HIV-1 Envelope Sequence Diversity Within the Latent Reservoir in HIV-1 Infected Individuals Initiated on Antiretroviral Therapy (ART) During Acute and Chronic Infection.

Published: 25-03-2019
Last updated: 10-01-2025

To determine the frequency of R5-tropic N332+ viral isolates present within the latent reservoir while on suppressive ART.

Ethical review	Approved WMO
Status	Completed
Health condition type	Immunodeficiency syndromes
Study type	Observational invasive

Summary

ID

NL-OMON47974

Source
ToetsingOnline

Brief title
GS-US-420-3903

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
HIV-1; Human immunodeficiency virus type-1

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc

Intervention

Keyword: ART, HIV-1, HIV-1 Envelope diversity

Outcome measures

Primary outcome

To determine the frequency of R5-tropic N332+ viral isolates present within the latent reservoir while on suppressive ART.

Secondary outcome

- To determine the frequency of R5-tropic N332+ viral isolates present in plasma prior to ART initiation.

- To evaluate HIV-1 envelope diversity prior to initiation of ART in plasma and within the latent reservoir in ART suppressed individuals who initiated ART in acute (including hyperacute infection [Fiebig I & II]) versus chronic infection.

- To compare neutralization sensitivity to GS-9722 and other HIV-1 broadly neutralizing antibodies of replication competent reservoir virus isolates from ART suppressed individuals who initiated ART in acute versus chronic infection.

- To compare the size of latent reservoir in peripheral blood mononuclear cells (PBMCs) of individuals initiated on ART in acute versus chronic HIV-1 infection following long-term suppressive ART.

Study description

Background summary

Human immunodeficiency virus type-1 (HIV-1) causes a serious life threatening disease and remains one of the leading causes of morbidity and mortality worldwide. In the US, there are approximately 1 million people living with HIV infection, and globally over 36.7 million {Centers for Disease Control (CDC) , UNAIDS 2016}. Advances in combination antiretroviral therapy (cART) for HIV have led to significant improvements in morbidity and mortality by suppressing viral replication, preserving immunologic function, and averting disease progression to acquired immunodeficiency syndrome (AIDS). However, current therapeutic strategies have been unable to eliminate the virus and cure HIV-1 infection.

The life cycle of HIV-1 infection includes integration of viral DNA into host DNA in infected CD4+ T cells. Early in acute infection, a small pool of resting memory CD4+ T cells is established that contains integrated HIV-1 DNA {Chun 1997a, Chun 1995}. These latently HIV-1 infected cells establish a viral reservoir that persists despite treatment with highly active antiretroviral therapy (HAART) {Chun 1997b, Finzi 1997, Wong 1997}.

The reservoir of latently HIV-1 infected cells is long-lived with an estimated half-life of several decades {Siliciano 2003}. Eliminating the viral reservoir has been challenged by the inability to identify and target therapies against the reservoir. The reversal of latency may be achieved by inducing viral replication in resting reservoir cells, leading to expression of viral proteins on the cell surface, and targeting those cells for immune mediated clearance. HIV eradication efforts are now centered on a *kick and kill* strategy aimed at driving the virus out of latency, followed by rapid elimination of these infected cells by enhancing host immune functions. Antibodies that can recognize target cells expressing viral protein, and recruit effector cells, such as natural killer
(NK) cells and macrophages, could contribute to the *kill* portion of the *kick and kill* strategy.

Study objective

To determine the frequency of R5-tropic N332+ viral isolates present within the latent reservoir while on suppressive ART.

Study design

A Cross-sectional cohort study with no study drug administration. Study will include analysis of pre-ART baseline laboratory samples, and historical clinical and laboratory data.

Study burden and risks

Collecting a blood sample from a vein may cause pain, bruising,

lightheadedness, fainting, and very rarely, infection at the site of the needle stick.
Side effects that can occur during leukapheresis include: nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing (redness and warmness of the skin, usually the face), blood loss, and infection. Tingling of the lips, muscle cramping and, very rarely, changes in the heart rhythm can occur. Very rarely, clotting may occur in the apheresis machine or in a patient and is potentially life-threatening.

Participants will not have any direct benefit from participation in the study themselves, but the study will provide more insights in characteristics of HIV-1 virus. This information can be of importance for the development of future treatments.

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

• Ages >= 18 years of age
• Ability and willingness to provide informed consent
• Clinically stable on ART without changes in ARV status in the 24 weeks prior to screening. A change in ART >= 60 days prior to study visit for reasons other than virologic failure (eg, tolerability, simplification, drug-drug interaction profile) is allowed
• Plasma HIV-1 RNA plasma levels < 50 copies/mL at screening
• At least two documented HIV-1 RNA plasma levels < 50 copies/mL within the last 24 weeks (may include screening HIV-1 RNA plasma level). Results must come from a licensed assay with a lower limit of quantification of <50 copies/mL
o Unconfirmed virologic elevations of >= 50 copies/mL (transient detectable viremia, or *blip*) >= 12 weeks prior to screening are acceptable. If the lower limit of detection of the local HIV-1 RNA assay is <50 copies/mL, the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests
• Have an absolute neutrophil count >= 1500 cell/mm3, platelets >= 150,000/mm3; hemoglobin (Hgb) >= 11.5g/dL (females) or >= 13g/dL (Males)
• Have a creatinine clearance (CLcr) >=70 mL/min (>=90 mL/min for leukapharesis subjects only) (using the Cockcroft-Gault method {Cockcroft 1976} based on serum creatinine and actual body weight as measured at screening
• Ionized calcium level of >=1.1 mmol/L (4.4 mg/dL), serum Mg >= 1.6 mg/dL (for subjects undergoing leukapharesis only)
• Have liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin normal or below the upper limit of normal at screening
• Prothrombin Time (PT) < 1 × Upper Limit of Normal (ULN), International Normalized Ratio of prothrombin time (INR) <1.1 × ULN and Activated Partial Thromboplastin Time (APTT) < 1 × ULN
• Available documented baseline demographic and clinical data

Exclusion criteria

• Positive urine pregnancy test
• Subjects weighing less than 110 lbs
• Subjects who have donated more than 400 ml of blood within 56 days of Day 1
• For subjects undergoing leukapheresis, known allergic reactions to any component(s) of leukapheresis (e.g., citrate, heparin etc)
• History of opportunistic illness indicative of stage 3 HIV
• Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with subject assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders other than HIV-1 infection, active infection, or malignancy that are clinically

significant or requiring treatment.
• Have been treated with systemic steroids, immunosuppressant therapies, immunomodulatory therapies, chemotherapeutic agents within 3 months prior to enrollment.
• Acute or chronic bleeding disorder or use of blood thinners within 2 weeks of Day 1

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-04-2019
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO

Date:	25-03-2019
Application type:	First submission
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
CCMO	NL67528.078.18

Study results

Date completed: 01-02-2022

Results posted: 19-08-2020

First publication
02-06-2020