Study on PhArmacokiNetics of first liNe Antiretrovirals in healthy Breastfeeding volunteers (PANNA-B PK)

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This study has been transitioned to CTIS with ID 2023-510232-36-00 check the CTIS register for the current data. to determine the concentration of currently often used ARV (doravirine, raltegravir, bictegravir, tenofovir alafenamide, emtricitabine)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON53659

Source
ToetsingOnline

Brief title
PANNA-B PK

Condition

- Viral infectious disorders

Synonym
HIV

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Antiretrovirals, Breastmilk, HIV, Pharmacokinetics

Outcome measures

Primary outcome

Area under the plasma and milk concentration curve are used to calculate milk

to plasma ratio.

Secondary outcome

The following pharmacokinetic parameters of ARV in plasma and/or

breastmilk will be described:

o AUC0-tau (AUC over a dosing interval) estimated using the rectangular method

(41).

o Peak plasma concentration (Cmax)

o Time to Cmax

o Concentration at end of dosing interval (Ctrough)

o Clearance

o Apparent volume of distribution

o Half life

o Parameter estimation trough compartmental modelling

Study description

Background summary

Although current guidelines advise against breastfeeding while using antiretrovirals in people living with HIV, some women choose to breastfeed

because advantages of breastfeeding may exceed the possible risk of HIV transmission to the newborn. However, no sound recommendation can be made on which antiretrovirals are most suitable during breastfeeding, because no to little data on penetration of these drugs in breastmilk exist. Too high concentrations may lead to infant toxicity and too low concentrations may lead to development of resistance in case the infant inadvertently becomes infected with the virus.

Study objective

This study has been transitioned to CTIS with ID 2023-510232-36-00 check the CTIS register for the current data.

to determine the concentration of currently often used ARV (doravirine, raltegravir, bictegravir, tenofovir alafenamide, emtricitabine) in breast milk after administration of a single dose

Study design

This is a single centre, single dose, open label, pharmacokinetic study in healthy volunteers.

Intervention

Administration of one dose of either doravirine (DOR) 100mg, raltegravir (RAL) 1200mg or a combination of tenofovir alafenamide 25mg, emtricitabine 200mg and bictegravir 50mg (BIC/FTC/TAF).

Study burden and risks

Subjects will not directly benefit from this study, but will contribute to knowledge on breastmilk transfer of ARV and possibly enable people living with HIV to make a better informed decision on breastfeeding while using these medications.
No harm is expected from participation in this study, but possible side effects should be anticipated. Known side effects of DOR are nausea (4%) and headache (3%), abnormal dreams and insomnia (1-10%), dizziness and somnolence and fatigue (1-10%). BIC/FTC/TAFs known side effects are: headache (5%), diarrhoea (5%) and nausea (4%), depression and abnormal dreams and fatigue (1-10%), suicidal ideation (0,1-1%), angio-edema (0,1-1%), Steven Johnson syndrome (0,01-0,1%). Due to the fact that only one dose of the drugs will be ingested, the risk of development of one or more of these side effects is considered to be low.
Side effects of RAL are comparable with those seen in bictegravir.
Gastro-intestinal (dyspepsia, abdominal pain, diarrhea), psychiatric (depression, sleeping disturbances and abnormal dreams) and nervous system

effects (dizziness, vertigo) are noticed in 1-10% of users. On investigation 1-10% of the users of RAL have elevated liver enzymes or triglyceride levels. Several cases of osteonecrosis and severe skin reactions (Steven Johnson syndrome, toxic epidermal necrolysis etc) are reported.
Participation in this study requires subjects to be admitted during 24hours and a return visit 7 days later. During the sampling day an intravenous indwelling catheter is installed for collection of blood samples. A total volume of 25-50ml of blood, 2 urine samples and 6 breastmilk samples (expressed using a personal electronic pump) are collected. No harm is to be expected from these sample collection procedures.
In subjects who chose to sustain from breastfeeding for a minimum of four days, the risk of toxicity for their infants will be negligibly small. All study drugs are metabolized by first line kinetics, which means that after 4-5 times the elimination half-life of the drug, the plasma concentrations will be near to zero. Because breastmilk concentrations are mainly determined by passive diffusion from plasma, the breastmilk concentrations will most likely be lower than the plasma concentrations. So, when a near to zero concentration in plasma has been reached after 4-5 elimination half-life periods, the risk of getting exposed to toxic concentrations via breastmilk will be nihil. Therefore, subjects who agree to feed their infants in an alternative way (formula, pre-pumped milk form before ingestion of study drug, donor milk etc) will have to plan this alternative feeding in advance and might need to pump during this period to retain milk-production. This might be conceived as an inconvenience.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• At least 18 years of age at the moment of screening
• At least 10 days post partum
• At the end of breastfeeding period; subject is able to produce breastmilk at least two times a day and is no longer feeding infant at start of study or willing and able to sustain from breastfeeding during four days after ingestion of study medication
• Able and willing to sign an informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Relevant co-medication or comorbidity that might interfere with drug absorption, distribution, metabolism or excretion
• Inability to take drugs according to the instructions (i.e. with food)
• Presence of positive HIV screening or HIV RNA
• Presence of HBsAg or HBcAg without anti-HBs
• Presence of grade III/IV anaemia (i.e. Hb <4.6 mmol/L or <7.4 g/dL).
• Presence of hereditary forms of severe galactose intolerance, total lactase deficiency or glucose-galactose malabsorption

Participation to other studies is not an exclusion criterion per se, when other in- and exclusion criteria are met and the other study does not interfere with the outcomes of the current study.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-09-2023
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Biktarvy
Generic name:	Tenofovir alafenamide/emtricitabine/bictegravir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Issentres
Generic name:	Raltegavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pifeltro
Generic name:	Doravirine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-02-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	27-02-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-05-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EU-CTR	CTIS2023-510232-36-00
EudraCT	EUCTR2022-003715-29-NL
CCMO	NL83180.091.22