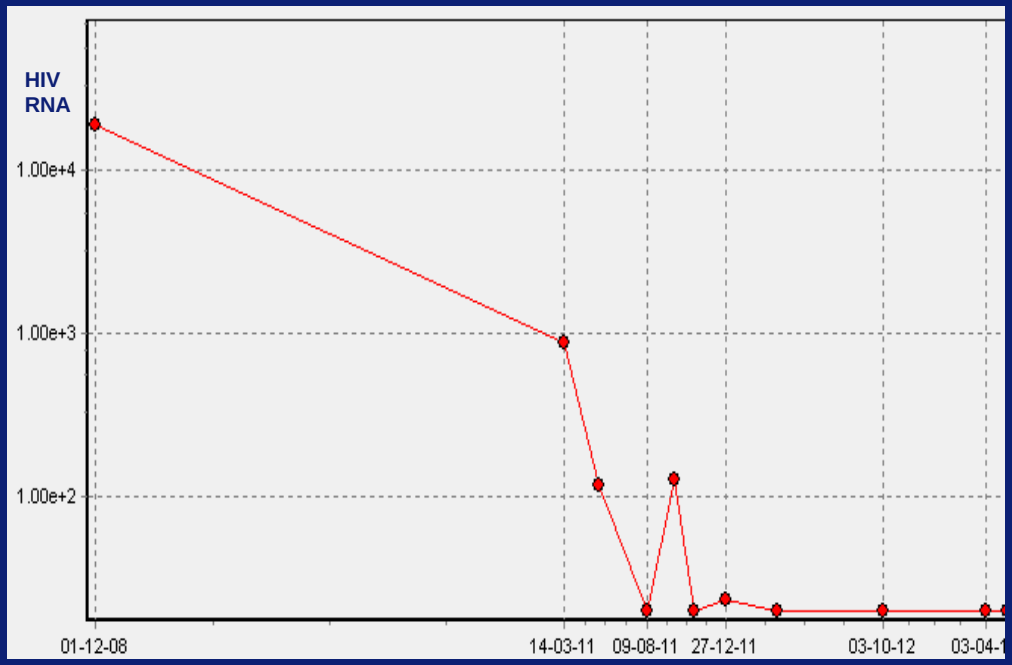
The single patient with virologic failure in the DOLUMONO group:

- Had nadir CD4 of 290 and peak HIV-RNA of 18.500 c/ml
- Was on cART for 4 years (RPV/FTC/TDF) when he 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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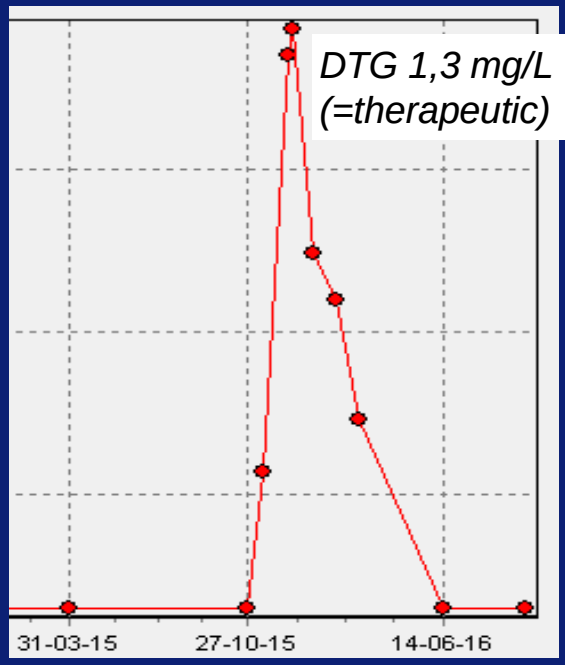

Virological failures

The patient with virological failure from 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

Conclusions

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

However:

2 of 85 patiens had VF at week 24

But little if any loss of future treatment options

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

104 brave and motivated patients !