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)\textsuperscript{1}:
  • Viral suppression -8.3\% [CI -11.9 tot -4.8\%]

• PROTEA-study\textsuperscript{2}:
  • Multivariate analysis W48:
    non-inferiority in subset with favorable virological/CD4 criteria.

\textsuperscript{1} Arribas et al, HIV Med 2015
\textsuperscript{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 < 1,0^5
- CD4-nadir ≥ 200
- HIV-RNA <50 ≥24w
- Never failed
- No resistance
- HBV immune
- >95% estimated compliance
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• **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
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• Sample size N=104 to show non-inferiority of DTG versus con-cART:
  • $P_a = P_b = 0.95$  $\delta = -0.12$  $1 - \beta = 0.80$  $\alpha = 0.025$
+- 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

<table>
<thead>
<tr>
<th></th>
<th>DOLUMONO (N=51)</th>
<th>Con-cART (N=53)</th>
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</thead>
<tbody>
<tr>
<td>Male sex, N(%)</td>
<td>47 (92)</td>
<td>48 (91)</td>
</tr>
<tr>
<td>Age, median (Q1,Q3)</td>
<td>46 (37-56)</td>
<td>45 (40-51)</td>
</tr>
<tr>
<td>Transmission route MSM, N(%)</td>
<td>41 (80)</td>
<td>41 (77)</td>
</tr>
<tr>
<td>Ethnicity Caucasian, N(%)</td>
<td>42 (82)</td>
<td>44 (83)</td>
</tr>
<tr>
<td>TDF, N(%)</td>
<td>44 (86)</td>
<td>45 (85)</td>
</tr>
<tr>
<td>Median (Q1,Q3) time on cART, months</td>
<td>35 (24-61)</td>
<td>43 (25-68)</td>
</tr>
<tr>
<td>Median (Q1,Q3) HIV-RNA zenith</td>
<td>21.500 (7.555-64.800)</td>
<td>27.800 (5.200-55.900)</td>
</tr>
<tr>
<td>Median (Q1,Q3) CD4 T-cell nadir</td>
<td>320 (250-490)</td>
<td>380 (285-515)</td>
</tr>
</tbody>
</table>
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

DTG 1.3 mg/L (=therapeutic)
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 patients 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
104 brave and motivated patients!