Switching to Tenofovir Alafenamide Fumarate or ABACavir in patients with Tenofovir Disoproxil Fumarate associated eGFR decline. A randomized clinical trial.

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To study the renal safety when HIV patients with TDF related renal toxicity switch to TAF compared to the current practice of switching to ABC.

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

Summary

ID

NL-OMON46033

Source
ToetsingOnline

Brief title
BACTAF

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: Gilead Sciences,Gilead Sciences Inc.

Intervention

Keyword: antiretroviral therapy, HIV, tenofovir alafenamide fumarate

Outcome measures

Primary outcome

* Recovery of renal dysfunction in the TAF arm versus the ABC arm at 48 weeks after the switch from TDF to TAF or ABC using the time to the first eGFR within 75% of the eGFR at the time of TDF initiation.

Secondary outcome

* The between group differences (TAF vs ABC) with respect to the time to recovery of renal dysfunction (eGFR improvement to within 75% of eGFR at TDF initiation) at week 96, with adjustment for potentially important confounders.
* The mean eGFR at week 48 and 96 on ABC and TAF will be compared to week 0. The slopes of eGFR-decline/increase between week 0, week 48 and 96 will be compared between the ABC and TAF group.
* The median (IQR) of uPCR, uACR, uAPR, uB2MG/CR changes at week 48 and 96 compared to week 0 within the ABC and TAF group and difference in change between both groups.
* Changes in the number of patients with at least 2 markers of PTD from week 0 to week 48 within the ABC and TAF group and difference in change of PTD markers between both groups .

OTHER:

* HIV-RNA suppression rate <50 ABC versus TAF at week 48 and 96.
* Tolerability of TAF versus ABC, defined in terms of adverse events (%).

* Change in framingham risk-score, blood pressure, lipids and inflammation

parameters at week 0, 48 and 96 within the ABC and TAF group and comparison of

between group differences of these parameters.

Study description

Background summary

The majority of HIV-1 infected patients in resource rich countries take the tenofovir prodrug tenofovir disoproxil fumarate (TDF) as part of their combination antiretroviral therapy (cART) against HIV-1. Long-term exposure to TDF is associated with an accelerated estimated glomerular filtration rate (eGFR) decline and proximal tubular dysfunction (PTD) in a significant part of these patients. The current practice in patients in which TDF related renal toxicity becomes apparent is to substitute abacavir (ABC) for TDF. However, ABC is contraindicated in patients with HLAB57*01 and has been associated with an increased risk of cardiovascular disease. Recently, a new tenofovir prodrug, tenofovir alafenamide (TAF) was developed by Gilead Sciences and is available in a coformulation with emtricitabine (FTC). Due to the targeted delivery of tenofovir inside the CD4 positive cell by this prodrug, only 25 mg TAF is needed for the same antiviral effect observed in patients taking 250 mg of TDF. In recently completed phase III studies in which patients with a normal kidney function where included, the resulting lower tenofovir exposure in patients on TAF was shown to prevent off-target renal and bone toxicity significantly in comparison with patients taking TDF. However, whether an already established TDF related renal toxicity in a HIV patient can be reversed after a switch to TAF, remains to be shown.

Study objective

To study the renal safety when HIV patients with TDF related renal toxicity switch to TAF compared to the current practice of switching to ABC.

Study design

To study the renal safety when HIV patients with TDF related renal toxicity switch to TAF compared to the current practice of switching to ABC.

Intervention

HIV-1 infected adults, suppressed HIV-RNA <50c/mL on a TDF containing antiretroviral regimen, with signs of TDF related renal toxicity as indicated

by an accelerated eGFR decline.

Study burden and risks

Burden: maximum of 4 extra visits for blood sampling (week 0, week 4, week 12, week 36) and study drug accountability for all patients in the study. The other visits at week 24, 48, 72 and 96 are the same as usual care, in which patients are scheduled to visit their HIV physician at least every 24 weeks.

Risks: Risks associated with the study are the side effects of TAF or ABC. ABC is EMA and FDA approved and recommended by international guidelines for use in HIV patients. All patients will be tested for HLA-B57*01 which is associated with a hypersensitivity reaction and patients who test positive will not be randomized. ABC is safe, and the main side effects are gastro-intestinal. TAF has been proven to be safe in 2 registration 96 weeks phase 3 randomized clinical trials. Outside the context of this study, both switching to ABC or TAF are advised by treatment guidelines as switch-strategy in patients with TDF related renal toxicity.The virological properties of TAF and the low risk of acquired resistance show that TAF is non-inferior to current practice (TDF) but with lower (halved) eGFR decline over 48 weeks. The safety profile of TAF was excellent in these trials and better than TDF. Nevertheless, because subjects will be exposed to a small dose of the potential nephrotoxic agent, a delayed recovery of eGFR or even a further decline of renal function might be possible. The risk associated with standard blood sampling is very small (brusing, syncope) and blood sampling is always done in the recumbent position to prevent injury when syncope would occur). Patients will replace a mostly 1 pill cART for a 2 pill cART (both in the ABC and in the TAF arm). However, this is also often the current practice when these patients are treated outside the context of a clinical trial.

Benefits: We cannot guarantee any specific benefits for the patients at this time when they participate in the trial. However, both ABC and TAF are anticipated to halt or ameliorate renal dysfunction If this indeed is the case, the advantage will be that patients on TAF instead of ABC do not take ABC, a drug that has been associated with in increased risk for myocardial infarction.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3015CE
NL

Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3015CE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* 18 years or older.
* Stable on TDF/FTC or TDF/3TC for ><=12 months (365 days) in combination with a third antiretroviral agent (NNRTI, INI, or PI) and with an unchanged 3th agent for at least 1 month .
* HIV-1 RNA <50 copies/mL for * 6 months.
* Confirmed/probable TDF-related accelerated eGFR decline
* Concomittantly used medication does not interfere with trial procedures (on investigators* discretion).
* Patient is negative for the HLA B5701 allele.

Exclusion criteria

* Likely other cause of non-TDF-related accelerated GFR decline:
* Diabetic patients
* Hypertensive patients (defined as the use of more than 2 antihypertensives or untreated systolic (>=160mmHg) or diastolic (>=95mmHg) hypertension) or hypertension with use of antihypertensives and with proteinuria at the screening visit..
* Nephrotic syndromes/nephrotic range proteinuria (uACR >300mg/mmol and uAPR * 0.4, or total 24hrs proteinuria >3.5g/24hr, or biopsy proven)
* Nephrotic syndromes including rapid progressive glomerulonephritis and tubular interstitial nephritis (defined as active urine sediment with erythrocyturia and leucocyturia and

proteinuria with eGFR decline, with or without the presence of systemic disease, or biopsy proven).
* Obvious other renal toxic effects related to lifestyle or medication (e.g. creatin use) suspected by the investigators or biopsy proven.;* HLA-B5701 positivity.
* Active hepatitis C or B.
- Intermediate or high level resistance to ABC
- eGFR <30 ml/min
Symptomatic arterial disease e.g. a history of coronary artery disease, ischemic cerebrovascular accident or claudication intermittens in medical history.
* Any other disease or medical condition that, in the opinion of the investigators, would interfere with the safety of the participant or the conduct of the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2016
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Descovy
Generic name:	Tenofovir alafenamide fumarate
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Kivexa
Generic name:	Abacavir/Lamivudine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-02-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2017
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	EUCTR2015-005045-31-NL
ClinicalTrials.gov	NCT02957864
CCMO	NL55668.078.16