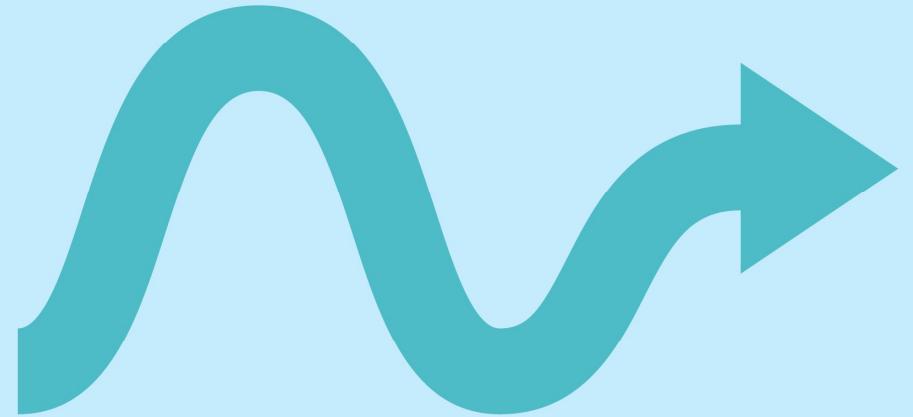




TTV GUIDE

Torque Teno Virus
Based Immune Monitoring



Torque Teno Virus-based immunologic monitoring

Gregor Bond; Medical University of Vienna, Austria

15th of October, 2024

TAVI Forum 11

LA, CA, USA

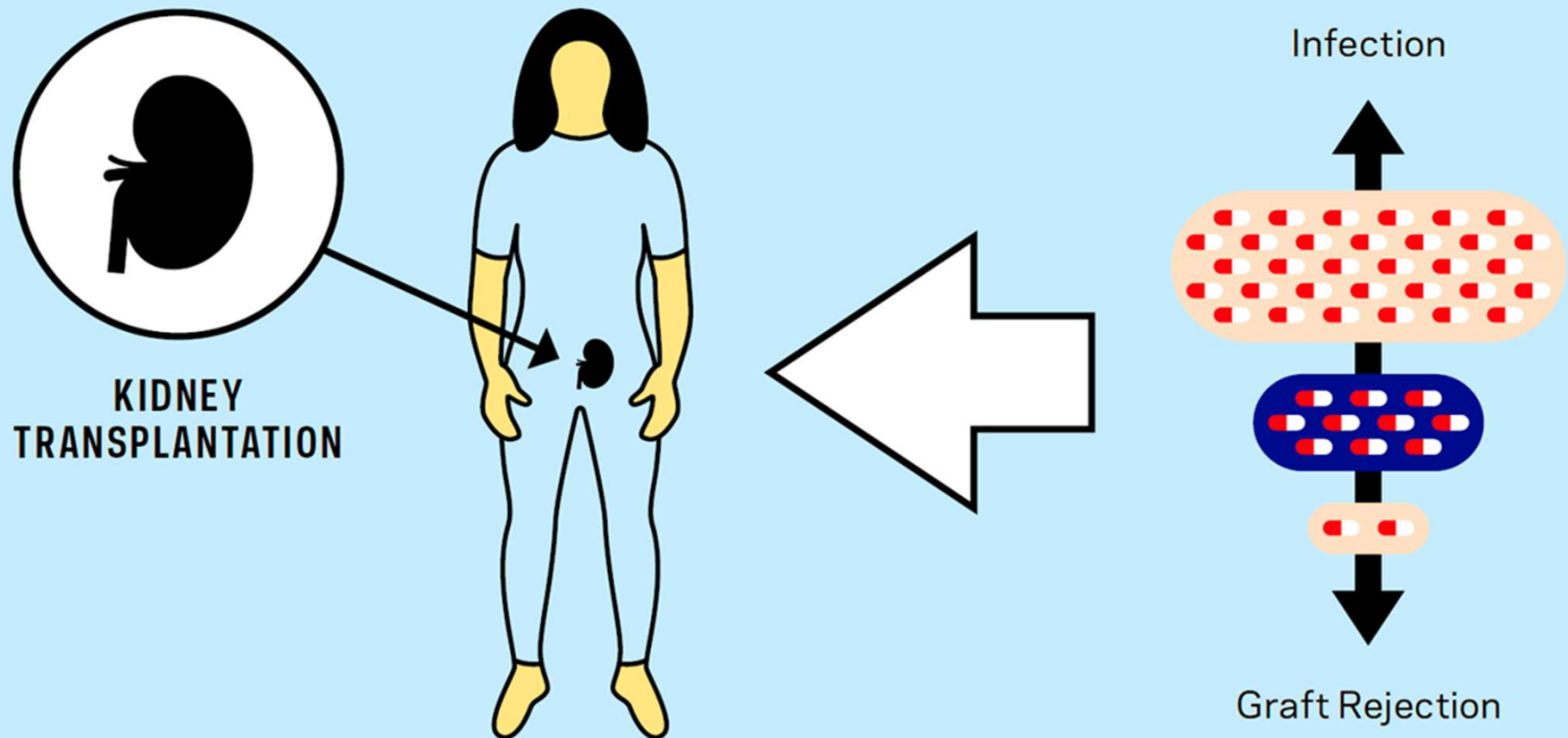
TTV-GUIDE.EU

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 896932.

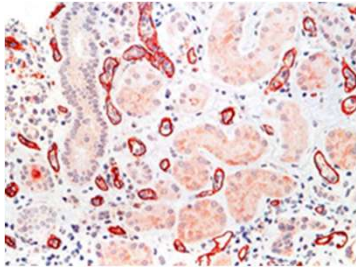


THE CLINICAL PROBLEM

Immunosuppressive drug guidance after kidney transplantation (KTX)



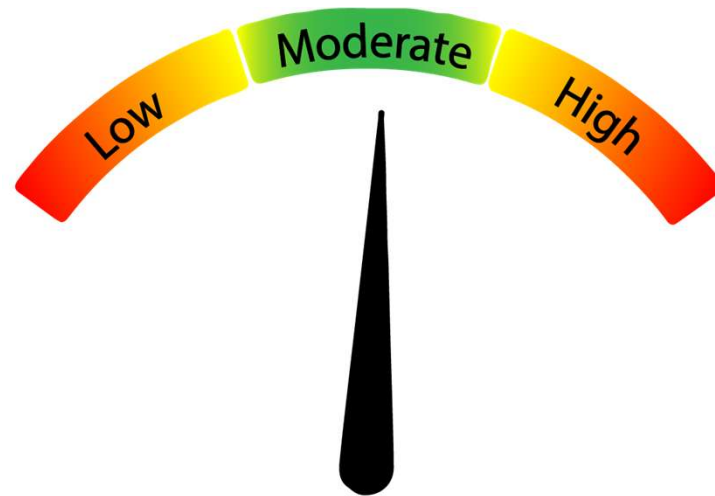
We need an '*Immunometer*'



SOT: graft rejection

AI: remission?

Vaccination: response?



AE: Infection, cancer

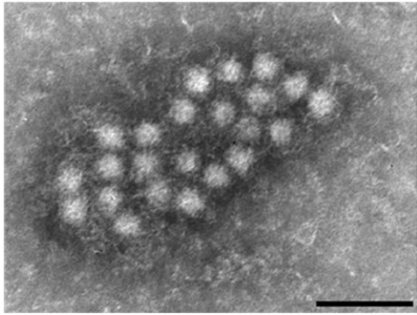
Onco: response?

Infection: outcome?



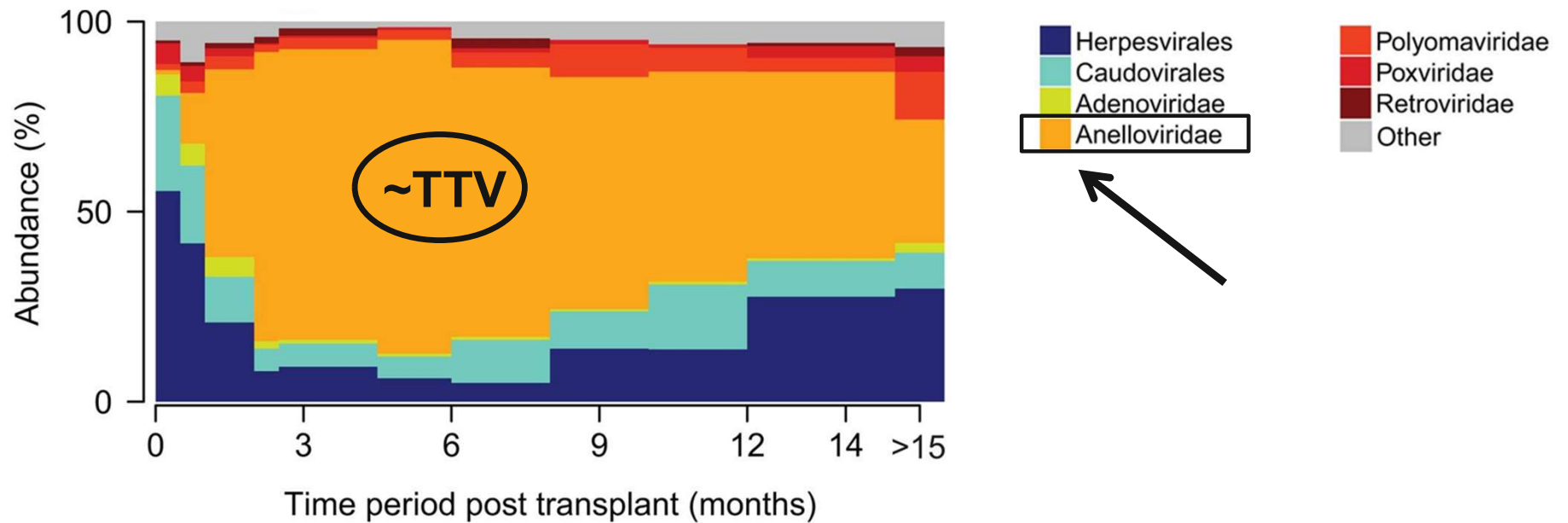
Immunosuppression

Might Torque Teno virus (TTV) be such a tool ?



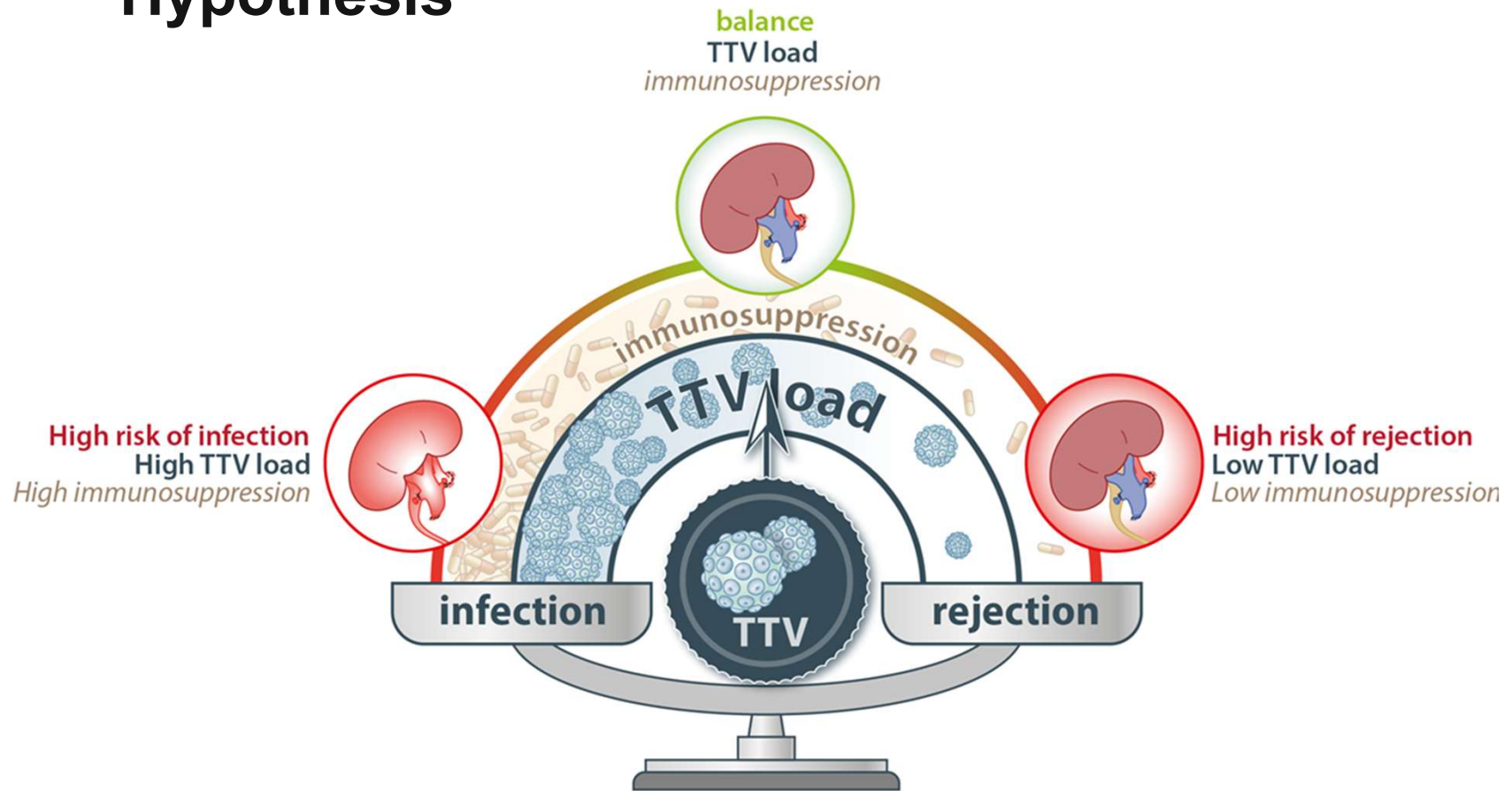
- Anellovirus (~20 TTV species in human)
- **high prevalence:** 90% healthy adults; **~99% (all?) patients on IS**
- route of infection: (almost) any
- replication: everywhere (a lot in lymphocytes, hepatocytes)
- **causes no disease**
- **viral control involves major (all?) immune compartments**
- resistant to conventional antiviral therapy
- **association w. immune-function** (TX, AI, ID, Onco...)

What happens to TTV if we switch on IS?



De Vlamincx et al., Cell, 2013 (Steve Quake, Stanford)

Hypothesis





JOURNAL OF
MEDICAL VIROLOGY

TT virus (TTV) loads associated with different peripheral blood cell types and evidence for TTV replication in activated mononuclear cells

Fabrizio Maggi, Claudia Fornai, Lucia Zaccaro, Antonietta Morrica, Maria Linda Vatteroni, Patrizia Isola, Santino Marchi, Angelo Ricchiuti, Mauro Pistello, Mauro Bendinelli ✉

First published: 30 April 2001 | <https://doi.org/10.1002/jmv.1035> | Citations: 69

Maggi 'in-house' qPCR

(EUROFINS: TTViWATCH: US 6/24)

Quantity: 200ul (also less) / swap

Type: plasma/ serum/ whole blood/ resp. material/ urine

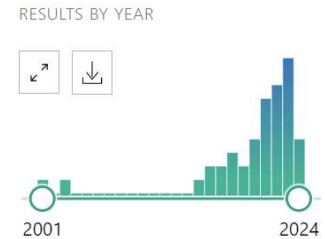


CE-IVDR commercial qPCR

TTV R-GENE: EU 2022, US 2025?

TTV evidence in SOT: narrative review

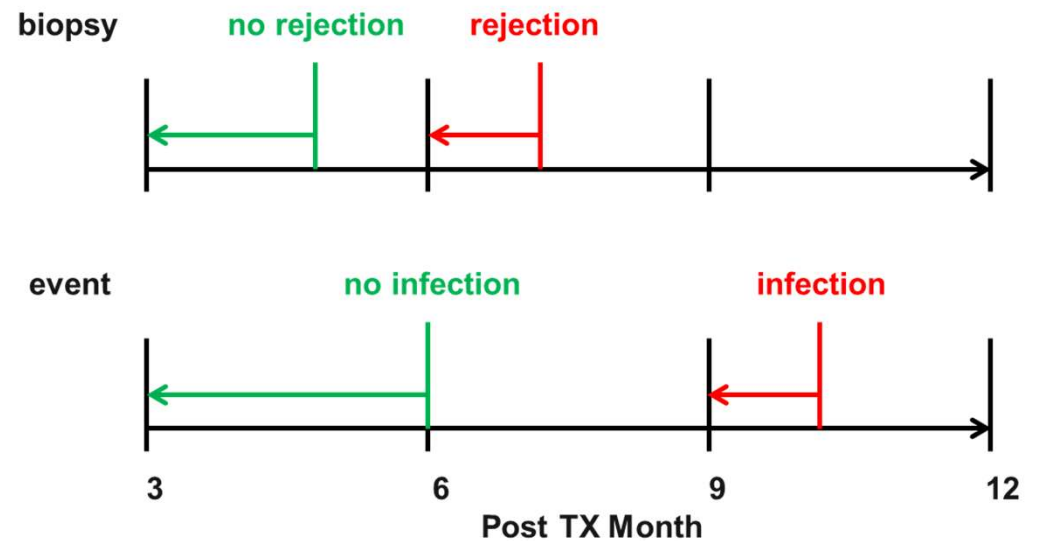
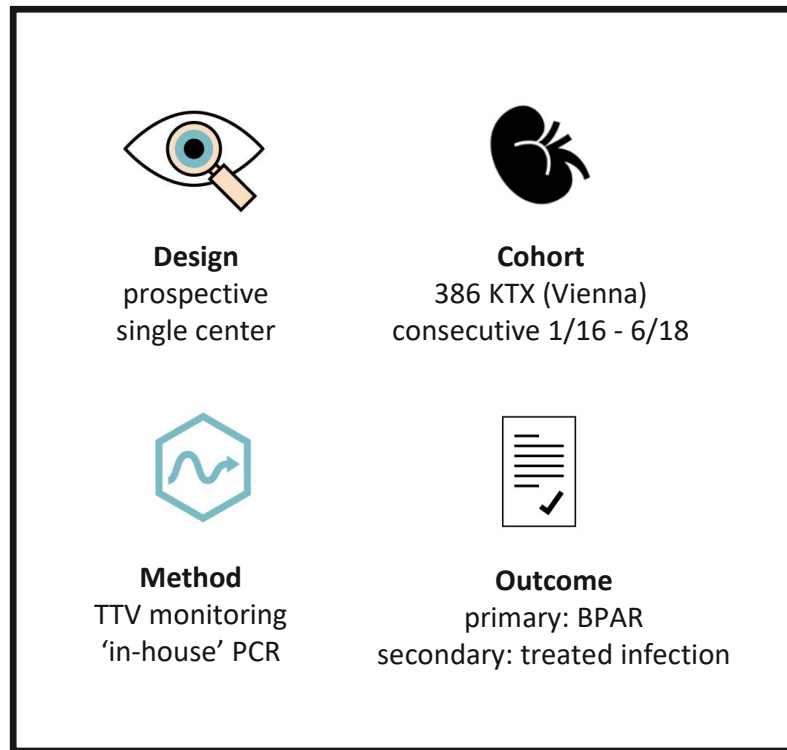
Cave: single center, non-interventional, study design limitations



Rejection (~15 paper): ABMR, TCMR, BL-TCMR; late/ early, subclinical/ overt, *de novo* DSA; adult/ pediatric

Infection (~20 paper): opportunistic/ all; severe/ non-severe

TTV POET trial – TTV predictive for infection/rejection in KTX



Infection

adjusted OR 1.09 (95%CI 1.04-1.14)

TTV preceded subsequent infection by 27 days

BKV pPVAN/ PVAN (consequence concerning IS)

OR 1.21 (95% CI 1.06-1.39)

CMV viraemia/syndrome/organ (consequence concerning IS)

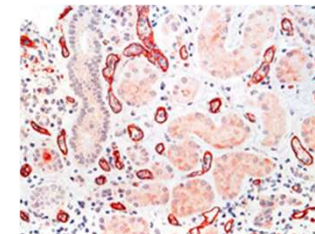
OR 1.16 (95% CI 1.05-1.27)



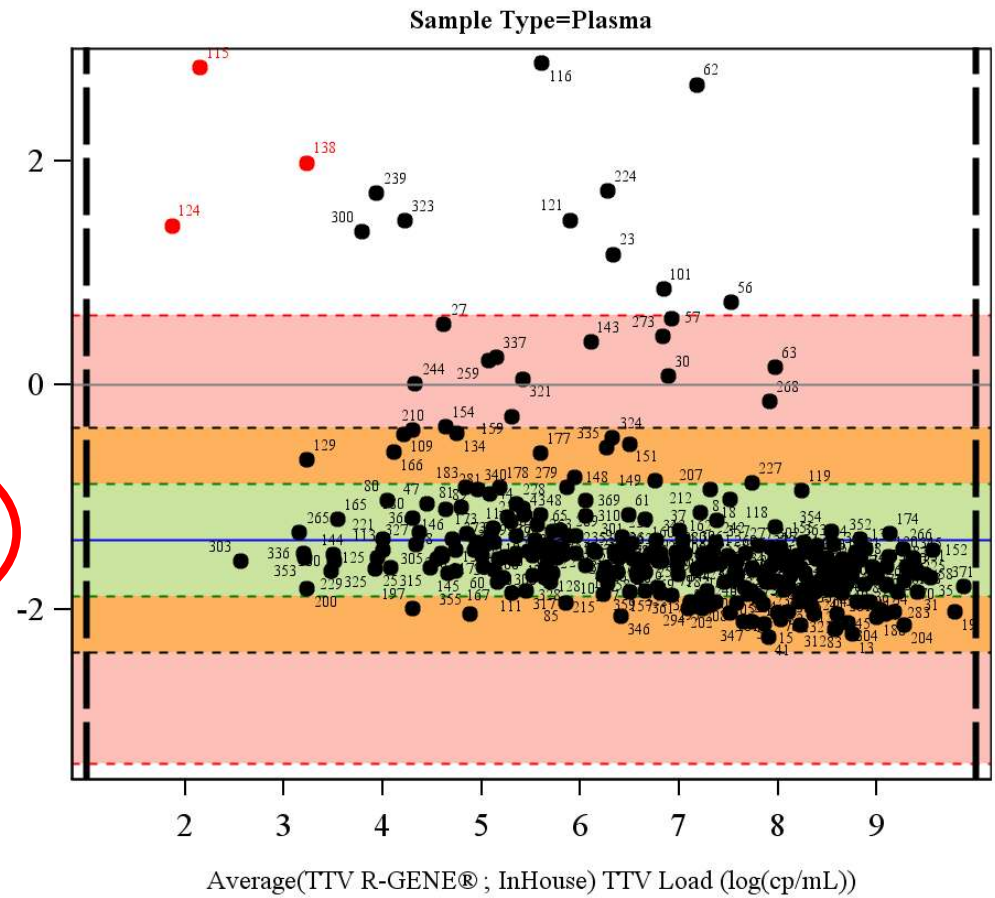
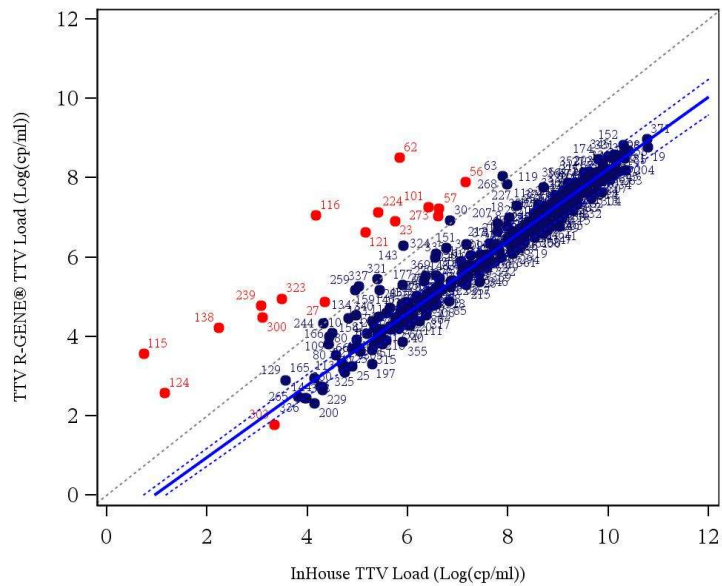
Rejection

OR 0.78 (95% CI 0.62-0.97)

TTV preceded subsequent rejection by 14 days



CUT- OFF? -> KNOW YOUR PCR!



Görzer et al., Journal of Clinical Virology, 2022

CUT-OFF?

TTV R-GENE (commercially available IVDR CE marked)

REJECTION

Diagnostic accuracy to detect rejection by TTV load

TTV c/mL	NPV	PPV	Sensitivity	Specificity
<8 log10	0.86	0.22	0.94	0.12
<7 log10	0.97	0.31	0.94	0.46
<6 log10	0.92	0.42	0.78	0.73
<5 log10	0.92	0.62	0.67	0.90
<4 log10	0.84	0.67	0.33	0.97

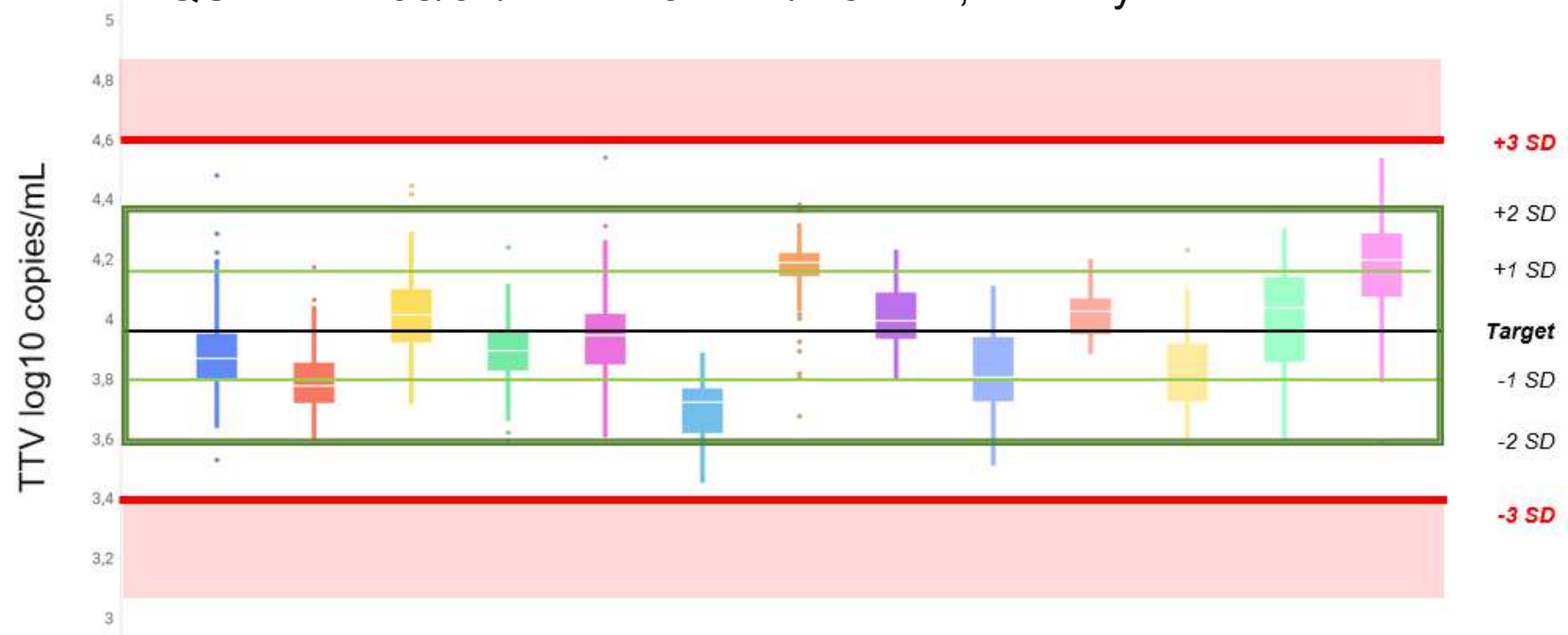
INFECTION

Diagnostic accuracy to detect infection by TTV load

TTV c/mL	NPV	PPV	Sensitivity	Specificity
>8 log10	0.72	0.38	0.14	0.91
>7 log10	0.76	0.38	0.49	0.67
>6 log10	0.78	0.34	0.68	0.47
>5 log10	0.75	0.30	0.77	0.28
>4 log10	0.65	0.28	0.89	0.09

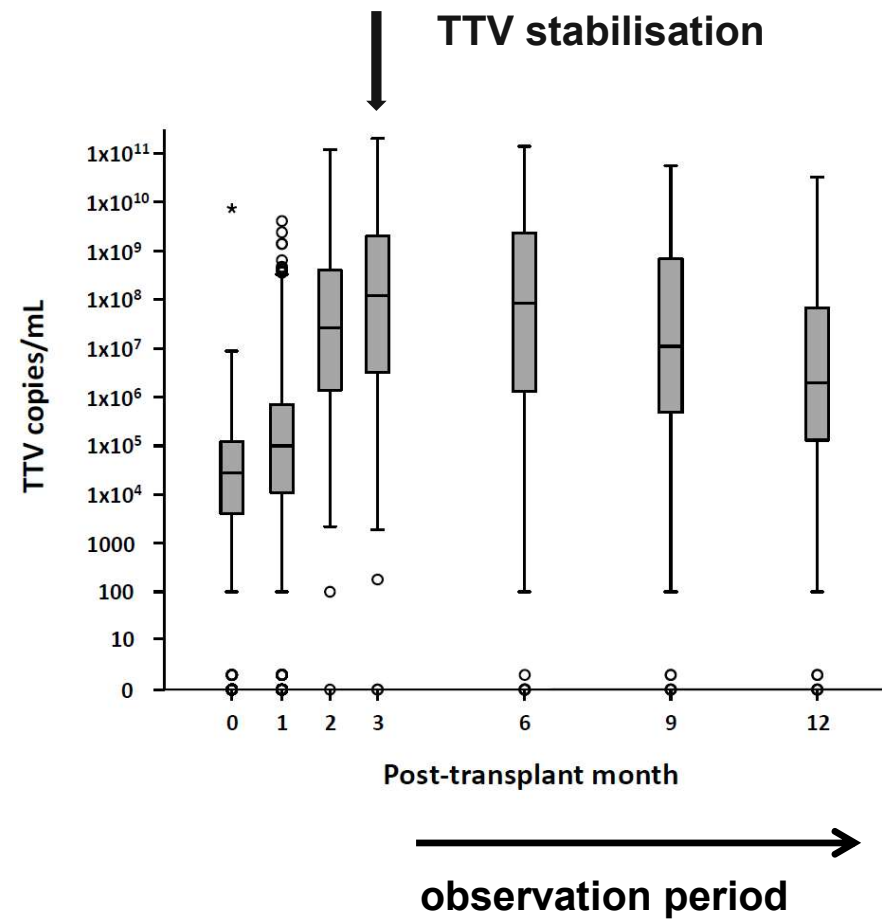
EU HORIZON 2020 TTVguideTX project (TTV R-GENE)

IQC results 08/02/24: 1125 tests/ 13 labs; not fully automated



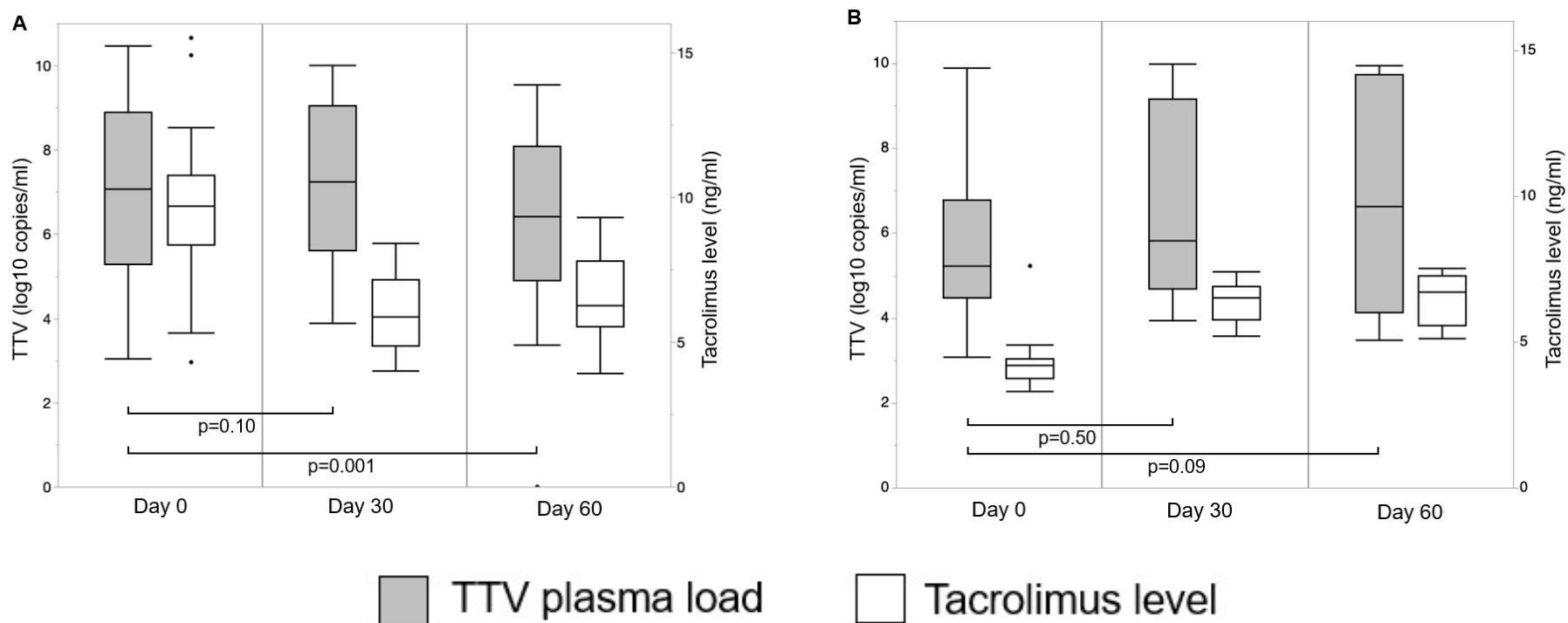
Gore et al., Journal of Medical Virology, under review

TTV kinetic following IS start



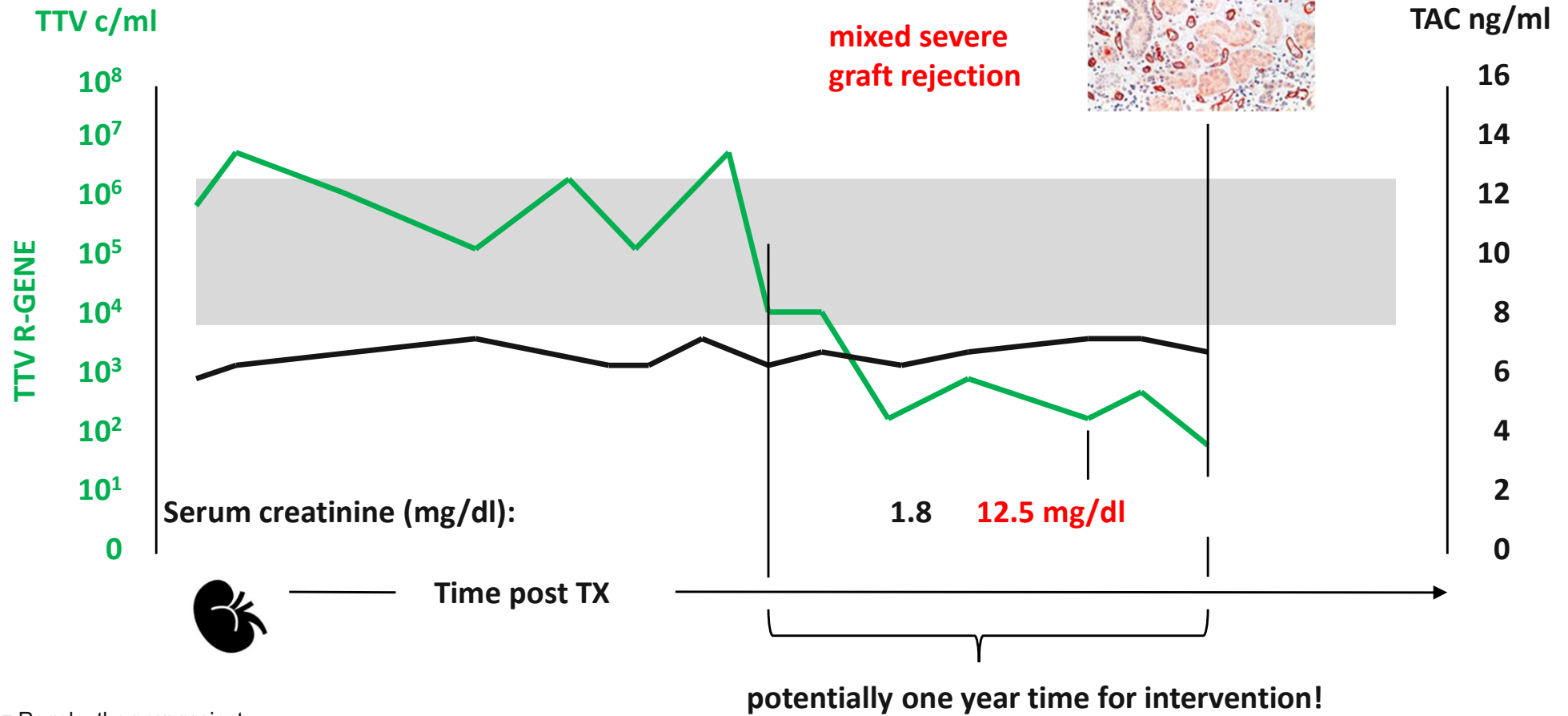
Doberer et al., AJT, 2020

TTV kinetic following CNI dose changes

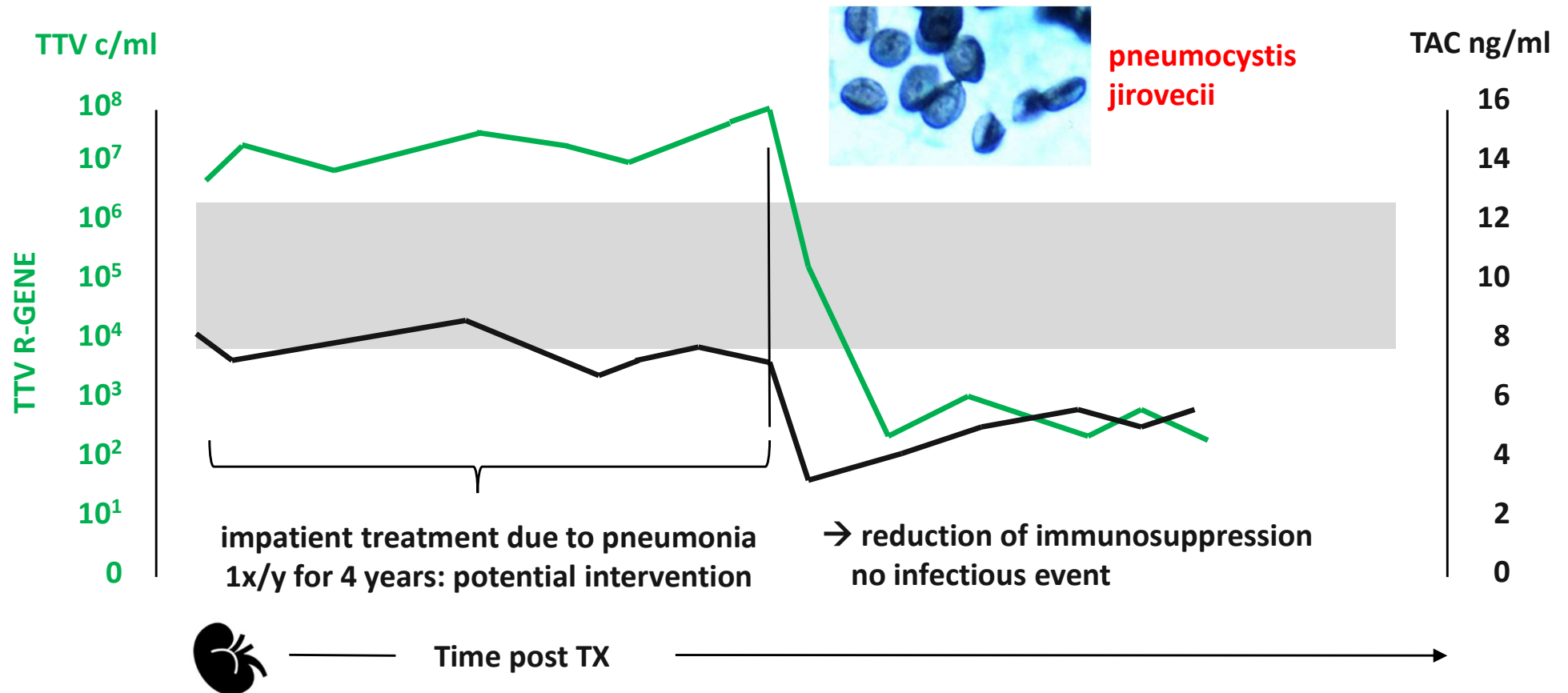


Regele et al., Journal of Medical Virology, 2024

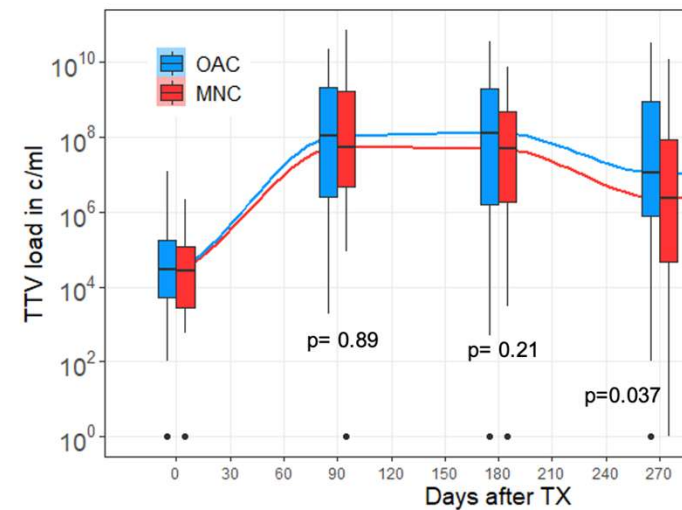
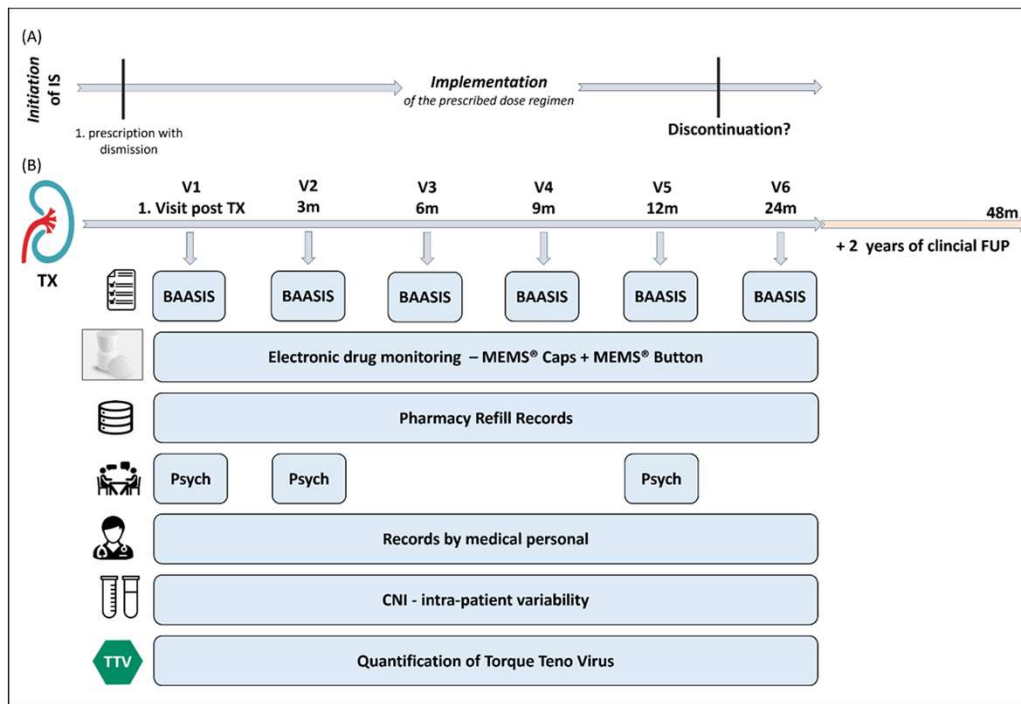
Case report #1; 23a, m, LD



Case report #2; 67a, m, LD, ABOi



TTV for non-adherence monitoring in KTX: AdTorque trial

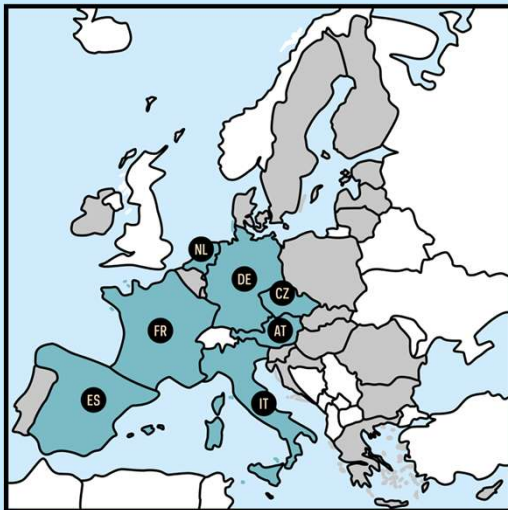


Hauptenthal et al., under review

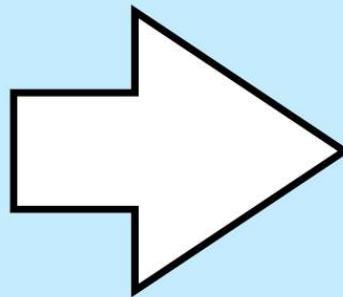


HOW WE TEST IT

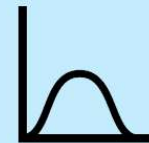
Clinical trial: compare dosing of immunosuppressive drugs
► Outcome: reduction in infection / graft rejection



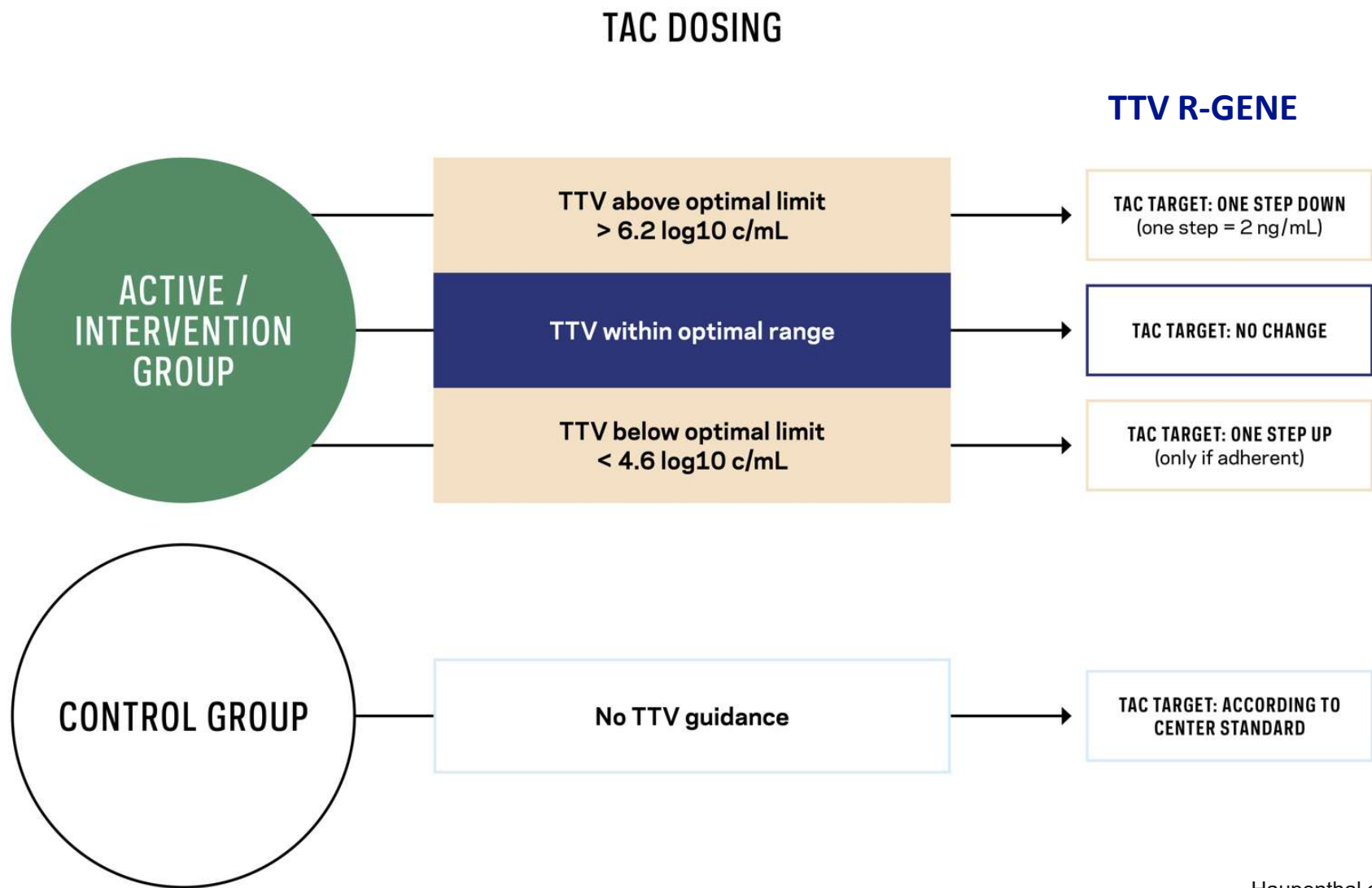
~300 KTX RECIPIENTS
13 CITES



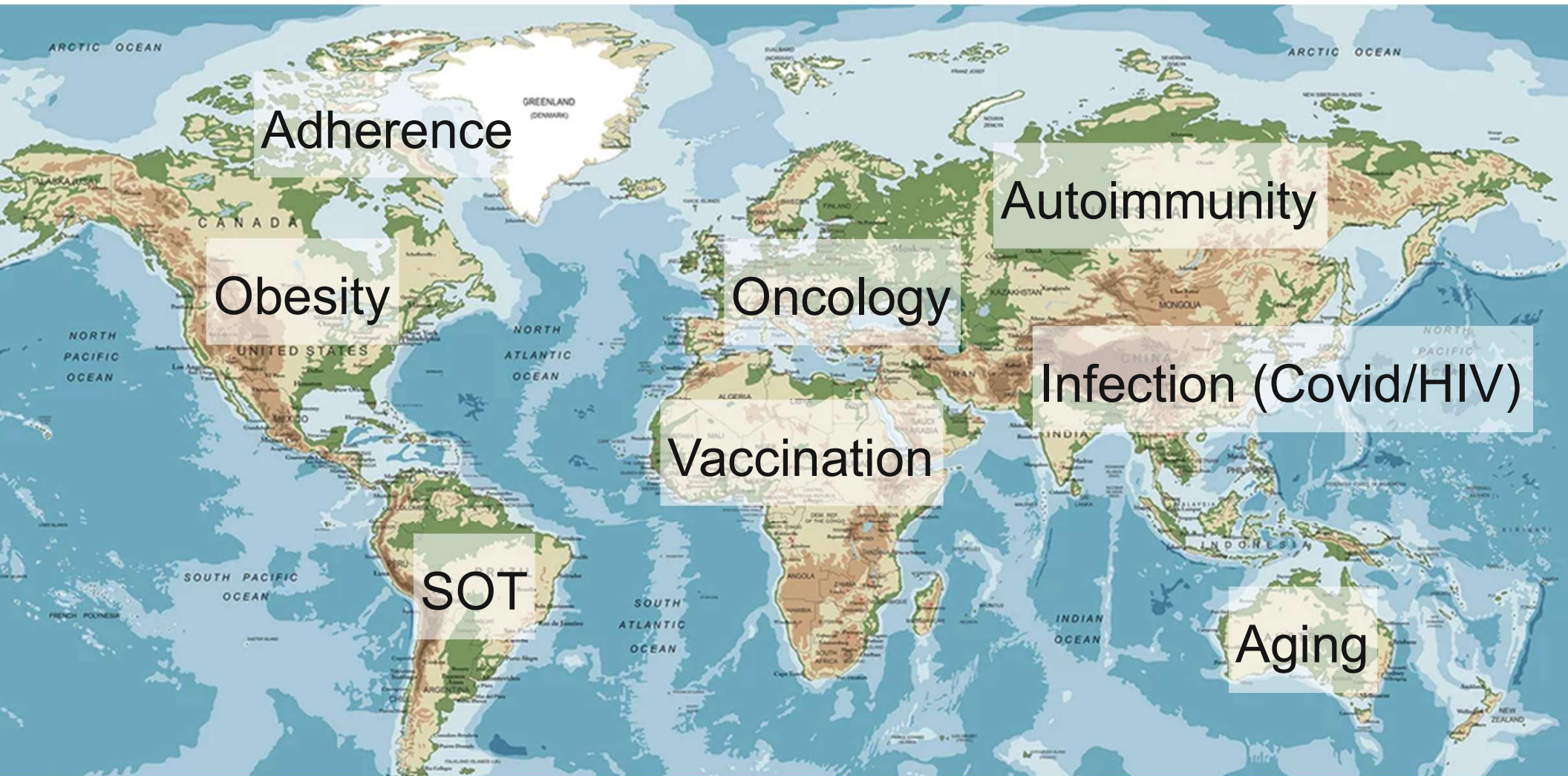
TTV GUIDED
group A



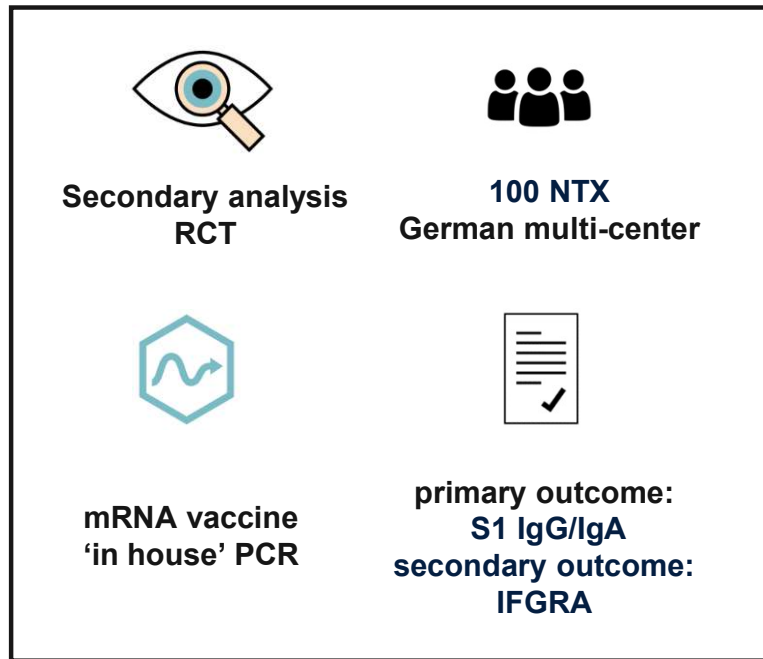
CONVENTIONAL
(DRUG LEVEL GUIDED)
group B



The world according to Anelloviruses



TTV load - response to SARS-CoV-2 vaccination in KTX

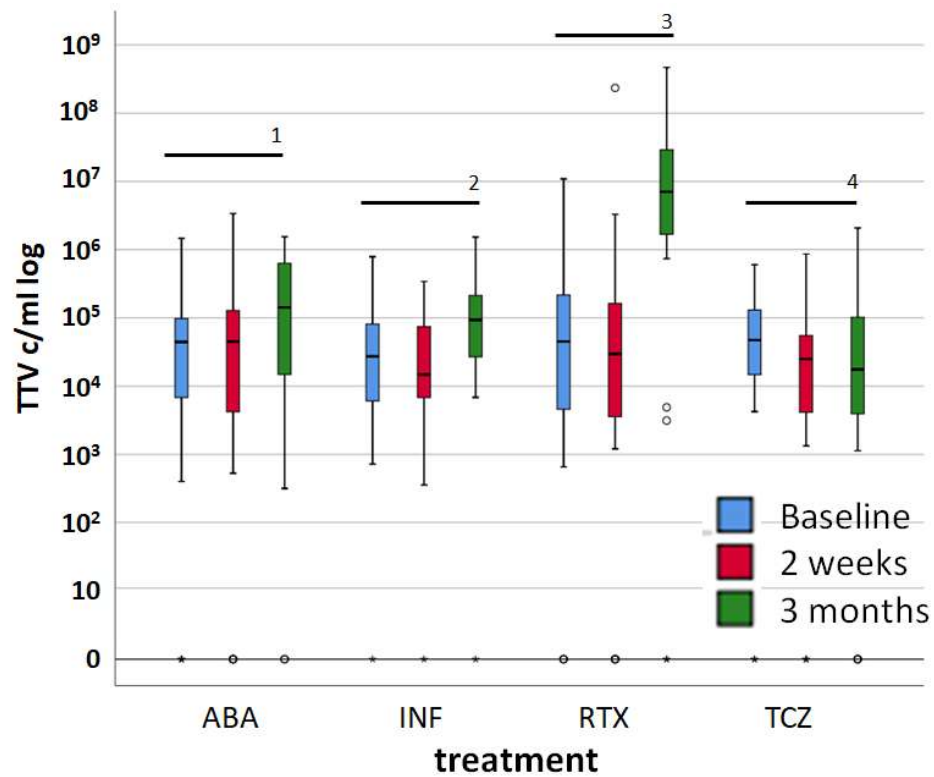


TTV c/ml	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)
10^3	6.5 (1.2-20.7)	97.1 (90.0-99.5)	50.0 (8.9-91.1)	69.8 (60.0-78.1)
10^4	25.8 (13.7-43.3)	75.4 (64.0-84.0)	32.0 (17.2-51.6)	69.3 (58.2-78.6)
10^5	71.0 (53.4-83.9)	47.8 (36.5-59.4)	37.9 (26.6-50.8)	78.6 (64.1-88.3)
10^6	93.6 (79.3-98.9)	21.7 (13.6-32.8)	34.9 (25.6-45.7)	88.2 (65.7-97.9)
10^7	96.7 (83.8-99.8)	15.9 (9.1-26.3)	34.1 (25.0-44.5)	91.7 (64.6-99.6)

TTV levels > 6log c/ml = 4.6log (CE-IVDR PCR)

**-> only 12% serological response (S1 IgG/IgA)
no cellular response (IFGRA)**

TTV load associates with treatment response in RA

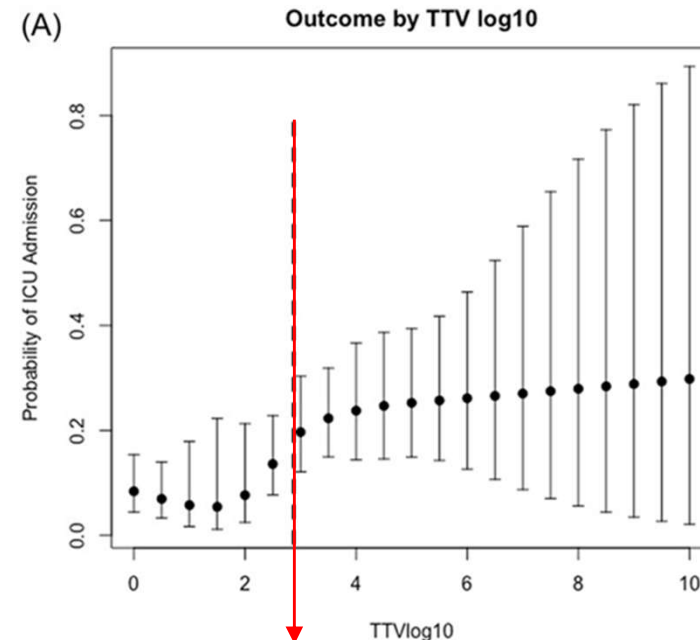


	SDAI85		CDAI85	
	No	Yes	No	Yes
Lowest 25% in TTV	100%	0%	92.90%	7.10%
Highest 25% in TTV	61.50%	38.50%	53.30%	46.70%

→ SQUEEZE
cordis.europa.eu/project/id/101095052

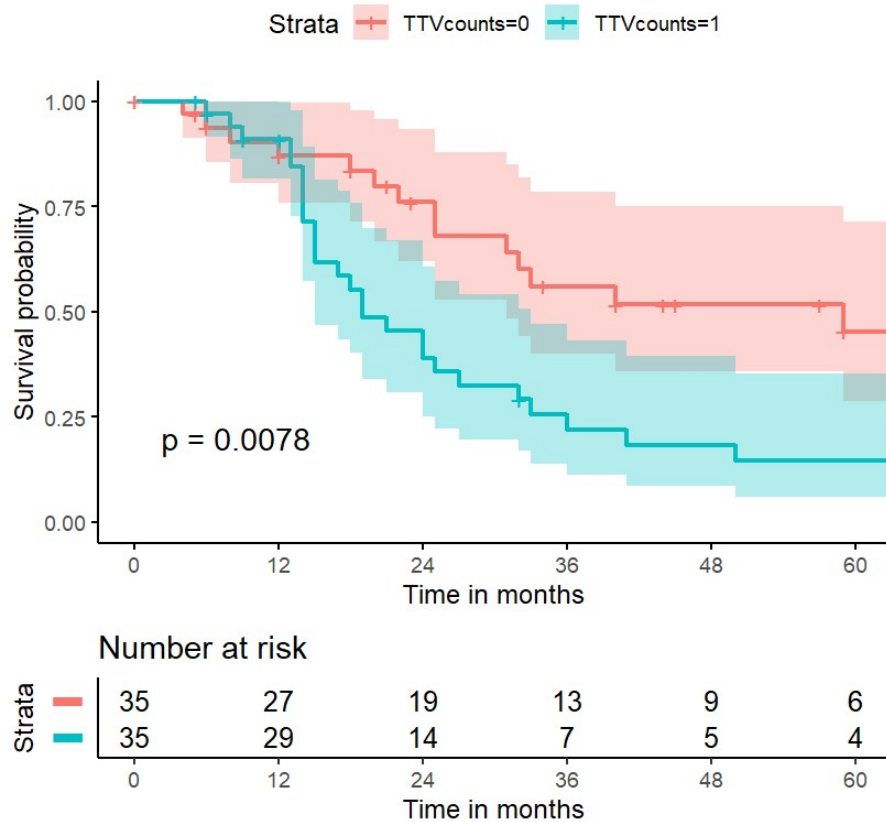
TTV load associates with ICU admission of SARS-CoV-2 infected patients

Variable	N	Odds ratio	p
Obesity	259	3.28 (1.32, 8.07)	0.010
Hepatitis	259	7.82 (1.26, 48.98)	0.025
TimeSince1stSymptoms	259	0.92 (0.84, 0.99)	0.040
Temperature	259	1.45 (0.99, 2.15)	0.058
Dyspnea	259	2.10 (0.85, 5.59)	0.120
Oxygen	259	2.44 (1.06, 5.84)	0.039
TTV.above	259	2.93 (1.36, 6.50)	0.007
age	259	1.00 (0.97, 1.03)	0.936
sexe	F 102	Reference	
	M 157	1.65 (0.74, 3.92)	0.235
is	0 240	Reference	
	1 19	1.61 (0.29, 6.80)	0.543



Feghoul et al. (Paris), Journal of Medical Virology, 2023

Role of TTV in ovarian cancer



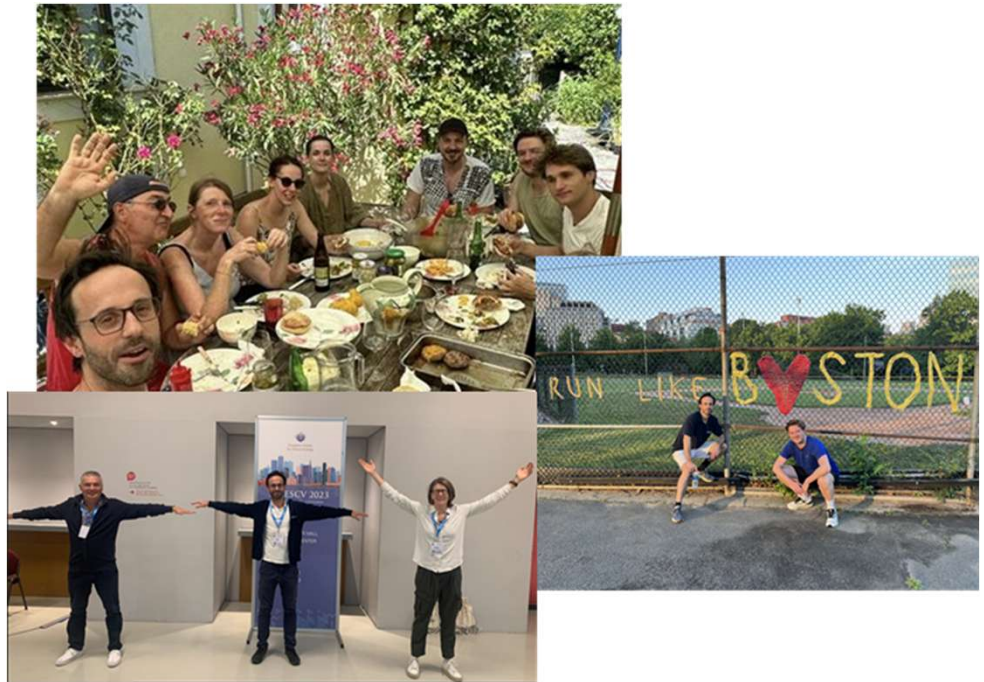
80 newly-diagnosed patients

	progression-free survival (PFS)			
2a. parameters	univariate analysis		multivariable analysis	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Ln TTV PCR	0.002	1.23 (1.08-1.40)	0.021	1.18 (1.03-1.35)
age at diagnosis (years)	0.054	1.03 (1.00-1.05)	0.147	1.02 (0.99-1.05)
FIGO stage (1 vs. 2 vs. 3 vs. 4)	<0.001	2.58 (1.62-4.08)	0.001	2.71 (1.48-4.96)
complete resection (R0)	<0.001	4.45 (2.39-8.27)	0.004	2.71 (1.38-5.31)

T. Bartl (MUV), unpublished data, 2024

Who is doing all that work (current team in alphabetic order)

- Carsten Herz, PhD student
- Felix Herkner, PhD student
- Florian Bauernfeind (statistician), MSc
- Florina Regle, PhD student
- Frederik Hauptenthal, PhD student
- Habiba Ahmed, MD student
- Karin Schliegl, study nurse
- Katharina Mayer, post doc
- Konstantin Doberer, PhD student
- Markus Wahrmann, senior post doc
- Sebastian Kapps, PhD student
- Stefan Steinringer, MD student





29 June-2 July 2025

#ESOTcongress



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