A pilot study on the efficacy and pharmacokinetics of a switch from nevirapine with emtricitabine, tenofovir or lamivudine, tenofovir or lamivudine, zidovudine to rilpivirine with emtricitabine, tenofovir in virologically suppressed HIV-1 infected patients.

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Primary objective:To evaluate the efficacy of a RPV based HAART in patients that switch from NVP with FTC, TDF or lamivudine (3TC), TDF or 3TC, zidovudine (ZDV) to RPV/FTC/TDF.Secondary objectives:To measure the impact (strength and duration) of NVP...

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

Summary

ID

NL-OMON39388

Source
ToetsingOnline

Brief title
rilpivirine switch study

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym

HIV AIDS

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: farmaceutische industrie,Gilead Sciences

Intervention

Keyword: AIDS, HIV, rilpivirine, Therapy

Outcome measures

Primary outcome

Percentage of subjects with HIV-1 RNA <50 c/mL at week 12 post-switch (ITT population, snapshot analysis)

Secondary outcome

Comparison of serum Cmin of RPV at 1, 2, 3, 4, 8, and 24 weeks in subset of 20 patients with Cmin at these timepoints in phase III studies.

Percentage of subjects with HIV-1 RNA <50 c/mL at Week 24 post-switch (ITT population, snapshot analysis)

Percentage of subjects with HIV-1 RNA <50 c/mL at Week 48 post-switch (ITT population, snapshot analysis)

Questionnaire on satisfaction with treatment at 48 weeks in comparison with baseline.

Study description

Background summary

Rilpivirine (RPV) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against HIV-1. A phase 2b, dose-finding study in ARV-naïve, HIV-1-infected subjects demonstrated sustained and comparable efficacy of TMC278 25, 75 and 150mg once daily (qd) over 192 weeks. Furthermore, 2 large phase 3 studies in ARV-naïve, HIV-1- infected subjects, ECHO and THRIVE have demonstrated noninferiority of RPV 25 mg qd in combination with emtricitabine (FTC) and tenofovir (TDF) when it was compared with efavirenz (EFV) 600 mg qd which is the current standard of care in resource rich countries (1,2). Furthermore, RPV 25 mg was associated with statistically significantly lower incidences of grades 2-4 adverse events (AE) related to study drugs, AE leading to discontinuation, rash, dizziness, and little change in cholesterol and triglycerides compared to increases with EFV. The only single tablet regimen currently available for the treatment of HIV is Atripla® in which efavirenz, FTC and TDF are combined in a 1 pill once a day regimen. Now that the efficacy and improved tolerability of RPV in comparison with the current standard of care has been documented, Gilead Sciences has incorporated RPV, FTC and TDF in a new single tablet regimen (STR) for the treatment of HIV-1. This STR is called Eviplera® and received EMA approval 30th of November 2011 for the treatment of HIV-1 infected patients with a plasma HIV-RNA load <100.000 copies/ml. Because of its excellent tolerability and ease of administration it will make HIV management in future patients easier. For further information on RPV product characteristics, preclinical or clinical data, please refer to the latest version of the FTC/RPV/TDF single tablet regimen SPC.
Currently, there are more than 10 antiretroviral drugs in the Netherlands that are frequently used for the treatment of HIV. However, all these drugs are associated with mild to sometimes life-threatening side-effects and because it is as yet impossible to predict which patient will experience side-effects they often have to switch drugs at some time during there treatment. A recent study including 25499 HIV patients from 19 European and North-American cohorts that started HAART after the year 2002. After 3 years of follow-up 60% had changed one or more antiviral drugs, mostly for toxicity(3).

Because of its well-documented antiviral activity and broad availability and reduced costs, nevirapine (NVP) is the most frequently used NNRTI for the treatment of HIV in resource-limited countries. Also in the Netherlands, several hundreds of patients start NVP as part of their HAART each year. However, during the first 6 weeks of NVP therapy 2 well-known treatment-limiting side effects occur in around 10% of patients (rash and hepatitis). Hence, in the near future a switch from NVP to RPV will be a valid option for patients experiencing NVP-related AEs. Because NVP-related AEs often

occur during the first 6 weeks of treatment initiation, the plasma HIV RNA load will usually not be undetectable at time of a switch from NVP to RPV. Therefore, it is important to assure therapeutic levels of RPV during the weeks after the NVP to RPV switch to avoid selection of drug resistance. However, as a result of NVP mediated CYP3A induction of RPV metabolism, it can be expected that the RPV Cmin concentrations will be significantly lower for some time (days to weeks) after the NVP to RPV switch.

This study will evaluate the efficacy and safety of RPV in patients with an undetectable HIV plasma viral load for >6 months while treated with a NVP containing HAART regimen when they replace NVP by RPV. In a subset of patients the impact of NVP CYP 3A4 induction on RPV serum levels will be measured. In patients on HAART with undetectable HIV RNA it takes on average 4 to 8 weeks before HIV replication can be documented in plasma after all antivirals are discontinued(4). Furthermore, when NVP is replaced by RPV, the 2 other antiretrovirals that the patient is taking are continued or replaced by the current standard of care. Another recent study measured the pharmacokinetic consequences of CYP3A4 induction by previous efavirenz exposure which is another NNRTI frequently used for the treatment of HIV. All of the 49 patients included in this study remained HIV RNA undetectable 12 weeks after the switch from efavirenz to RPV despite a mean reduction of RPV serum levels of 50% during the first 2 weeks after the switch. Therefore, the potentially lower RPV levels during the first days to weeks after the switch from NVP to RPV while the CYP3A4 induction is waning are not expected to impact HIV control in patients with an undetectable HIV plasma viral load at the time of switch. However, the insight that this study will generate on de RPV metabolism induction by previous NVP use will be valuable to design future pharmacokinetic studies and find the correct dosing for future patients that switch from NVP to RPV at a time that their plasma HIV RNA load is not yet undetectable.

Study objective

Primary objective:
To evaluate the efficacy of a RPV based HAART in patients that switch from NVP with FTC, TDF or lamivudine (3TC), TDF or 3TC, zidovudine (ZDV) to RPV/FTC/TDF.

Secondary objectives:
To measure the impact (strength and duration) of NVP CYP 3A4 induction on serum levels of RPV when patients switch therapy from NVP to RPV.

To evaluate efficacy and safety of RPV at 24 and 48weeks after a switch from NVP.

Study design

Open label single arm intervention study. 50 patients will discontinue NVP on

day 1 and start RPV 25mg in combination with emtricitabine and tenofovir given as a single combination tablet qd (Eviplera®).

For the PK analysis, Cmin levels of a subset of 20 of these 50 patients will be compared with mean Cmin levels from the 2 phase III registration trials at 1, 2, 3, 4 and 8 weeks

Intervention

Switch from NVP (Viramune) with FTC, TDF (Truvada) or 3TC, TDF or 3TC, ZDV to RPV, FTC, TDF (=Eviplera)

Study burden and risks

Burden: 3 extra visits for blood sampling (30cc) for all 30 of the 50 patients. 7 extra visits for blood sampling for 20 of the 50 patients.

Risks: Risks associated with the study are the side effects of RPV as observed in the phase III clinical trials. In these studies RPV was well tolerated and only 4% discontinued RPV for AE after 96 weeks of treatment (9% in control arm). No life threatening drug-related AE were observed. We do not anticipate clinically relevant consequences of the lower RPV serum levels during the first days to weeks after the switch from NVP to RPV because patients are HIV-RNA undetectable at the time of switch. Even if all antiretroviral drugs are discontinued in patients with undetectable HIV-RNA in plasma, it takes on average 4-8 weeks before HIV replication in plasma reappears. Furthermore, when NVP is replaced by RPV, the 2 other antiretrovirals that the patient is taking are continued or replaced by the current standard of care NRTI backbone.

Benefit: Decrease in pill count from 3 to 1 pill per day as RPV will be given as a single tablet regimen(STR) which incorporates TDF, FTC and RPV in 1 pill.

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

Able to take medication with a 500 kcal meal
Treated with NVP and FTC, TDF or 3TC, TDF or 3TC, ZDV for at least the last 9 months
No history of HIV virologic failure
The last 2 measured HIV-RNA levels in plasma were <50 copies/ml
>=6 months between the first and last plasma with <50 copies/ HIV RNA/ml

Exclusion criteria

Use of proton pump inhibitors.
Use of H2-antagonists
Use of other contraindicated concurrent medication

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-11-2013
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eviplera
Generic name:	rilpivirine + emtricitabine + tenofovir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-04-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-08-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2013
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

ID: 26054
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-001142-18-NL
CCMO	NL40306.078.12
OMON	NL-OMON26054