The Dolutegravir Antiretroviral Mono-Therapy for HIV Trial

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OT population excludes patients lost to follow-up, or that discontinued DTG for reasons of intolerance or toxicity. ITT = all patients that took at least 1 DTG tabletPrimary objective:* To evaluate the efficacy of DTG monotherapy in maintaining...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON41743

Source
ToetsingOnline

Brief title
DOMONO

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: antiretroviral therapy, dolutegravir, HIV

Outcome measures

Primary outcome

* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <200 c/mL at week 24 by OT analysis.

Secondary outcome

* To evaluate the time to loss of virological response (TLOVR) in the OT population defined as the first of two confirmed HIV-RNA >50c/mL at least 1 week apart.

* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <200 c/mL at week 24 by OT analysis in the entire study population (n=104) which consists of the immediate switchers group (n=52) and the delayed switchers from the control arm (n=52).

* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <50 and <200 at week 24 and 48 by OT and ITT analysis.

* To evaluate the safety (acquired resistance, and AE according to CTC 4.0) of DTG monotherapy

* To evaluate the evolution of CD4 associated HIV-1 reservoir (total/integrated HIV-DNA and 2LTR) at baseline and during DTG monotherapy.

* To evaluate the number and type of INI resistance mutation in patients with confirmed HIV-RNA >200 c/mL.

* To evaluate the CD4 cell count change at week 48.

* To evaluate blood-pressure, weight, BMI, fasting serum lipids, Framingham

risk score, ATP-III treatment goals, inflammatory markers, renal function,

urinalysis, bone mineral density at week 24 and 48.

* To evaluate the cost effectiveness of DTG monotherapy.

Study description

Background summary

Dolutegravir (DTG) is an integrase inhibitor (INI) with in vitro activity against HIV-1 and has recently been approved by the European Medicines Agency for the use in combination antiretroviral therapy (cART) for ART experienced and naïve HIV patients.[1] INI inhibit HIV-1 DNA transfer into host DNA, which is a pivotal step in lasting forward HIV-1 transmission and disease progression. DTG is a second generation INI and its molecular structure allows for greater binding activity leading to a potential for more potent activity and a higher barrier to resistance in wild type and ART and INI resistant HIV-1 compared to the first generation INI raltegravir (RAL) and elvitegravir (EVG) in vitro.[2, 3] Available data also indicate that most RAL and EVG resistant strains with double or more INI mutations remain susceptible to DTG with only 2 mutant viruses (Q138K/Q148K and Q148R/N155H) leading to a >10 fold chance in EC50 against HIV-1 in vitro.[4] In contrast to RAL or EVG, 112 days of DTG monotherapy in vitro selects for only T124A, S153Y, T124A/S153Y, L101I/T124A/S153F, all associated with <5 fold resistance compared to wild-type HIV. Furthermore, DTG exhibits broad potency across HIV types in different cell types.
Phase I and Phase IIa trials results show that DTG at a dose of 50mg once-daily (QD) has a 14 hour half-life, maintains concentrations above in vitro IC90 for over 30 hours following a single dose, reaches steady-state after 5 days and has lower intra-subject variability compared to first-generation INI.[5, 6] Cerebrospinal fluid (CSF) concentrations of DTG are similar to plasma concentrations exceeding IC50 for wild-type HIV-1 (0.2ng/mL) with similar HIV-RNA reduction in CSF and plasma, indicating therapeutic concentrations in the central nervous system.[7] DTG is predominantly metabolized by hepatic uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and cytochrome P450 (CYP)3A4. In contrast to EVG, DTG does not need a PK booster. Excretion of DTG is in part renally where DTG can inhibit tubular OCT-2 creatinine transport, which results in a non-pathological creatinine increase and therefore a decrease in creatinine-based eGFR measurements but not the real GFR (when measured with exact eGFR measurements like inuline). DTG can be administered with or without food. It cannot be taken with antacids as they can lower DTG plasma exposure when taken within an 8 hour window of DTG administration. DTG does not induce or inhibit CYP isoenzymes or UGT and has therefore a low

potential for drug-drug interactions.
DTG*s safety, good clinical efficacy against HIV-1 and absent potential for acquiring resistance have been demonstrated in 1 phase IIb and 3 large phase III randomized clinical trials in a total of 2344 ART naïve patients. The phase II dose finding partially blinded trial SPRING-1 randomized 205 naïve HIV-1 patients to DTG 10, 25 and 50mg and efavirenz 600mg with abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) as nucleoside reverse transcriptase inhibitor (NRTI) backbones and found sustained and comparable virological efficacy over 96 weeks of DTG and EFV.[8] These results were confirmed in the randomized phase III double blind double dummy SINGLE on 833 naïve HIV-1 patients on QD DTG + ABC/3TC versus co-formulated EFV/TDF/FTC over 96 weeks with superior DTG activity by intention to treat (ITT) analysis due to more adverse events (AE) related discontinuation in the EFV group.[9] DTG was well tolerated with only 2% discontinuations due to AE compared to 10% on EFV. Reported AE in >10% of DTG patients were diarrhea (17%), insomnia (15%), nasopharyngitis (15%), nausea (14%), headache (13%) and fatigue (13%). More subjects in the EFV group (4%) experienced ALT>3x ULN compared to DTG (1%) and renal safety was similar.
SPRING-2 and FLAMINGO were both double blind double dummy trials on 822 HIV-1 naïve HIV-1 patients randomized to DTG 50mg QD or RAL 400mg BID and 484 naïve HIV-1 patients randomized to DTG or ritonavir boosted darunavir (DRV/r) 800/100mg QD respectively, both with NRTI backbones. In SPRING2, DTG 50mg QD showed equal virological efficacy to RAL 400mg BID over 96 weeks of follow-up.[10] Both groups had good tolerability with 2% withdrawal to AE, 6% grade 2-4 related AE and only 3/29 serious AE (SAE) were considered DTG related. Reported AE occurring in >10% of DTG group were similar to SINGLE although insomnia and fatigue were not reported over 10%. Hepatic safety and fasting lipid profiles were good and similar in both groups. In FLAMINGO, DTG 50mg QD demonstrated superior virological efficacy at week 48 in achieving HIV-RNA <50c/mL by intention to treat analysis.[11] The HIV-RNA in the week 48 window were not <50c/mL in 2% of DTG group versus 5% of DRV/r group. Discontinuations for AE were infrequent on DTG (1%) and DRV/r (4%).
In summary, the trials of DTG use in ART naïve HIV-1 patients showed that DTG had similar or superior virological efficacy regardless of baseline HIV-RNA to comparators* arms as high as 90% at week 48. Importantly, DTG*s safety and tolerability were equal or superior, had comparable CD4 count increases and there has not been a single case of acquired resistance INI/NRTI or protease inhibitors (PI); all patients had wild-type HIV-1 strains upon virological failure.
These data combined indicate that DTG is a valuable addition to the antiretroviral drugs repertoire because of its efficacy and safety profile. The current standard of care, as stated in international guidelines, includes the use of an INI, NNRTI or boosted PI with FTC/TDF or ABC/3TC for ART naïve patients.[16-18] Although currently 4 single tablet regimens are available, all consist of at least 3 antiretroviral drugs. These drugs have their specific mild to sometimes serious side effects, drug-drug interactions and other contra-indications. As HIV-1 treatment is lifelong and discontinuation of

therapy would result in virological rebound with immunological decay, AIDS and ultimately death, the long-term side-effects of cART are becoming increasingly important. As it is as yet impossible to predict which patient will experience side-effects they often have to switch drugs at some time during treatment. A recent study on 21.801 ART naïve HIV patients from 18 European and North-American cohorts that started HAART after the year 2002 showed a 60% switch rate of one or more drugs within 3 years and mostly for drug toxicity.[19, 20] Furthermore, the increased focus on cost-containment in HIV-1 care could result in the need for more cost-effective treatments.[21] Reducing the drug burden in cART to dual or antiretroviral monotherapy could be a preferable option for a considerable number of patients who have to switch cART for various reasons, especially if virological suppression can be maintained. Studies have been undertaken to evaluate this potential strategy with 1 specific group of antiretrovirals, namely boosted PI. The OK pilot study was followed by the first randomized open-label trial to evaluate the efficacy of boosted lopinavir (LPV/r) monotherapy in 205 HIV suppressed patients and found comparable efficacy in mono and triple-therapy without development of significant drug resistance >2.7 fold change in IC50 on monotherapy or differences in AE and CD4 cell counts.[22, 23] The 96 week KAIMO randomized pilot trial on 60 HIV suppressed patients reported equal efficacy, no drug resistance, CD4 counts, AE and HIV-RNA in semen remained undetectable in 93% of patients on LPV/r monotherapy.[24] The MONARK trial was a randomized trial in 2008 comparing LPV/r monotherapy with LPV/r plus zidovudine and lamivudine in 136 ART naïve patients and demonstrated week 48 HIV-RNA <400c/mL in 64% and 75% of patients respectively without differences in CD4 cell count change or tolerance.[25] Three patients on monotherapy developed minor genotypic mutations to PI resulting in a maximum 2.7 fold change in phenotypic sensitivity. Darunavir/ritonavir (DRV/r) monotherapy, another more recent PI was associated with 94% virological efficacy at week 48 compared to 99% with triple therapy in 225 randomized HIV-1 suppressed patients of the open-label MONO-ANRS136 trial.[26] No genotypic resistance to PI emerged and no differences in CD4 counts or AE were observed. Of 256 HIV-1 suppressed patients randomized to DRV/r 800/100mg QD or triple therapy in the open-label MONET trial, non-inferiority of monotherapy was shown without differences in CD4 cell count, AE or significant emerging drug resistance to PI.[27] DRV monotherapy was not shown to be non-inferior to DRV+2NRTI triple therapy in the subset of enrolled HIV suppressed patients with CD4<200 (N=66) of the open-label PROTEA trial (N=273).[28]

In the GARDEL trial, 217 ART naïve patients were randomized to LPV/r with 2 NRTI (triple therapy) or LPV/r with 3TC (dual therapy) and demonstrated non-inferiority of the latter in achieving HIV-RNA <50 c/mL at week 48 with comparable CD4 increases and significantly fewer side-effects in the dual therapy arm.[29] The open-label MODAT trial randomized 103 HIV-1 suppressed patients to continuing boosted atazanavir (ATV/r) 300/100mg with 2 NRTI or ATV/r monotherapy. By week 48, 73% of patients on monotherapy and 85% triple therapy had continued virological suppression. In patients with virological rebound (2 consecutive HIV-RNA >50c/mL), no acquired resistance was detected

and all were re-suppressed with the introduction of their previous NRTI backbone. CD4 count changes did not differ between groups. Grade 3/4 AE were observed less often and estimated glomerular filtration rate improved with monotherapy.
Although the studies described above have shown that PI monotherapy can be a valid treatment option to maintain virological suppression, it has not been widely adopted because the pill-burden and size of the PI pills much higher (2 to 4 large-size pills per day). Also, all drugs of the PI class have to be combined with ritonavir as a CYP450 3A4 pharmacological booster. The coadministration of ritonavir poses patiens at risk for other, sometimes dangerous, drug-drug interactions.
As DTG therapy consists of a small single tablet and has very little drug-drug interactions it would be an attractive monotherapy drug. However, no DTGmonotherapy trial has been undertaken in ART naïve or ART experienced patients. A small pilot study with DTG/3TC dual therapy trial (PADDLE) is ongoing.[30] In conclusion, the use of ART monotherapy has only been evaluated with boosted PI monotherapy and seems associated with non-inferior virological responses to comparators* arms, absent rates of significant treatment emerging resistance, equal CD4 counts and less AE in the trials of HIV-1 suppressed patients.
This study will expand the experience with the monotherapy treatment strategy and evaluate the efficacy and safety of DTG monotherapy in HIV-1 suppressed patients in an open-label randomized clinical trial with patients continuing their original cART as controls. The studies mentioned above show that reducing the pill burden could result in ongoing virological efficacy, improve safety and without detrimental effects on immunological function. Because DTG has been shown to be superior to boosted PI cART regimens, this regimen has the potential to be as effective as monotherapy as DRV/r monotherapy in HIV-1 suppressed patients. The insight that this study will generate on DTG potential as monotherapy will be valuable for future patients with difficult to manage HIV-1 infections.
An important secondary virological endpoint in this study is the effect of DTG monotherapy on the cellular HIV reservoir. The effect of DTG on the viral reservoir is unknown. Furthermore, there is no study assessing the effect of ART monotherapy on viral reservoir kinetics. All included patients will be chronically infected HIV-1 patients on long-term cART. However, cART is not able to clear the virus and in patients with no detectable plasma vireamia, a latent (pro)viral reservoir persists. Interruption of cART in these patients usually results in rapid viral rebound.[31] The pro-viral reservoir*s decay rate with cART follows a linear pattern with a half-life estimated up to 44 months, dependent partially on the timing of cART initiation.[32, 33] In perspective of potential future treatment strategies to diminish or eradicate HIV reservoir size, data on the impact of DTG monotherapy on the viral reservoir are needed and will be collected.

Study objective

OT population excludes patients lost to follow-up, or that discontinued DTG for reasons of intolerance or toxicity. ITT = all patients that took at least 1 DTG tablet

Primary objective:
* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <200 c/mL at week 24 by OT analysis.

Secondary objectives:
* To evaluate the time to loss of virological response (TLOVR) in the OT population defined as the first of two confirmed HIV-RNA >50c/mL at least 1 week apart.
* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <200 c/mL at week 24 by OT analysis in the entire study population (n=104) which consists of the immediate switchers group (n=52) and the delayed switchers from the control arm (n=52).
* To evaluate the efficacy of DTG monotherapy in maintaining virological suppression with HIV-RNA <50 and <200 at week 24 and 48 by OT and ITT analysis.
* To evaluate the safety (acquired resistance, and AE according to CTC 4.0) of DTG monotherapy
* To evaluate the evolution of CD4 associated HIV-1 reservoir (total/integrated HIV-DNA and 2LTR) at baseline and during DTG monotherapy.
* To evaluate the number and type of INI resistance mutation in patients with confirmed HIV-RNA >200 c/mL.
* To evaluate the CD4 cell count change at week 48.
* To evaluate blood-pressure, weight, BMI, fasting serum lipids, Framingham risk score, ATP-III treatment goals, inflammatory markers, renal function, urinalysis, bone mineral density at week 24 and 48.
* To evaluate the cost effectiveness of DTG monotherapy.

Study design

Randomized open-label phase IV intervention study (figure below). HIV-1 infected patients on suppressive cART with HIV-RNA <50 c/mL for >24weeks, a CD4 nadir >200 cells/mm3, and a HIV-RNA plasma load before cART initiation <100.000 c/ml will be randomized 1:1 to immediate switch to DTG monotherapy or to continue current cART till delayed switch at week 24 to DTG monotherapy. Patients will be assessed at screening, day 1 (baseline) and weeks 4, 8, 12, 18, 24, 36 and 48. Patients will return to their previous cART regimen when criteria of treatment failure are met.

Intervention

Patients on current standard cART will switch to dolutegravir, an INI active against wild-type, *2 ART classes including or excluding INI resistant HIV-1 will be given as a single tablet 50mg QD. The branded name for DTG is Tivicay®

and DTG is produced by ViiV Healthcare.

Study burden and risks

Burden: 5 extra visits for a total of 8 visits. Extra blood sampling (190mL in 48 weeks). DEXA scan will be done at week 0 and 24 on DTG monotherapy.

Risks: Risks associated with the study are the side effects of DTG as observed in the phase III clinical trials. In these studies DTG was well tolerated and DTG discontinuation were less frequent compared to frequently used comparators arms at 96 weeks of follow-up. No life threatening drug-related AE were observed.

The virological properties of DTG and absent treatment emergent DTG resistance in the clinical trials are reassuring and show that DTG is a potent drug with a high genetic barrier to resistance. However, although patients will be carefully monitored and cART will be reinitiated promptly at the time of virological rebound, there is a chance that DTG monotherapy will fail in a small subset of patients. Because, none of the study participants have experienced virological failure in the past, these patients can restart their previous cART regimen if DTG monotherapy fails. As only patients with a high CD4 count are included, the restart of their previous cART regimen will be possible before a clinically relevant decrease in CD4 cell count is observed.

The risks associated with blood sampling are small. Severe adverse events are very infrequent with these procedures.

Benefits: In some patients: decrease in pill count from 3 or 2 medicines to 1 pill per day. Decrease in pill volume (in all). Decrease in antiretroviral compounds from 3 to 1 and therefore the risk of side effects due to these discontinued antiretroviral compounds.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

18 years or older;On cART and HIV-RNA <50 for last >24 weeks;pre-cART: baseline HIVRNA <100.000;pre-cART: CD4 nadir >200;Not on co-medication inducing UGT1A1/CYP3A4 as stated in DTG SPC;General medical condition does not interfere with trial procedures

Exclusion criteria

Planning to be pregnant;No use of double barrier contraceptive methods;Previous virological failure on any ART.;Patient without documented anti-HBs antibodies.;Subjects positive for hepatitis B at screening (HBsAg+).;Any documented genotypic HIV-1 resistance with at least low-level resistance according to stanford HIV drug resistance database ;No record of the historical baseline plasma viral load available;Subjects with concomitant CDC-C opportunistic infections within 90 days of screening.;Subjects with history of allergy to INI.;Subjects with creatinine clearance <50mL/min according to CKD-EPI.;Subjects with hepatic impairment of at least Child-Pugh B.;Exposure to experimental drug or experimental HIV-1 vaccine within 90 days of start of DTG.;Screening ALT >5x ULN or ALT>3xULN and bilirubin >2 ULN.;Patient (man or woman) planning or hoping to conceive a child/become pregnant during the study;Patients who cannot take DTG 2 hours before or 6 hours after antacids, calciumcarbonate or iron supplements.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-03-2015
Enrollment:	104
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tivicay
Generic name:	Dolutegravir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005454-19-NL
CCMO	NL51858.078.14