Defining the potency of DTG/3TC for suppressed HIV patients in real-life: the DUALING study.

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Sponsor : Erasmus MC

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2 Synopsis

Rationale	Dolutegravir (DTG) based dual antiretroviral therapy constitutes a paradigm shift from triple drug based therapy. Data outside clinical trials are scarce. This study evaluates the value of DTG/3TC in real life.
Primary objective	Determine real-life clinical efficacy of plasma HIVRNA suppressed patienst switching to DTG/3TC compared to DTG triple drug cART controls
Study design	Prospective cohort study
Study population	HIV patients, age 18 years or older with suppressed plasma HIV-RNA on triple drug based cART. Cases will switch to DTG/3TC. Controls will continue DTG based triple drug cART.
Duration of follow up	For the primary endpoint: 1 year. Total follow up is 5 years.
Target number of patients	Estimated at 2 groups of 480 HIV patients per group
Benefit and nature and extent of the burden and risks associated with participation	DTG/3TC is an approved first line regimen in the Netherlands. We will use DTG/3TC according to national guidelines and instructions in the SPC. Therefore, DUALING is not subject to the Medical Research involving Human Subjects Act law (WMO), thus legally exempted from having to obtain IRB approval. There is no risk for study participation. Patients might benefit from being treated with 2 instead of 3 drugs by having less side effects.

3 Investigators and study administrative structure

Responsibility	**Name**
Sponsor	Erasmus MC
Principal Investigator	Casper Rokx and Bart Rijnders
Co-investigators	Charles Boucher (prof. virology) Carlijn Jordans (PhD candidate) Rosanne Verwijs (PhD candidate) Henrieke Prins (PhD candidate) Grigorios Papageorgiou (statistician) Collaborators from the ATHENA cohort
Subsiding party	ViiV ISS grant DTG/3TC data gaps Contact: Reon van Dyk
Study sites:	1. Erasmus MC, University Hospital, Rotterdam 2. Maasstad Hospital Rotterdam 3. MC Haaglanden The Hague 4. Catharina Ziekenhuis Eindhoven 5. Elisabeth Ziekenhuis Tilburg 6. Rijnstate Hospital Arnhem 7. Admiraal de Ruyter Ziekenhuis Goes 8. Spaarne gasthuis, Haarlem 9. MST, Twente

4 Introduction and rationale

For more than 20 years, the standard of care treatment for an HIV-1 infection has been a combination of 2 nucleoside reverse transcriptase inhibitors (NRTI) and a third drug with a different mode of action. Indeed, studies in the eighties and nineties showed that regimens containing only 1 or 2 drugs were associated with an unacceptably high incidence of virological failure. This was the result of the low genetic barrier against resistance of the antiviral drugs available at that time. After studies in the nineties showed that 3-drug regimens (known as combination antiretroviral regimen, cART) were able to induce prolonged viral suppression, they became the standard of care[1,2]. Over the last 5 years this 3-drug dogma was rejected when it became clear that duo-therapy consisting of a protease inhibitor (PI) and lamivudine was as effective as conventional cART[3,4]. The cornerstone of this duo-therapy is the high genetic barrier against resistance of the PI. However, because the PIs available today have important side effects as well as several drug-drug interactions, these 2-drug regimens are used infrequently. With the introduction of dolutegravir (DTG) as a second-generation integrase inhibitor (INI) in the Netherlands as of 2014 a new compound with a high genetic barrier against resistance became available but without the limitations of a PI. This high genetic barrier against resistance was confirmed in clinical trials and in post-marketing studies with DTG containing cART[5]. Indeed, no dolutegravir resistance developed in any of the 1067 treatment naïve patients treated with DTG containing cART in the phase III registration trials[6-8]. These observations led to the hypothesis that a combination of DTG with lamivudine (3TC) alone would be equally effective as a conventional cART regimen consisting of DTG plus two NRTIs. To test this hypothesis the GEMINI-1 and 2, the TANGO and more recently the SIMPLE'HIV studies were designed[9-11]. All 4 studies confirmed the non-inferiority of DTG plus 3TC or emtricitabine (a drug with a mode of action very similar to 3TC) to DTG plus 2 NRTIs. Furthermore, important subgroup analyses regarding low-level viremia could not detect different outcomes in patients on DTG + 3TC versus those on DTG plus 2 NRTIs. These findings on DTG/3TC duo-therapy led to the incorporation of DTG/3TC in the November 2019 version of the EACS guideline and in the December 2019 version of the American DHHS guidelines as one of the recommended treatment options.

The findings on DTG/3TC duo-therapy also support the notion that for a substantial number of patients on conventional cART, the continued exposure to a third antiretroviral agent is unnecessary. Moreover, given the associated potential toxicities of the third agent it can be considered potentially harmful. However, because until very recently, DTG and 3TC were only available as separate pills but DTG in combination with 3TC and abacavir (ABC) was available as one combination tablet, a switch to DTG/3TC from DTG/3TC/ABC would mean an increase of the pill burden from 1 to 2 pills. As the latter may decrease compliance, this was considered a disadvantage. As of October 2019, DTG/3TC became available as a combination tablet as well. Therefore, the argument of an increased pill burden is now no longer relevant either.

For all the reasons mentioned above, we and colleagues from other HIV treatment centers in the Netherlands have started switching patients from a 3-drug cART regimen to DTG/3TC. This will allow us to prospectively collect real-life data on the efficacy of DTG/3TC compared with conventional DTG containing cART. The PI's of this study lead the established Erasmus MC clinical HIV research unit with a multicenter trial network and have successfully conducted large clinical studies.(e.g. FTC/3TC CID 2015, DOMONO LANCET 2017, DAHHS LANCET 2018, VTE in HIV LANCET 2019 and PLoS Med 2020). The Netherlands has a unique infrastructure for prospective cohort studies, enabled through the ATHENA cohort coordinated by the Dutch HIV Monitoring Foundation. In it, over 98% of *all* HIV patients in care are included. In the ATHENA cohort, data are registered from the day of entry into HIV care in one of the 25 treatment centers and include data regarding genotypic resistance tests and subtypes. As long as these patients receive HIV care in the Netherlands, data are collected, even if patients move to another location within the Netherlands. Therefore, data over several years of follow-up are readily available. Given the multicenter design of our proposal and the size of the intended study population, we consider it to be a good representation of the full Dutch HIV cohort.

The primary purpose of the study described below therefore is to collect data on the efficacy of a switch to DTG/3TC duo-therapy in a real life setting within the well-organized HIV care and ATHENA cohort infrastructure of our centers in the Netherlands.

5 Study objectives

Primary objective

- Determine real-life clinical efficacy of virally suppressed patienst switching to DTG/3TC compared to DTG triple drug cART controls

Secondary objectives

- Evaluate differences in time to treatment failure, switches for AE, LLV rates, blips, and emerging mutations associated with resistance in virally suppressed patienst switching to DTG/3TC compared to DTG triple drug cART controls
- Evaluate differences in proportion and time to treatment failure, switches for AE, LLV rates, blips, and emerging mutations associated resistance in virally suppressed patienst switching to DTG/3TC compared to non-DTG containing triple drug cART controls.
- Evaluate clinical efficacy in DTG/3TC switchers vs controls in relevant subgroups according to sex, ethnicity, pre-cART CD4 nadir/HIVRNA zenith/CD4-CD8 ratio, duration of suppressive cART, previous RAMs, and previous documented virological failure or inadherence.

6 Study design

The study is designed as a 5 year prospective cohort study. Cases are HIV infected patients on triple drug based cART and are in routine care in the 9 participating centers. Switches to DTG/3TC are decided on by the treating physician and according to current guidelines. Matching controls on triple drug DTG based cART will be selected from other centres in the ATHENA cohort. For secondary objective nr2, to determine the treatment efficacy in all switchers to DTG/3TC from non-DTG INSTI basedtriple drug based cART, similar matching strategies but then selecting for non-DTG +2NRTI controls will be followed (if possible due to numbers).

Since the study is on the implementation of national guidelines in real-life, no separate informed consent is necessary.

7 Study population

To be eligible as case in the study, plasma HIVRNA must be <50c/mL on triple drug cART containing 2NRTI at switch to DTG/3TC and no key mutations associated with major 3TC (i.e. M184V/I only) or DTG resistance of at least low level according to the Stanford HIV drug resistance database should be present. Patients with no genotyping results available at baseline will be eligible for inclusion in this study. Cases should not have documented inadherence in the preceding 3 months or HepB coinfections. These data on adherence and HepB is routinely collected at switching to DTG/3TC.

For the primary analysis, patients eligible as controls have plasma HIVRNA <50 on DTG+2NRTI, will continue this regimen, and do not have documented key mutations associated with major DTG/3TC resistance according to the Stanford HIV drug resistance database. For each case, 1 but if possible 2 controls will be identified. Controls included in ATHENA at dates closest to DTG/3TC (Dovato) EMA approval of 01 Jul 2019 will be used. For the secondary analysis of treatment efficacy in all switchers to DTG/3TC from non-DTG triple drug based cART, similar matching strategies (if numbers allow) but then selecting for non-DTG +2NRTI controls will be followed.

Cases and controls will be 1:2 matched on sex, HIV risk group (MSM vs non-MSM), CD4 T-cell nadir </>200 cells/mm3, and HIVRNA zenith </>100.000 c/mL. If matching by these criteria is suboptimal to find suitable controls, we will alter the criteria for matching in discussion with a statistician and VH.

7.1.1 Inclusion criteria

- Plasma HIVRNA <50c/mL on triple drug cART regimen including 2NRTI
- In care in a HIV treatment center in the Netherlands
- Consented to ATHENA participation

7.1.2 Exclusion criteria

- Documented mutations associated with 3TC or DTG resistance of at least low level
- Documented inadherence by the treating physician or HepB coinfection (cases only)

8 Treatment

No intervention is done in this study. Patients will remain in routine care and the choice on cART is done by the treating physician.

9 Study procedures

Patients who switch to DTG/3TC will be followed up with HIVRNA measured in plasma after 3 months, and 6-monthly thereafter conform HIV care in the Netherlands. Plasma HIVRNA is measured by routine validated RT-qPCR procedures with quantitative limits of detection at 20c/mL or 50c/mL. Sanger sequencing upon virological failure is conducted in routine care if indicated by the treating physician and with sufficiently high plasma HIV-RNA. Patients in the Netherlands who are virologically suppressed and remain stably on their cART are typically seen with plasma HIVRNA measured at the outpatient clinic twice a year (so every 26 weeks). Routinely acquired data through clinical visits on baseline variables, side effects and laboratory data (CD4, HIVRNA, mutations before cART initiation) will be obtained through ATHENA. A detectable plasma HIVRNA above cutoff for cases and controls will be followed up according to usual care. If available and clinically or research indicated, we can assess the presence of a pre-cART sample to evaluate for baseline resistance associated mutations if not yet known. Clinical research coordinators will collect the data for cases. The data of controls will be derived from the ATHENA database.

Routinely collected switches due to side effects and deaths are registered. A yearly study report on the number of patients in the study will be generated.

10 Withdrawal of patients or premature termination of the study

Controls who switch to DTG/3TC during follow-up will be censored for the primary endpoint analysis. Patients who retract their consent for ATHENA will be withdrawn from the analysis. We will end the study prematurely should the number of patients during follow up become too small for meaningfull analyses. This can be decided on by agreement of the 2 main coordinating PIs (Rijnders/Rokx).

Since this is not an interventional study, no legal obligation is present for METC approval or to inform the sponsor (Erasmus MC) regarding SAE, deaths or premature study termination. However, through ATHENA, all patients have provided consent for the use of their data for this study.

11 Safety

Not applicable. DTG/3TC is an approved treatment for HIV infections. Standard safety regulations according to routine care are in place including monitoring for adverse drug reactions within routine care which are the responsibility of the treating physician.

12 AEs and SAEs

Adverse events (AE) collected in this study are related to the antiretroviral medication and are defined as any undesirable experience occurring to a subject due to cART. We will collect significant AEs resulting in therapy switches in all patients. SAEs are untoward medical occurrences or effects related to the cART and resulting in death or therapy switch due to life threatening events, hospitalization, significant disability or incapacity, congenital anomaly or birth defects. In addition, any other important medical event can be an SAE that did not result in any of these outcomes but could have been based upon judgement by the PI and led to a therapy switch. All AE and SAEs are followed up in routine care and under the responsibility of the treating physician.

The sponsor should report to ViiV, as Individual Case Safety Reports (ICSRs) all SAEs and pregnancy exposures either disclosed by study subjects or identified from review of the Medical Records, which are considered causally related to a known ViiV product regardless of expectedness, and where the specific diagnosis is known (e.g. depression rather than an unspecified psychiatric disorder), within 24 hours of the diagnosis being identified. Similarly, non-serious AEs considered causally related to a known ViiV product, and where the specific diagnosis is known need to be reported to ViiV within 5 days of the diagnosis being identified.

In addition to a known ViiV product, and the specific diagnosis and a narrative describing the event, the following minimal information must be available to the sponsor to be reportable to ViiV: Identifiable patient (i.e. age group and gender) and Identifiable reporter.

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Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable. In case of any unexpected emerging safety issue with DTG/3TC or triple drug cART (e.g from a peer reviewed publication, altered guidelines, or black box warnings), the main coordinating PIs (Rijnders/Rokx) will decide on further study conduct.

13 Endpoints

Treatment failure is defined as having 2x plasma HIV-RNA >50 c/mL consecutively on the same regimen. Lost to follow up (LFU) is defined as having no plasma HIVRNA measurement for more than 52 weeks (so missing more than 1 visit)

The OT population is defined as all patients who fulfilled the inclusion criteria and who switched to DTG/3TC (cases) and the patients who remained on 3-drug cART who were matched to the cases (controls). Patients who die, are LFU or patients who switch to another cART regimen while the last observed viral load was <=50c/ml will not be considered treatment failures in the OT population. Patients who die, are LFU, or switch to another regimen while last HIVRNA >50 are considered treatment failures.

The ITT population is defined as all patients who fulfilled the inclusion criteria and who switched to DTG/3TC (cases) and the patients who remained on 3-drug based cART who were matched to the

cases (controls). Patients who die, are LFU, or who switch to another regimen are considered treatment failures. The only exception being a switch from 3drug cART to DTG/3TC. These patients will be censored for the analysis.

Primary endpoint

- Proportion of subjects with treatment failure in the DTG/3TC versus 3-drug DTG containing cART group up to 1 year of follow up in the OT population.
- Proportion of subjects with treatment failure in the DTG/3TC versus 3-drug DTG containing cART group up to 1 year of follow up in the ITT population.

Secondary endpoints

1. Proportion of subjects with treatment failure in the DTG/3TC versus 3-drug DTG containing cART group after 2 and 5 year of follow up in the OT and ITT population.
2. Proportion of subjects with treatment failure in the DTG/3TC versus 3-drug cART overall, and according to INSTI/PI/NNRTI (non-DTG) subgroups, after 1, 2 and 5 year of follow up in the OT and ITT population.
3. Time to treatment failure in the DTG/3TC versus 3-drug DTG containing cART group and 3drug cART overall (including according to INSTI/PI/NNRTI (non-DTG) subgroups) according to the ITT and the OT population during 1, 2 and 5 years of follow up.
4. Proportion of plasma viral load measurements above the limit of detection of the PCR but <50 (between 20 and 50 c/mL), proportion of viral blips of HIVRNA >50 once with plasma HIVRNA measured <=50 c/mL before and after, proportion of plasma HIVRNA >200 and >1000c/mL on DTG/3TC versus 3-drug DTG containing cART group and 3drug cART overall and according to INSTI/PI/NNRTI (non-DTG) subgroups.
5. Proportion of patients with emergent mutations associated with resistance to DTG, 3TC or the third antiviral agent in cases versus controls. RAMs will be described.
6. Predictor variables for treatment failure in the DTG/3TC, 3-drug (non) DTG containing cART group and 3drug cART overall at the 1, 2, and 5 years of follow up in the OT and ITT population according to 1) sex, 2) ethnicity (Caucasian, African, other), 3) CD4+Tcell nadir, 4) HIVRNA zenith, duration of suppressive cART (</>1year and </>5 year), 5) presence of mutations, 6) CD4/CD8 ratio nadir 7) documented history in ATHENA database of virological failure (without selection of M184VI or major DTG related RAMs) or inadherence.

Anticipated exploratory analysis

1. Analysis of the secondary endpoints at the 3 and 4 year timepoints of follow up.
2. Proportion of subjects with switches due to side effects in the DTG/3TC versus 3-drug (non) DTG containing cART group and 3drug cART overall after 1, 2, 3, 4 and 5 years of follow up
3. Cost-effectiveness analysis of the switch from triple cART to DTG/3TC.

14 Statistical considerations

Patient numbers and power considerations

Over 20.000 HIV patients are in care in the Netherlands of whom over 98% has consented to ATHENA with data collection approved from routine clinical care for study purposes. Together, the participating centers have approximately 8000 HIV patients in care for the cases. As for controls, they can be recruited from one of the 16 other HIV centers in the Netherlands, who have HIV-RNA<50c/mL on triple drug based cART including 2NRTI.

Cases will be matched using propensity score matching to a 1:2 ratio of cases to controls by the following variables: sex, HIV risk group (MSM or non-MSM), nadir CD4+T-cell count (<or>200 cells/mm^3) and zenith plasma HIV-RNA before cART initiation (<or>100.000 c/mL) and absence of M184VI or major DTG RAMs. If by unlikely chance strong statistical objections arise against 1:2 matching or matching criteria, we will alter matching e.g. to 1:1 matching after consultation with statistician and VH.

Sample Size and Power Considerations

The minimum number of patients on DTG/3TC included in the study is 480. We aim for 90% power, using an anticipated undetectable loads rate of 0.95 (95%) in both the control and active groups in both the ITT and the OT population, with a control to intervention ratio of 2:1 and a non-inferiority margin $\delta = 0.05$, the sample size for the active arm needs to be 480 with a one-sided alpha level of 0.025 (because of the 2 primary endpoints) . To account for potential variability introduced by propensity score matching we also conducted a simulation based approach to explore the impact of different scenarios regarding the magnitude of the intra-class correlation (ratio of between-matched groups variance to total variance). We assumed three scenarios for the intra-class correlation that correspond to 1) none, 2) slight, 3) moderate, 4) high. We anticipate that the estimated ICC is 0.2. The table below shows how the power is affected by ICC We believe the maximum ICC expected to be observed is ~0.6 so the maximum planned sample size to retain at least 90% power in this scenario is 700 patients on DTG/3TC in this study. This supports doing exploratory analysis including for resistance, and efficacy of DTG /3TC compared to non-DTG triple cART drug regimens. Also, this accounts to retain power of 90% should unexpectedly a higher ICC be observed.

	ICC = 0 (none)	ICC = 0.1 (mild)	ICC = 0.2 (moderate)	ICC = 0.6 (high)
90% power	N=300	N=390	N=480	N=700

Power and sample size calculations were done with R (version 3.6.3).

Given the epidemic in the Netherlands as explained above, these sample sizes are all considered feasible.

Covariates and study outcomes

We will use routinely collected data (e.g. sex, age at switch, cART history) for the baseline descriptives table and matching as explained above. The main study outcome will be the proportion with treatment failure in the ITT and OT population. We will report on relevant subset analyses as secondary study outcomes as defined in the endpoints.

Statistical analysis plan

We will report continuous data as means with standard deviation or medians with interquartile range, dependent on their distribution per group. Categorical data will be reported as percentages. We will use the independent T test, Mann-Whitney U test and Chi-square test for continuous and categorical baseline data between cases and controls, as is appropriate to the distribution of the data. Analyses will be done in collaboration with a statistician.

For the primary endpoint, a binomial logistic regression model will be used for the analysis of proportion of treatment failure for both the ITT and OT populations. Treatment center will be included as random effect. The logistic regression models for each population will include the propensity score variable to correct for the variables used for propensity score matching (see below). A binary variable indicating cases or controls will be included in the models. A 1-sided Wald test will then be used to compare the cases receiving duo-therapy with the controls. A Bonferroni correction will be applied to adjust for the fact that two primary endpoints are being analyzed in order to retain the global alpha

significance level at 5%. Cases will be matched using propensity score matching to a 1:1 or 1:2 ratio of cases to controls by the following variables: sex, HIV risk group (MSM or non-MSM), nadir CD4+T-cell count (<or>200 cells/mm^3) and zenith plasma HIV-RNA before cART initiation (<or>100.000 c/mL).

Secondary endpoint 1 will be analysed by binomial logistic regression models DTG/3TC versus 3-drug DTG containing cART group for the analysis of proportion of treatment failure at years 2 and 5 for both the ITT and OT populations.

Secondary endpoint 2 on proportion of treatment failure in DTG/3TC cases versus 3drug cART overall, and non-DTG cART, controls will be analysed by binomial logistic regression models for both the ITT and OT populations. Subgroup analysis on INSTI, bPI and NNRTI will be described.

Secondary endpoint 3 on time to treatment failure DTG/3TC versus 3-drug DTG containing cART group and 3drug cART overall, and non-DTG cART, will be analysed by restricted mean survival time (RMST) using the area under the survival curve over a 1, 2 and 5 year follow up between cases and controls in the ITT and OT populations.

Secondary endpoint 4 on the number and proportion of measureable viral loads will be as proportions of plasma viral load measurements above the quantitative limit of detection of the PCR (between 20 and 50 c/mL), proportion >200 and >1000, and viral blips (>50 with <50 before and after) of all available plasma viral load measurements in cases vs controls as per the defined groups (3 drug DTG containing cART, 3drug cART overall, 3 drug non-DTG containing cART)

Secondary endpoint 5 on the emergence of mutations associated with resistance will be analysed as the proportions of patients (number of patients with mutations associated with resistance to DTG, 3TC or third antiretroviral agent divided by total number of patients) for both the case and the control group. Subgroups of resistance associated mutations will be described.

For secondary endpoint 6, proportion of treatment failure will be compared between cases and controls as per the defined groups (DTG/3TC, 3 drug DTG containing cART, 3drug cART overall, 3 drug non-DTG containing cART) in the OT and ITT population at 1, 2 and 5 years follow up, using logistic regression models, stratified by known clinical determinants of virological failure, such as pre-cART CD4+ T-cellcount, HIV-RNA zenith and duration of suppressive cART, previous RAMs, or history of documented virological failure or inadherence in SHM.

Interim efficacy and safety analysis

See above.

Stopping rules

In case of any unexpected emerging safety issue with DTG/3TC or triple drug cART (e.g peer reviewed publication, altered guidelines, or black box warnings), the main coordinating PIs (Rijnders/Rokx) will decide on further study conduct.

15 Registration and randomization

Regulatory documentation

DUALING is not subject to the Medical Research involving Human Subjects Act law (WMO), thus legally exempted from having to obtain IRB approval. Decisions to switch are done in routine care

between HIV treating physician and patient, and conducted within existing guidelines. This data can be used in all cases for research unless patients explicitly state that they do not want that.

Registration

Eligible patients are identified through the hospital's electronic patient files and unique ATHENA cohort M-numbers.

16 Data collection and quality assurance

Case Report Forms

Data will be collected through case report forms (CRF) within the ATHENA infrastructure to document eligibility, safety and efficacy parameters, and other parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- Inclusion and exclusion criteria;
- Baseline status of patient including documented RAMs, CD4 T-cell and HIVRNA;
- Any other parameters necessary to evaluate the study endpoints;
- Documentation from ATHENA regarding survival status of patient, LFU, adherence and medication switches;

Data quality assurance

The ATHENA cohort is a longstanding high-quality cohort that is continuously monitored by trained monitors on site. Data checks are done by the ATHENA headquarters to further improve data quality. Furthermore, the investigators will check the data of those who switch to DTG/3TC by CRF. If necessary, queries can be sent to the investigational site to clarify the data on the CRF.

Monitoring

Not applicable.

Audits and inspections

Not applicable. All data will however be stored on encrypted internal hard drives at Erasmus MC with password protected backups. In addition, the routine data protection from ATHENA infrastructure is in place.

17 Ethics

Accredited Ethics Committee

DUALING is not subject to the Medical Research involving Human Subjects Act law (WMO), thus legally exempted from having to obtain IRB approval. Decisions to switch are done in routine care between HIV treating physician and patient, and conducted within existing guidelines. This data can be used in all cases for research unless patients explicitly state that they do not want that.

Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the applicable regulatory requirements in the Netherlands for non-WMO research.

Patient information and consent

Since this is non-WMO research, no separate written informed consent is necessary. Data collected within routine care can be used for research unless patients have explicitly stated that they do not want that.

Benefits and risks assessment.

DTG/3TC is an approved first line regimen in the Netherlands. We will use DTG/3TC according to national guidelines and instructions in the SPC. Therefore, there is no risk for study participation. Patients might benefit from being treated with 2 instead of 3 drugs by having less side effects.

18 Administrative aspects and publication

Handling and storage of data and documents

Data and documents will be controlled and processed conform the EU General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG).

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number by ATHENA (M-number). In study documents the patient's identity is coded by patient study number as assigned at entry in care in the Netherlands.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a study and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies). This is not applicable to non-WMO research. However, we will file all essential documents relevant to the conduct of the study in the investigator site file. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

The data of patients are generated in routine care and stored within ATHENA. The data is therefore retained after the study ends.

18.1.4 Storage and sharing of data

Encoded data may be shared with other study groups for research purposes. If data are sent to countries outside de EU, patients confidentiality will be ensured at an equal level of EU regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

18.1.5 Storage of samples

Not applicable.

18.1.6 Amendments

Not applicable since no IRB approval is necessary. Future developments with respect to unexpected limitations in the data of relevance for the study conduct or outcomes can lead to necessary alterations in the protocol. We will inform the subsiding party of these developments, if this happens.

Annual progress report

We will evaluate the number of patients in the study on a yearly basis.

Temporary halt and (prematurely) end of study report

See above.

Publication policy

Study results will always be submitted for publication in a peer reviewed scientific journal and/or abstract to conference regardless of the outcome of the study – unless the study was terminated prematurely and did not yield sufficient data for a publication.

19 STRUCTURED RISK ANALYSIS

Not applicable for non-WMO research.

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