European Society for
TRANSLATIONAL ANTIVIRAL RESEARCH

ROSETTA

A global registry on second generation and long-acting integrase inhibitor failures

Protocol

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome, end-stage of HIV infection
BIC	Bictegravir, a second-generation integrase inhibitor
CAB	Cabotegravir, a second-generation integrase inhibitor
cART	combination antiretroviral therapy
CD4 cells	T lymphocytes expressing CD4. Target cells of HIV which are of major importance for the immune system.
CSF	Cerebrospinal fluid
DBS	Dried blood spot
DTG	Dolutegravir, a second-generation integrase inhibitor
EMA	European Medicines Agency
EMC	Erasmus Medical Center, Rotterdam
ESAR	European Society for translational Antiviral Research
EVG	Elvitegravir, a first-generation integrase inhibitor
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus. HIV is a retrovirus. This implies that HIV reverse transcribes its genetic material (RNA) into DNA and integrates this into the genome of target cells
INSTI	Integrase strand transfer inhibitors, a class of drugs used to inhibit replication of HIV.
LCMS	Liquid chromatography mass spectrometry
LIH	Luxembourg Institute of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor, a class of drugs which is used to inhibit replication of HIV
PI	Protease Inhibitor, a class of drug which is used to inhibit replication of HIV.
PPT	Polypurine tract
RAL	Raltegravir, a first-generation integrase inhibitor
RT	Reverse transcriptase
UMCU	University Medical Center Utrecht
Viral load	Quantification of HIV RNA in plasma (in copies (cp)/mL)
WHO	World Health Organization

1. Executive summary

Integrase strand transfer inhibitors (INSTI) are recommended in all treatment guidelines for first-line and second-line therapy of HIV infection. For the newer generation INSTIs dolutegravir (DTG), bictegravir (BIC) and cabotegravir (CAB) selection of known INSTI resistance mutations in integrase during virological failure is rare.

Therefore, the number of patients with virologic failure and selection of INSTI resistance mutations in single clinical trials is too low to obtain a clear insight in INSTI resistance patterns for these newer generation INSTIs. In addition, it is not clear if and to what extent mutations outside of integrase such as the 3'-polypurine tract (3'-PPT) cause resistance to INSTIs.

The resolution for this knowledge-gap is to set up a registry that systematically collects otherwise scattered information on individual patient cases failing newer generation INSTIs. The ROSETTA study collects high quality clinical data of cases of virological failure during ART combination with newer generation INSTIs.

2. Summary

Integrase strand transfer inhibitors (INSTI) inhibit HIV replication by preventing the integration of viral HIV DNA into the host's genome. INSTIs are used as part of combination antiretroviral therapy (cART) regimens for both treatment-naive and treatment experienced patients. Five, INSTIs have been approved so far for the treatment of HIV infection: first generation elvitegravir (EVG) and raltegravir (RAL), and second generation dolutegravir (DTG), bictegravir (BIC) and cabotegravir (CAB).

In clinical practice, virological failure to second generation INSTIs is rare and often without selection of known resistance mutations. Considering the use of INSTIs in first line regimens in high income countries and the increasing roll-out in lower and middle income countries, a better understanding of relevant resistance development and clinical failure is urgently needed.

The ROSETTA registry aims at systematically collecting otherwise scattered information on individual patient cases failing second generation integrase inhibitors, with the goal to inform policy and future use of INSTIs in the treatment of HIV infected patients.

Attending physicians of patients who are experiencing virological failure on a second generation integrase inhibitor-containing regimen are invited to contribute data to the registry. Genotypic resistance analyses of reverse transcriptase (RT), protease, integrase and on indication 3'-PPT will be performed. Results relevant for individual patient care will be reported back to the submitter. In selected cases full length HIV sequencing and phenotypic resistance analyses will be performed, providing additional funding can be assured. Submission of the data does not affect original ownership of data. Data of the registry will be published following the ESAR guidance for authorship.

3. Background

The majority of patients infected with HIV are treated with cART, a combination of two or more antiretroviral compounds. One of the drug classes used as part of cART are INSTIs. The HIV integrase enzyme faciliates a two-step insertion of HIV-DNA into the host genome. INSTIs specifically target the second step of this process by inhibiting strand transfer through competitive binding to the enzyme's active site. Five INSTIs have been approved to date: first generation elvitegravir (EVG) and raltegravir (RAL) and second generation dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB).

First generation INSTIs EVG and RAL are effective in the treatment of HIV and recommended as part of first-line therapy. However, these compounds have a low genetic barrier to resistance. Due to cross-resistance to these compounds, sequential use of RAL and EVG is not recommended [1].

DTG, BIC, and CAB were approved by the FDA for the treatment of HIV in 2013, 2018, and 2021 respectively. INSTIs in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) is one of the preferred treatment regimens recommended for HIV treatment-naive individuals in developed countries [2]. DTG combined with rilpivirine in a fixed dose combination (a dual-therapy regimen) has been studied as maintenance therapy [3] and was approved by the FDA and EMA. Monotherapy DTG was shown to be inferior in several cohorts due to the selection and replication of drug resistant viruses [4]. Use of DTG-based regimens in resource-limited settings has already been implemented in a few early adaptor countries as part of first-line cART. The treatment guidelines of the World Health Organization (WHO) for low and middle income countries have changed to recommending DTG based regimens as

first-line and second-line therapy for all HIV-infected patients. This change would result in widespread use of second generation INSTIs globally.

Various properties make second generation INSTIs attractive drugs for wide-scale use. They are highly efficacious, once daily single tablet regimens are available and they have a favorable safety profile with low potential for drug-drug interactions. Moreover, second generation INSTI have a high genetic barrier to resistance when used in combination therapy and transmission of resistance to INSTIs is currently negligible.

The genetic barrier to resistance for DTG is reported to be higher than for first-generation INSTIs. In clinical trials of DTG-containing cART in therapy-naive individuals, a decreased virological response was rare and selection of resistance in integrase was not observed [5,6]. In treatment-experienced but INSTI-naive individuals on DTG-containing cART, virologic failure with development of mutations associated to INSTI resistance was also rare [7]. The clinical trial investigating DTG (dosed twice daily) in patients with prior failure on first-generation INSTI, showed virological suppression in 69% at week 24 [8]. Various mutations that confer resistance to the first generation RAL an EVG have limited impact on DTG susceptibility. However certain mutations, in particular mutations at position Q148 in combination with ≥2 other mutations in integrase, resulted in a decreased virologic response, even when DTG was dosed twice daily.

Both BIC and CAB have shown outcomes that match the efficacy of DTG. In treatment-naive patients non-inferiority of BIC to DTG was shown and no known treatment-emergent INSTI resistance mutations were detected in those experiencing virologic failure [9,10]. CAB shares most of its structure with DTG. In the phase 2b LATTE clinical trial, in one patient receiving CAB and rilpivirine dual therapy the Q148R resistance mutation emerged during virologic failure [11]. The FLAIR study on the use of CAB and rilpivirine dual therapy in treatment-naive patients reported three patients with virologic failure and selection of INSTI resistance mutations (two patients with Q148R and one patient with G140R) [12]. Interestingly, the L74I polymorphism in integrase was present at baseline in these three patients. The role of the L74I polymorphism in virologic failure and selection of INSTI resistance mutations is currently unknown. The ATLAS study on the use of CAB and rilpivirine dual therapy in treatment-experienced patients reported one patient with virologic failure and detection of the N155H INSTI resistance mutation in integrase. The N155H mutation was not present at baseline, however it should be noted that this patient was previously treated with RAL [12].

BIC and CAB retain efficacy *in vitro* against HIV mutants harboring various resistance mutations in integrase [13]. Regarding the efficacy *in vivo*, there is still limited experience with BIC and CAB treatment in INSTI-experienced patients.

Although data are limited, dual therapy with DTG results in a high proportion of patients being virologically suppressed and if virological failure occurs, selection of mutations associated with resistance seems rare [14]. In contrast, DTG monotherapy is inferior to cART [4] and mutations were selected relatively frequently in the event of virological failure [15].

In clinical practice, virological failure during cART with DTG-containing regimens, although rare, is being observed for both naïve and INSTI pretreated patients, often without selection of known resistance mutations in integrase. This may point to alternative resistance pathways. Recent *in vitro* data showed that mutations in the 3'-polypurine tract (3'-PPT), a highly conserved region outside integrase, resulted in high level resistance to RAL, EVG and DTG [16]. Mutations in this region were also observed in one patient with virological failure during DTG maintenance monotherapy who had no resistance mutations in integrase [15]. The

mechanism of resistance is still unknown, but could be due to altering the substrate of integrase as 3'-PPT defines the terminal bases of the long terminal repeat [17].

For a better understanding of relevant resistance to the second generation INSTIs, systematic analysis of otherwise scattered information on individual patient cases of therapy failure is urgently needed. Detailled analysis of clinical information and assessment of genotypic resistance, will help to understand failure in individual cases and guide the choice of future therapy which is not available in all settings.

The ROSETTA study has been set up to address this need. It is a global registry that collects anonymized data on patients failing regimens containing second generation INSTIs. Within the primary clinical part of the study we offer genotypic resistance testing of RT, protease, integrase and 3'-PPT. to its submittors. In the secondary research part of the study we aim to determine the prevalence of resistance, to identify new mutations and determine their effect on susceptibility to current available INSTIs for all relevant subtypes.

The uniqueness of ROSETTA is that high-quality clinical data will be combined with genotypic and phenotypic data on a global scale. Detailed virological studies will be performed to analyze the role of viral subtype variation as well as alternative integrase resistance mechanisms.

4. Study aim and objectives

The aim of ROSETTA is to gain more insight in clinically relevant resistance to second generation INSTIs, which will allow to inform therapy guidelines and clinical interpretation algorithms. Detailled resistance data on pol (RT, protease, integrase) and 3'-PPT will be reported back to attending physicians.

4.1 Clinical objectives

1. To offer genotypic resistance testing and interpretation of pol and 3'-PPT for patients experiencing virological failure on a regimen containing a second generation INSTI

4.2 Research objectives

1. To set up a database with data of patients who have experienced virological failure on a regimen containing a second generation INSTI
2. To determine the prevalence of resistance mutations in integrase and 3'-PPT in the dataset
3. To identify possible new resistance mutations outside integrase and 3'-PPT. providing additional funding is retrieved.

5. Study design

5.1 Study design

The study design will be a multi-center observational cohort study. Patients will be included from HIV care centers in Europe, America and Africa, if they fullfill the inclusion criteria.

5.2 Duration of the study

Total duration of the project will be 3 years.

5.3 Expected Inclusions

We anticipate to include minimally 125 (a total of 250 in 2 years) patients per year. Based on an assumed virological failure rate of ~5%, 5000 patients would need to be treated to enable inclusion 250 patients experiencing virological failure in 2 years.

Over the total period of the study, we aim to include 33% of participants from Europe, 33% from America, and 33% from Africa. We aim for a balanced distribution between patients failing the different second generation inhibitors.

5.4 Study population

Patients are eligible for inclusion in the cohort, if they fullfill all of the following criteria:

- Confirmed HIV-1 infection
- Using cART (any regimen) for at least the last 6 months
- Experiencing virological failure* on a second generation INSTI-containing regimen (including monotherapy and dual-therapy regimens)
- Data on current regimen and previous INSTI exposure available (start/stop dates and dosing mandatory)
- Integrase genotypic data available (performed locally) or a plasma/DBS (or CSF if available) sample(s) drawn at time of failure available to perform genotypic testing centrally

* Virological failure is defined as at least 2 consecutive viral loads (VL) above 50 copies/mL in plasma or 1 VL above 200 copies/mL in plasma. We will also include patients who have a VL of >50 copies/mL in CSF, independent of the VL in plasma.

The study will include patients who are using INSTI as first-line therapy as well as previously therapy-experienced patients, including patients who have previously failed on integrase inhibitors.

Exclusion criteria:

- Submitted fasta file not passing quality control and unavailability of a stored sample to repeat sequence analysis
- Missing Mandatory data
- Documented treatment interruption for at least 2 weeks prior to viral load testing.

6. Methods and procedures

6.1 Inclusion

The attending physician of a patient who fullfills the inclusion criteria is invited to contribute their data, through the website of ESAR (www.esar-society.eu).

The coordination team will contact the attending physician, providing the necessary documents. Before data sharing, a data sharing agreement will be signed. Data can be submitted using an online data collection form, on a per-patient basis in the ROSETTA database. Access codes will be distributed on demand by one of our daily coordinators. Forms for batch uploading are available and can be requested.

6.2 Data collection

The collected data includes:

- Demographics (sex, birth year, route of infection)
- Treatment history
- Laboratory data (CD4 counts and viral loads)
- Sequence data (if available) or plasma/ DBS samples (if available)
- Drug levels during INSTI treatment, if available
- Follow up data if available

The full data collection form is available in Annex 1.

If there is a relevant change in the status (e.g. treatment) of patients who were already submitted to the database, then please contact the daily study coordinator for further steps.

6.3 Sample collection

Available samples (plasma and/or CSF and/or DBS) will be sent to the University Medical Center Utrecht (UMCU)/Erasmus MC (EMC). The daily coordinator will arrange the shipment. Samples of interest are those taken before start of the second generation INSTI and at time of virological failure.

The genotypic analyses will be performed at the UMCU/EMC. Both centers have extensive experience with genotypic analyses and participate in quality control programs to ensure good quality of sequence results.

For clinicians from centers who have genotypic testing available but are interested to participate in the research objectives only, shipment of viral RNA/DNA is also accepted.

6.4 Genotypic analysis

Genotypic resistance analyses will be performed for patients in whom this has not been performed locally. Genotypic analysis of RT, protease, integrase and 3'-PPT will be performed using Sanger sequencing. For genotypic analysis using a plasma sample, a volume of 200 µL is required if the viral load is above 1000 copies/mL. If the viral load is between 50 and 1000 copies/mL, a volume of 1 mL plasma is required. For genotypic analysis using DBS a minimal viral load of 1000 copies/mL is required.

For patients in whom genotypic analyses has been performed locally, fasta files of the sequences will be requested.

In individual cases, if HIV sequencing from plasma or DBS was unsuccesfull, PBMCs (if available) could also be used for proviral DNA sequencing.

Genotypic sequence files that have been generated by the data submitter will be checked for quality (e.g. length, ambiguity, stop codons) before entry in the ROSETTA database.

6.5 Full genome sequencing (this procedure will only be performed if additonal funding is secured)

In a subset of well defined cases, full genome sequencing will be performed. The following inclusion criteria must be fullfilled:

- Plasma sample (min. volume: 4 mL) with HIV-RNA levels ≥ 10,000 copies/mL, obtained during treatment with second generation INSTI available for full genome sequencing
- Plasma sample (min. volume: 4 mL) with HIV-RNA levels ≥ 10,000 copies/mL, obtained before start of second generation INSTI available for full genome sequencing

7. Data analysis

7.1 Clinical report

Results on individual cases from genotypic resistance analysis will be reported back to the clinician. Genotypic resistance test results will be accompanied by an interpretation using clinical interpretation algorithms and expert opinion, as is routinely done in current standard clinical care.

Questions regarding integrase resistance can be asked via the website of ESAR. All submitted questions will be circulated to an expert panel who will formulate an answer. Answers will be returned within one month by the study support team.

7.2 Prevalence of resistance mutations during failure

All sequences will be compared to reference sequences of the relevant subtype, available in Los Alamos public databases, to identify mutations. Preferably, sequences taken before therapy initiation and at time of virological failure will be compared to determine whether mutations were selected during failure on the specific second generation INSTI. The prevalence of all detected mutations will be reported.

8. Ethical considerations

8.1 Recruitment and consent

Data submitters are responsible for collection of the data with ethical approval according to their national regulations. By signing the data collection form, they confirm the applicable national procedure has been followed. Data submitters can contact the study support team to inquire whether previous submitters from their country have already set up the necessary ethical procedures.

The registry includes data that are already available from clinical records and uses samples that have already been drawn as part of routine clinical care. Additonal analyses i.e. full length HIV sequencing and phenotypic drug susceptibility analyses, will be performed on surplus plasma samples that have been obtained for routine patient care. No interventions

are included in this study and as such no risk or potential harm is anticipated. Results that are relevant for individual patient care will be reported to the submitter.

8.2 Data confidentiality

Patients are allocated a study ID, with which only the submitter can identify the patient. All data will be submitted to the database and stored using this study ID. In addition, only the year of birth and not the exact date will be recorded in the database. If samples are sent, these samples will be coded with the study ID only. Communication on individual cases will use this study ID.
Data will be stored on a secure server at the Luxembourg Institute of Health (Luxembourg). Database security has been previously assessed via external audits. Submitted datasets can only be accessed by the investigators and study coordinators. In addition, individual submitters can access, review and withdraw their submitted data at any time prior to analysis. ROSETTA does not give access to data, in whole or part, or any identifiable data derived from the data, to any third party without written consent from the data provider. After completion of the project and publication of the data, data submitters may request removal of their datasets from the database, providing storage of the removed datasets on their own secured server to enable to meet request of authorities or publication bodies.

9. Governance and guidelines for authorship

The ESAR ROSETTA database will contain all data submitted to the registry. Submission of data to the database does not affect original ownership of data. The owner of the data reserves the right to review or withdraw submitted data at any time prior to submission of the final manuscript. Permission of the submitters will be requested for any new analysis that is not described in the objectives of this protocol. ROSETTA encourages all her participants to publish their own data first.

Patient samples sent to the ROSETTA study group are allocated a study-specific sample number by the study coordinators. The study-specific sample number is linked to the patient data present in the ROSETTA database. The samples will be stored at the Erasmus MC and/or the UMC Utrecht until further analysis. After the project is completed the left-over samples will be destroyed or sent back to the submitter if requested. The owner of the sample has the right to request destruction of the sample at any time during the project.

Data of the registry will be published using the ESAR authorship guidelines.

10. Contribution of partners

10.1 European Society for translational Antiviral Research

The ROSETTA study will be coordinated in collaboration with the European Society for translational Antiviral Research (ESAR). One of the aims of ESAR is to unite scientists and clinicians throughout Europe to expand knowledge on viral drug resistance and to investigate the molecular epidemiology of drug-resistant viruses in Europe from public health and scientific perspectives. ESAR acts as a collaborative non-profit network for scientific studies, quality control, guidelines and training activities. In addition, ESAR has extensive experience in coordinating large studies like ROSETTA via the SPREAD Surveillance Program which collects data on transmission of drug-resistant HIV in Europe and via the HepCaRe study which collects data on patients failing hepatitis C virus treatment with direct-acting antivirals [19, 20].

10.2 Luxembourg Institute of Health

The ROSETTA database will be stored at a secure server of the Luxembourg Institute of Health (LIH). There is longstanding expertise regarding database management and data safety.

10.3 University Medical Center Utrecht

The following analyses will be performed at the UMCU:

- Genotypic resistance testing of RT, protease, integrase and 3'-PPT
- Full length HIV genome sequencing

10.4 Erasmus Medical Center

The following analyses will be performed at the EMC:

- Genotypic resistance testing of RT, protease, integrase and 3'-PPT
- Full length HIV genome sequencing

11. Structure of the collaboration

1. Monthly teleconference of the daily coordinators to discuss daily logistical issues.

2. Bimonthly meetings of the scientific committee to discuss analysis results and possibilities for in depth analyses.

3. Meetings with the funding partner to discuss progress and results of the analyses every six months. The funding partner can propose additional analyses on the available dataset.

12. PR and dissemination

12.1 PR

Information about the registry is available on the website of ESAR. This website also links to the webpage for online data submission.

At the start of the study, a newsletter will be send out to all members of ESAR to inform all members about the study. Furthermore, we will distribute flyers with information about the study and inclusion criteria, in major meetings and conferences. We will actively inform clinicians and researchers within our own network.

12.2 Dissemination

Results will be submitted to major HIV conferences, and finally submitted to peer-reviewed international journals.

Sequences generated within the study will be submitted to publicly available databases.

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