

# Viral load Guided Immunosuppression after Lung Transplantation (VIGILung) – study protocol for a randomized controlled trial

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## Study protocol

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# Abstract

## Background:

Immunosuppression including high dose calcineurin-inhibitors (CNI) is essential after lung transplantation. Dosing is usually guided by therapeutic drug monitoring adjusted to target trough levels of CNIs to keep the balance between over-dose causing severe toxicity and increased risk of infections or under-dose with risk of graft-injury.

Adaptation of CNI-based immunosuppression by monitoring of Torque-Teno-Virus (TTV) – a latent nonpathogenic DNA virus, measured in whole blood in addition to conventional therapeutic drug monitoring may reduce toxicity of immunosuppression with similar efficacy.

## Methods/Design:

An open-label, randomized, controlled, parallel-group, multicenter trial in lung transplant recipients will be conducted to investigate the safety and efficacy of immunosuppression guided by TTV monitoring as add-on to conventional therapeutic drug monitoring. Adult lung transplant recipients 21 - 42 days after transplantation are eligible to participate. Patients (N = 144) will be randomized 1:1 to the experimental intervention (Arm 1: Immunosuppression guided by TTV monitoring in addition to conventional therapeutic drug monitoring of tacrolimus trough levels) and control intervention (Arm 2: conventional therapeutic drug monitoring). Outcomes will be assessed 12 months after randomization with the change in glomerular filtration rate as the primary endpoint. Secondary endpoints will be additional measurements on renal function, allograft function, incidence of acute rejections, incidence of chronic lung allograft dysfunction, graft loss and infections.

## Discussion:

The results of this randomized controlled trial may reduce toxicity of immunosuppression after lung transplantation while maintaining efficacy of immunosuppression. Study results are transferable to all other solid organ transplantations.

Trial registration: ClinicalTrials.gov, NCT04198506. Registered 12 December 2019, <https://www.clinicaltrials.gov/show/NCT04198506>

# Background

High dose immunosuppression containing calcineurin-inhibitors (CNI) is essential after lung-transplantation. Dosing is usually guided by fixed target levels, established to keep the balance between over-dose causing toxicity and increased risk of infections or under-dose with risk of graft-injury.

Therapeutic drug monitoring represents the current gold standard of guiding immunosuppression after solid organ transplantation (1). Despite rigorous monitoring, acute rejection occurs in app. one third of

patients in the first year after lung transplantation (2). Immunosuppressive regimens are responsible for considerable toxicity. Approximately 24% of the recipients will develop kidney failure within one year of transplantation and 2% end stage kidney disease. Increased infection rates are associated with over-immunosuppression and infections are the leading cause of death during the first postoperative year.

Clinical experience suggests that individual tailoring of immunosuppression could potentially optimize patient outcome (3-6). Reliable, reproducible, cost effective and non-invasive biomarkers are needed to reduce the risk of graft injury and toxicity to guide immunosuppression.

Certain DNA-viruses in whole blood (e.g Torque-Teno-Virus - TTV) are detectable in the vast majority of lung transplant recipients (3). Load of these latent viruses was used as a surrogate biomarker of cell-mediated immunity (load increasing with the strength of immunosuppression) (7).

DNA-viruses in whole blood (Torque-Teno-Virus/TTV, HHV-6, EBV) and urine (BK Virus) can be detected in the majority of humans including transplant recipients. Some of them do not cause symptoms of infection, for example TTV. Viral load of TTV was used as a surrogate biomarker of cell-mediated immunity (load increasing with the strength of immunosuppression) but has never been studied in a prospective trial. It is suggested by pivotal studies (3) that CNI based immunosuppression may be reduced in the majority of lung transplant recipients during the first postoperative year.

Guiding immunosuppression by an immune response assay in a prospective trial resulted in reductions in CNI doses of 13%-25% within the first year after liver transplantation, with documented reductions in bacterial and fungal infections (6). In lung transplant recipients, a CNI reduction of 50% has led to an improvement of GFR (CKD-EPI) by 10 ml/min/1.73 m<sup>2</sup> after 12 months in a recent randomized trial (8). With the management of trough levels by TTV load it is expected that a similar CNI dose reduction can be achieved.

The results of the VIGILung trial may have an impact on therapeutic strategies for patients after lung transplantation. Study results may be transferable to all other solid organ transplantations.

## **Methods/design**

### *Objectives*

The aim of this randomized controlled trial is the prospective investigation of the safety and efficacy of an individual adaptation of the tacrolimus-based immunosuppression by a non-invasive biomarker (Torque-Teno-Virus (TTV) load in whole blood).

The primary endpoint will be  $\Delta$ -glomerular filtration rate (GFR) defined as the change of the glomerular filtration rate GFR between randomization and 12 months thereafter as indicator for toxicity. GFR will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (9).

Secondary outcomes include further parameters on renal function, parameters regarding lung allograft function forced expiratory volume in 1 second (FEV1) in % of baseline, incidence of acute rejections, lymphocytic bronchiolitis and/or chronic lung allograft dysfunction, re-transplantation or death due to graft failure), infections (Cytomegalovirus (CMV), community acquired respiratory viruses (CARV), fungal or bacterial infections), incidence of unscheduled emergency hospitalizations or admissions for intensive care unit (ICU), quality of life questionnaire (EQ-5D) and exercise capacity, the state of immune-system (cluster of differentiation 4 (CD4)-lymphocytes, donor specific antibodies (DSA), IgG-level and use of rescue immune therapy), and details on the tacrolimus immunosuppression (tacrolimus trough levels, tacrolimus doses and number of adjustment of immunosuppression).

## **Design and participants**

The screening of the patients will be performed in two participating study sites (Hannover Medical School and University of Vienna). We assume that screening of 250 patients will result in 144 subjects eligible for the study. The recruitment period is expected to be 39 months.

Selected in- and exclusion criteria:

### Inclusion criteria

- adult patients 21 to 42 days after de novo lung transplantation (bilateral or combined)
- tacrolimus based immunosuppression
- detectable TTV load at randomization ( $>2.7 \log_{10}$  copies/mL)
- women of childbearing potential: negative serum pregnancy test and highly effective methods of contraception throughout the study.

### Exclusion criteria

- history or high-risk of obstructive airway complications after lung transplantation
- respiratory failure (need for oxygen therapy or ventilation at screening) inability to undergo transbronchial biopsy
- advanced kidney failure (GFR CKD-EPI  $<30$  ml/min/1.73m<sup>2</sup> at inclusion and/or current renal replacement therapy at inclusion or randomization)
- advanced liver cirrhosis (CHILD-Pugh Score C) after lung transplantation
- fluctuating tacrolimus drug levels (less than 20% in target range after transplantation)
- symptoms of significant mental illness with inability to cooperate or communicate with the investigator.
- unlikeliness to comply with the study requirements
- HIV positivity

## **Randomization**

Randomization will be performed centrally by the Center for Clinical Trials of the Philipps-University Marburg for patients matching all eligibility criteria and will be stratified by high-risk CMV-status (D+R-) (yes/no) and center using random permuted blocks. The chance for allocation to the control and experimental group is 1:1.

## **Trial Intervention and control**

After lung transplantation (day 0), all patients will receive a standard tacrolimus-based triple immunosuppressive regime (tacrolimus, prednisolone and a cell-cycle inhibitor (depending on induction therapy with alemtuzumab)). Tacrolimus based immunosuppressive protocols represent the standard of care worldwide (2) and were therefore chosen as the comparator. Inclusion and screening will occur 21 to 42 days after lung transplantation, a further screening-visit will occur 4 weeks later, especially to evaluate achievement of a sufficient TTV-level.

## **Follow-up protocol**

At Visit 3 patients will be assigned to one of the two treatment groups detailed in Figure 1.

Study visits will be performed at month 1, 2 and 3 after transplantation and at month 3, 6, 9 and 12 after randomization. The final examination will be performed at month 12 after randomization or in case of a premature end of study treatment.

In both treatment arms, during maintenance immunosuppression temporary interruption of cell cycle inhibitors will be allowed e.g. in case of cell cycle inhibitors induce severe toxicity (e.g. leukopenia <4,000/ $\mu$ l, thrombocytopenia <50,000/ $\mu$ l, anemia with hemoglobin < 8g/dl).

After transplantation, tacrolimus and additional immunosuppressive drugs, usually a cell cycle inhibitor (mycophenolate mofetil, mycophenolate sodium, azathioprine) and prednisolone are given.

In case of induction therapy with alemtuzumab, tacrolimus and prednisolone are given from day 0 and cell cycle inhibitors delayed until restoration of lymphocyte count - usually after 12 months (10), (11)

Adjustment of tacrolimus immunosuppression will be established in predefined steps, derived from previous trials in immunosuppression (12). Immunosuppression (IS) will be managed according to predefined steps (with gradually reduced tacrolimus target levels from step 8 to 1. Patients without induction with alemtuzumab will start on step 6 (target trough level of tacrolimus 8-12 ng/ml), patients with induction with alemtuzumab will start on step 4 (target trough level of tacrolimus 6-10 ng/ml) in this scheme. Trough levels of tacrolimus will be determined according to liquid chromatography coupled with mass spectrometry (LC-MS) at least once a month.

All patients who experience an acute cellular rejection after reduction of CNIs will be put on increased doses of calcineurin inhibitors.

In Arm II the tacrolimus-based immunosuppression will be guided by conventional therapeutic drug monitoring (TDM). In patients randomized to the conventional CNI dosing the immunosuppressive drugs should be applied according to trough levels, signs of toxicity and center practice.

In Arm I the immunosuppression will be guided by the Torque Teno Virus (TTV) monitoring and conventional therapeutic drug monitoring (TDM) (Figure 2). Reduction in target trough levels will only be performed in stable patients after exclusion of silent rejection in transbronchial biopsy.

The TTV load reached after TTV stabilization (expected after three months) will be used to guide immunosuppression, which will be tailored according to the scheme above (Figure 2).

Maintenance immunosuppression will be guided by therapeutic drug monitoring (TDM) of tacrolimus trough levels. Furthermore, signs of toxicity of tacrolimus and cell-cycle inhibitors (e.g. leukopenia, gastrointestinal side effects, hypogammaglobulinemia) may lead to dose adaptation and switch between various cell-cycle inhibitors.

## Measurements

Most important measurement is creatinine (from blood chemistry) as the key-parameter to determine the primary endpoint  $\Delta$ GFR between randomization and 12 months thereafter.

Another key-measurement within this trial is the TTV-load in Arm-1 patients. TTV load is classified as low with TTV-load  $< 7 \log_{10}$ , as medium with TTV load from 7 to  $9,5 \log_{10}$  and as high with a TTV-load of  $> 9,5 \log_{10}$ .

TTV DNA quantitation will be done by TaqMan real-time PCR using probe and primers as described previously (13). The linear range of TTV quantitation ranges from 2.7 to  $10.7 \log_{10}$  copies/mL as determined by the use of 10-fold dilutions of a plasmid standard. The limit of detection in plasma is  $2.7 \log_{10}$  copies/ml. In each run a TTV DNA standard, and positive and negative controls will be included and any signs of PCR inhibition will be assessed by quantitation of known amount of control DNA spiked into the samples before DNA extraction (13).

## Outcome assessments

For the primary endpoint  $\Delta$ GFR between randomization and 12 months thereafter, Creatinine from serum will be measured to calculate GFR (CKD-EPI) at each visit

Main Secondary outcomes are assessed as follows

- Serum- creatinine at each visit, Cystatin C derived glomerular filtration rate at months 3, 9 and 12.

- Lung function as measured by forced expiratory volume in 1 second (FEV1) in % of Baseline at months 1, 3, 6, 9, and 12.
- Incidence of chronic lung allograft dysfunction (CLAD) between 12 months after randomization.
- Re-transplantation or death due to graft failure
- Number of biopsy proven acute rejections within 12 months after randomization
- Number of episodes of lymphocytic bronchiolitis 12 month after randomization Infections (CMV, CARV, fungal or bacterial infections) from Serum and/or, BAL
- Incidence of unscheduled emergency hospitalizations including ICU admission
- Quality of life: EuroQol instrument (EQ-5D) at screening visits and 0, 3, 6, 9 and 12 months after randomization
- Exercise capacity (6MWT) at randomization and 12 months thereafter.
- State of immune-system (CD4 lymphocytes, presence of donor specific antibodies DSA, IgG-level and use of rescue immune therapy) at months 0, 6 and 12 after randomization.
- State of the tacrolimus immunosuppression (TAC trough levels, TAC doses and number of adjustments of drug dosing after randomization.
- Safety outcome measures are assessed between randomization and 12 months thereafter: clinical laboratory evaluation (blood cell count, chemistry) according to the Common Terminology Criteria for Adverse Events 5.0 (CTCAE)

## Statistical analysis

### *Primary efficacy analysis*

The primary efficacy endpoint  $\Delta$ GFR is defined as the change of the glomerular filtration rate GFR between randomization and 12 months thereafter. GFR will be estimated using the CKD-EPI formula.

An analysis of covariance (ANCOVA) with strata used at randomization and treatment as fixed factors, and the baseline GFR as covariate is used to test for a difference in location of  $\Delta$ GFR (in ml/min/1.73m<sup>2</sup>) between groups (two-sided at a 0.05 significance level). The analysis of the primary endpoint will be based on the intention-to-treat populatio

### *Safety analyses*

The as-treated population is defined as all included patients who have undergone at least one blood sample for therapy monitoring after randomization. Analysis of safety will be based on the as-treated population i.e. patients will be analyzed according to the intervention they actually received.

### *Sample size calculation*

The sample size calculation is performed assuming a t-test of  $\Delta$ GFR. Because adjusting for stratification factors is assumed to reduce variability, the power for the ANCOVA test of the treatment variable is expected to be rather higher than lower compared to t-test.

The sample size calculation is based on the assumption of a mean decline in GFR of 15 between randomization and 12 months thereafter and a standard deviation of 20 in the control group. Compared to the control group, a mean decline in GFR of 5 in the experimental group (i.e. difference of 10 in GFR declines between the intervention groups) is regarded as clinically relevant. For a 2-sided significance level of 5 % and a power of 80 % 64 patients per group (n = 128 in total) are needed to detect achieve a power of 80% if the true difference in means is 10 and the standard deviation is 20 in both. Accounting for a dropout rate of 10% N=144 patients have to be randomized. The trial NCT00402532 (14) and the 4EverLung trial, EudraCT 2011-001539-21 (8) observed effect sizes of a similar magnitude.

### *Handling of missing data*

Missing data will be addressed by intention-to-treat (ITT) analysis by single and multiple imputations, weighted estimating equations or model-based strategies. Specific details on handling of missing data will be given in a Statistical Analysis Plan that will be finalized prior to database lock.

### **Safety endpoints**

Safety data will be summarized by using descriptive statistical methods. All adverse events (AEs) occurring during the conduct of the clinical trial will be monitored carefully and recorded on electronic case report forms (eCRFs). The causality assessment is performed by the investigator of the trial site concerned.

All serious adverse events (SAEs) will be reported by the investigators to the Philipps-University of Marburg (KKS Marburg) within 24 hours of becoming known. SAEs are recorded in the study-specific safety database. The SAE- Assessment is performed by KKS Marburg.

All suspected adverse reactions related to an investigational medicinal product that are both unexpected and serious (SUSARs) will be notified by KKS Marburg to the competent authority, the ethics committee and to all investigators involved.

*A Data and Safety Monitoring Committee (DSMC)*, two clinical experts and one statistician independent from the coordinating investigator was established to supervise the conduct of the study.

## **Discussion**

This is the first prospectively randomized trial to investigate tailoring of immunosuppression by a DNA-virus (Torque-Teno Virus) in comparison to conventional therapeutic drug monitoring in lung transplantation.

Viral infection may cause symptoms but some viruses can be found in healthy individuals without causing disease. Torque-teno virus (TTV) is a human DNA virus resulting in asymptomatic viremia. TTV-viremia is frequently detected in the general population without associated symptoms or disease. Epstein-Barr virus (EBV) represents another DNA virus, has a high prevalence in adults, causes latent infection in memory B cells after primary infection and viremia is usually asymptomatic in the transplant population. The levels of EBV in blood are correlated with the intensity of immunosuppression. Both TTV and EBV have therefore been suggested as surrogate markers of the net state of immunosuppression. In previous studies, TTV-DNA in blood but not EBV viremia is correlated positively with intensity of immunosuppression after transplantation. Another argument against the use of EBV load as a surrogate marker of immunosuppression is the influence of Valganciclovir on EBV load, a drug commonly used for preventing CMV infection after lung transplantation. Its use may reduce EBV load. In conclusion, TTV- but not EBV-DNA load better reflects the function of the immune system after lung transplantation. Immunosuppression depends on the type, combinations and dosing of immunosuppressive treatment.

In lung transplant recipients, a large benefit may be expected by tailoring immunosuppression by DNA virus monitoring because immunosuppression is usually more intense in comparison to other forms of solid organ transplantation. This hypothesis is optimally being studied in a prospective manner in comparison to conventional therapeutic drug monitoring.

The guidance of immunosuppression by monitoring of TTV load will be chosen because in contrast to EBV, Cytomegalovirus (CMV) is expected to be measurable in blood in the vast majority of lung transplant recipients and monitoring of this virus is therefore suitable for guidance of immunosuppression. Since less than 25% of recipients are expected to develop CMV-viremia during the first postoperative year, CMV load will not be suitable as a monitoring tool for immunosuppression. Furthermore, several publications have demonstrated changes in TTV load in relation to intensity of immunosuppression (3, 7). CMV load will be monitored routinely in addition in all recipients and prophylaxis will be given. However, randomization will be stratified by high-risk CMV-status (D + R-) (yes/no) as in the Vienna cohort (4) a lower TTV load was observed during CMV-infections. Blinding of patients and/or staff will not be applied as the primary endpoint will be determined by using laboratory values in the CKD-EPI formula.

To compare results regarding TTV levels between different transplantation centers, it is vital to reliably quantify the concentrations of TTV-DNA in a standardized manner. In the VIGILung trial this will be performed by central analysis of TTV load in a reference lab because real-time PCR is prone to inter-laboratory differences.

The effect size assumed for the sample size calculation were derived from the observed glomerular filtration rate (GFR) changes within 12 months in two recent immunosuppressive trials including reduced calcineurin inhibitor strategies (8, 14). All endpoints will be assessed by pre-defined definitions (9, 15–19). The CKD-EPI method was chosen to estimate GFR because it is the most robust creatinine-based method and is established in clinical routine and trials in lung transplantation (20). CLAD will be diagnosed by a persistent (at least 3 month) decline of FEV1 to 80% of baseline or below after adequate

treatment of secondary causes such as infection, acute cellular/antibody-mediated rejection, or airway stenosis

The results of this trial might have a large impact on therapeutic strategies for patients after lung transplantation. Furthermore, this study will contribute to improve evidence-based therapy in these patients. Study results are transferable to all other solid organ transplantations.

## Trial Status

The trial is recruiting patients since 2020-07-28 according to the VIGILung protocol version V03 from 2019-11-05. Recruitment time is planned to be 39 month.

## List Of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ATG	Antithymocyte Globulin
BAL	Bronchoalveolar Lavage
CA	Competent authority
CARV	Community Acquired Respiratory Viral Infections
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CRF	Case Report Form
CsA	Ciclosporin A
DNA	Deoxyribonucleic Acid
DSA	Donor Specific Antibodies
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
EBV	Epstein-Barr-Virus

EC	Ethics Committee
EC-MPS	Enteric Coated Mycophenolate Sodium
FEV1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAG	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HHV-6	Human Herpesvirus 6
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICH	International Conference on Harmonization
IS	Immunosuppression
ITT	Intention-to-Treat
LC-MS	Liquid Chromatography-Mass Spectrometry
LTx	Lung Transplantation
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
pO2	Oxygen partial pressure
PP	Per-Protocol
SAE	Serious Adverse Event
SaO2	Blood-oxygen saturation
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SpO2	SaO2 measurement determined by pulse oximetry

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	Tacrolimus
TBB	Transbronchial Biopsy
TDM	Therapeutic Drug Monitoring
TLC	Total Lung Capacity
TTV	Torque-Teno-Virus
UAR	Unexpected Adverse Reaction
6MWT	6 Minute Walk Test

## Declarations

### Acknowledgements

None

### Sponsor:

Philipps-University Marburg, Germany

### Representative of the sponsor:

Koordinierungszentrum für Klinische Studien (KKS)

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The DFG have granted 1.006.701€ over a period of 36 months to our project as part of their “clinical trials” programme. This funding will cover costs for both scientific and medical personnel, including case

payments for recruiting and treating individual patients.

Within the terms of the agreement, funding is subjected to bi-annual progress reporting. A prolongation of the application beyond the planned 36 months is permissible, subject to preliminary findings and agreed publication of these results.

Availability of data and materials:

As the study is ongoing data are not yet available. Materials about the study are available under registration number: EudraCT-Number 2019-001770-29

Author contributions:

Conceptualization and primary investigator: JG, Methodology: JG, AR, KM, KW, CS, SH, PJ, Project administration: KW, SH, Writing – original draft: SH, writing – review and editing: JG, AR, KM, KW, CS, SH, PJ.

Ethics, consent and permissions:

The study will be conducted in accordance with the protocol, with the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and applicable national laws and regulatory requirements.

The VIGILung study EudraCT No.: 2019-001770-29

Protocol version V03F, dated 2019-11-05 has been approved by the Ethics Committees of the Hannover Medical School, Germany (Nr. 8579\_AMG\_mono\_2019) and the Medical University of Vienna (EK Nr.: 1127/2020) as well as by the German and Austrian Competent Authorities, Bundesinstitut für Arzneimittel und Medizinprodukte (Vorlage Nr. 4043539) and Bundesamt für Sicherheit im Gesundheitswesen BASG, reference 12760630 on 29APR2020.

Any substantial amendments to the protocol will be submitted to the EC in accordance with national requirements. Additional study sites may only recruit patients, if the sponsor already obtained approval for the site.

Written informed consent will be obtained from all participants in the trial before inclusion. The patient information and consent form was approved by the Ethics Committee of the Hannover Medical School and Medical University of Vienna

#### Consent for publication

The ethical approval and patient information include consent to publish the collected data.

#### Competing interests

The authors declare to have no competing interests.

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## Figures

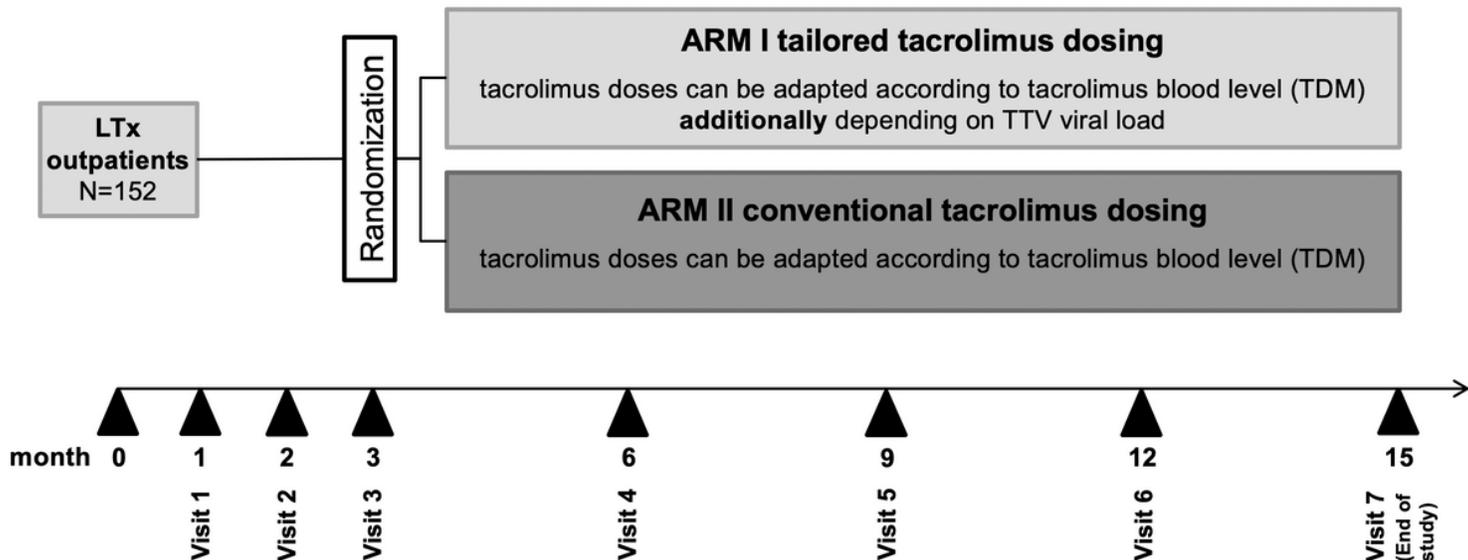


Figure 1

Trial flow chart and treatment groups

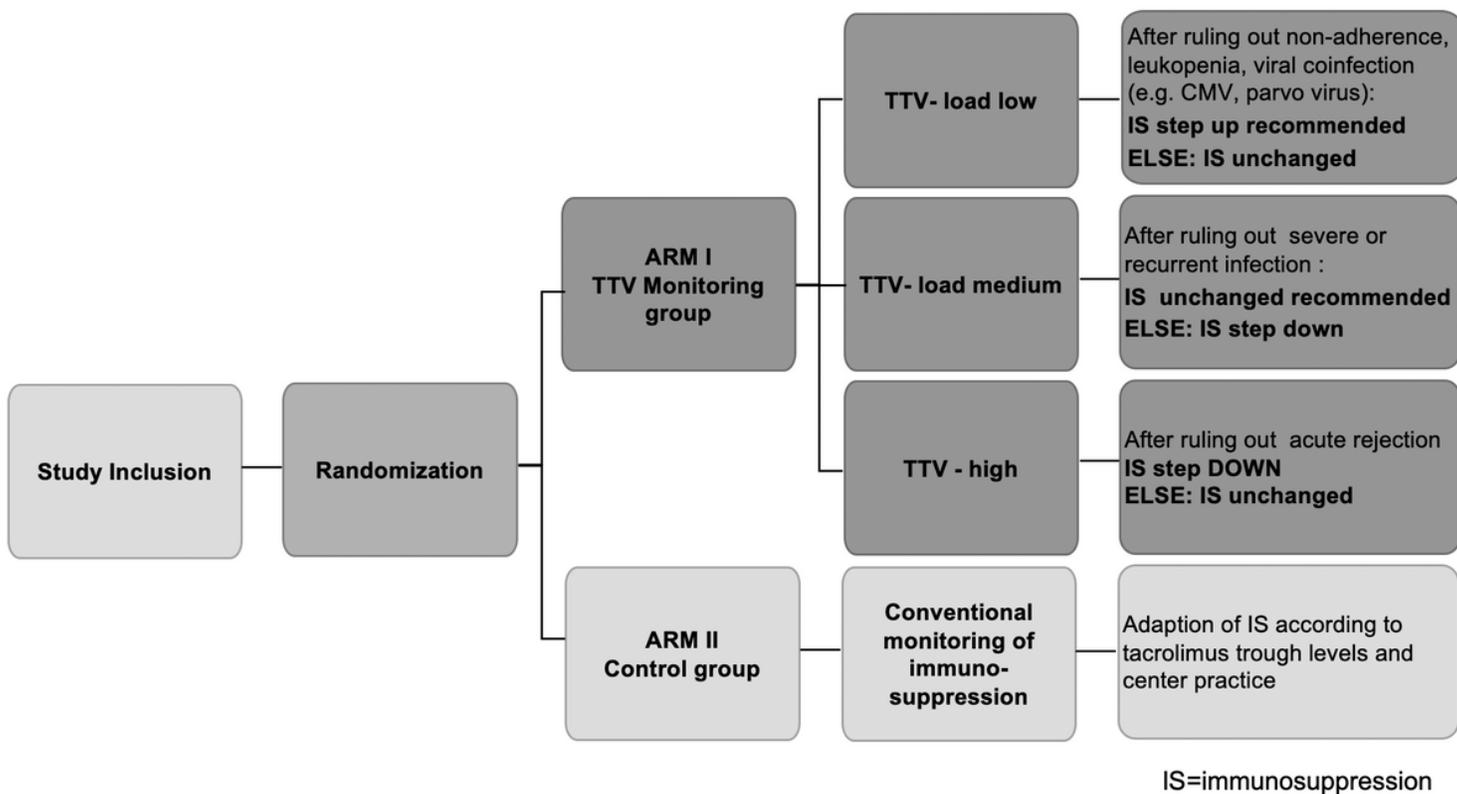


Figure 2

Study specific procedures

Timepoint	STUDY PERIOD						
	Enrolment		Allo- cation	Post-allocation			Close-out
	Visit 1 Screening I POD 32 +/- 10 days	Visit 2 Screening II POD 60 +/- 10 days	Visit 3 Randomiza. POD 90 +/- 10 days	Visit 4 POD 180 +/- 10 days	Visit 5 POD 270 +/- 10 days	Visit 6 POD 360 +/- 10 days	Visit 7 End of study or premature end POD 450 +/- 10 days
<b>ENROLMENT:</b>							
Patient information and consent	x						
Inclusion and exclusion criteria	x						
Enrolment	x						
Allocation (Randomization)			x				
<b>INTERVENTIONS:</b>							
TTV-Load guided Immunosuppression (Arm 1)				_____			
Therapeutic drug Monitoring (Arm 1+ 2)	_____						
<b>ASSESSMENTS</b>							
GFR (CDK EPI)	x	x	x	x	x	x	x
Bronchoscopy with Transbronchial Biopsy and Lavage	x		x	x		x	
General medical history, GFR pre-Tx and transplant information	x						
Total Lung Capacity	x		x				x
FVC, FEV1	x	x	x	x	x	x	x
Phys. Examination, blood chemistry & blood count	x	x	x	x	x	x	x
IgG, CD4 count	x		x		x		x
HLA antibody screen	x		x		x		x
Tacrolimus trough level	x	x	x	x	x	x	x
TTV viral load	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>
EQ-5D	x	x	x	x	x	x	x
Adverse Events (CTCAE 5.0)	x	x	x	x	x	x	x
6-Minute Walk Test	x		x				x

Abbreviations: POD: post-operative day; TTV: Torque Teno Virus, GFR: glomerular filtration rate; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration

<sup>1</sup>TTV load measurement is done 3-4 times for patients in both interventions until randomization.

<sup>2</sup>patients in the experimental intervention will have up to 10 additional TTV load measurements (if necessary unscheduled visits will take place). TTV load measurements will not be continued in Arm 2.

### Figure 3

SPRIT figure

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITchecklistVIGILung.pdf](#)