Anellovirus (TTV) load to predict complications and guide immuno-suppression in kidney transplant recipients

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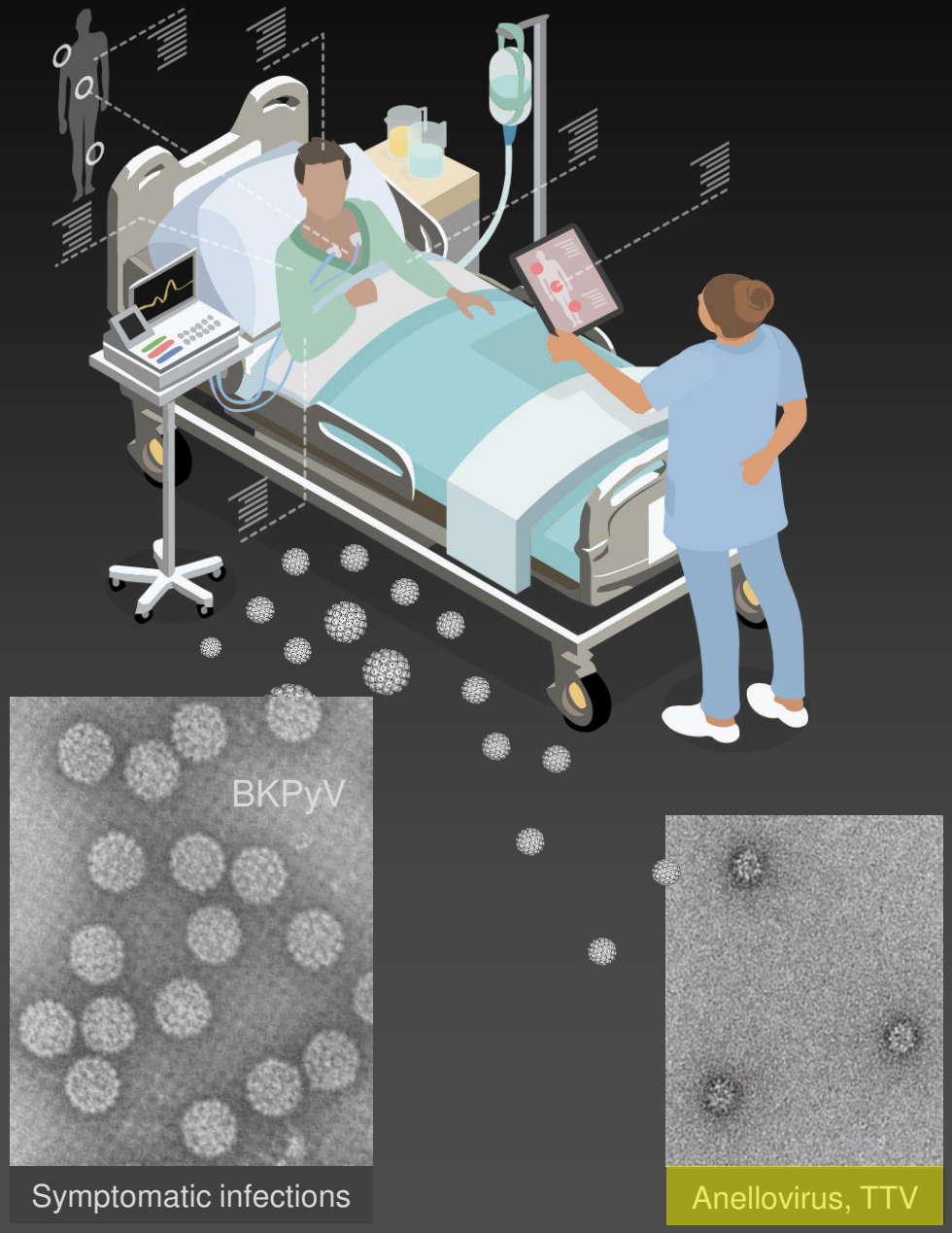
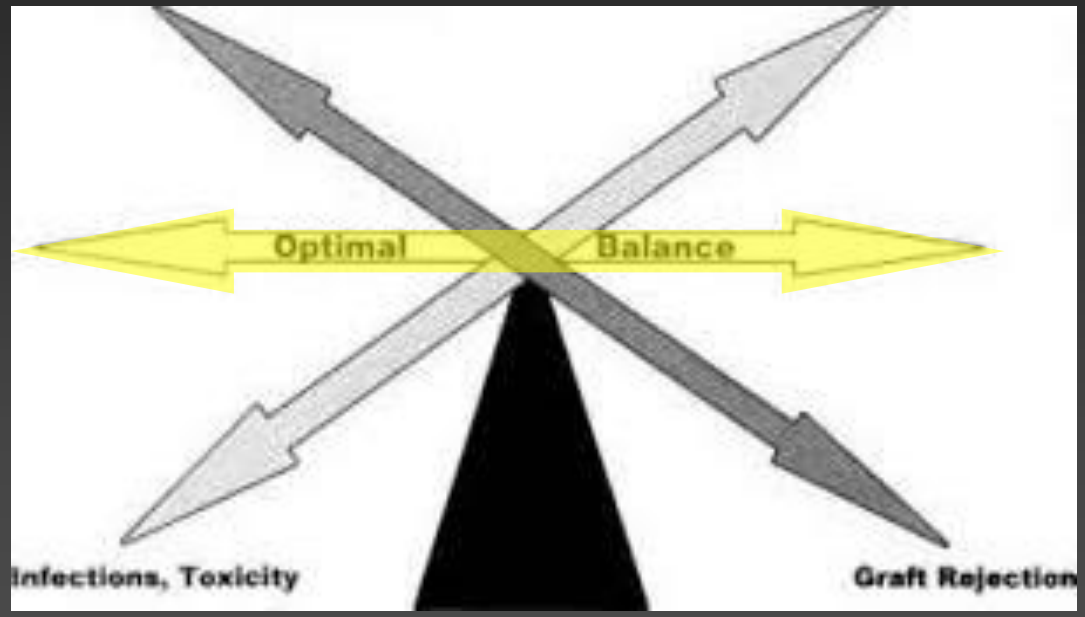
Sanquin

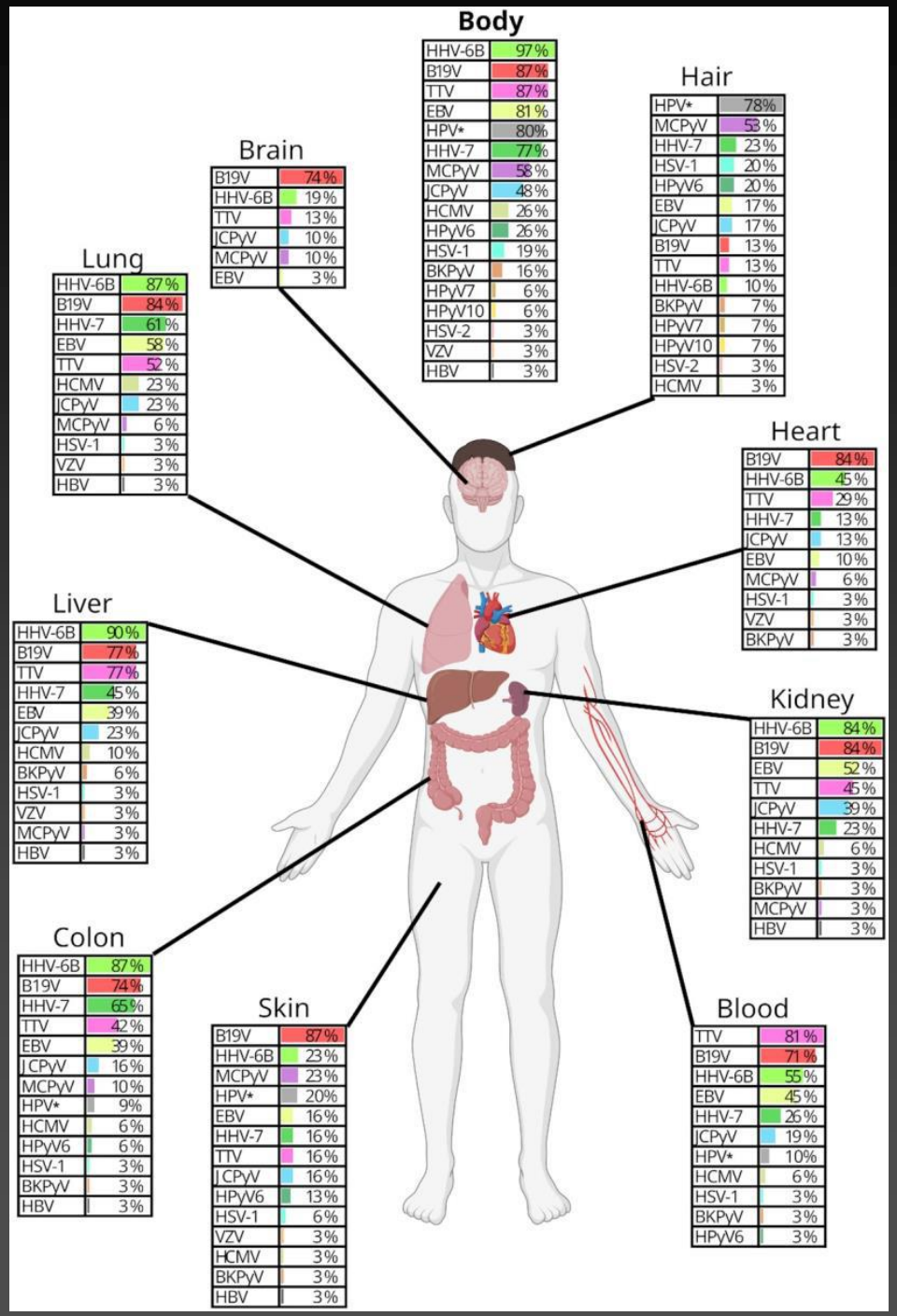
Kidney translantation patients

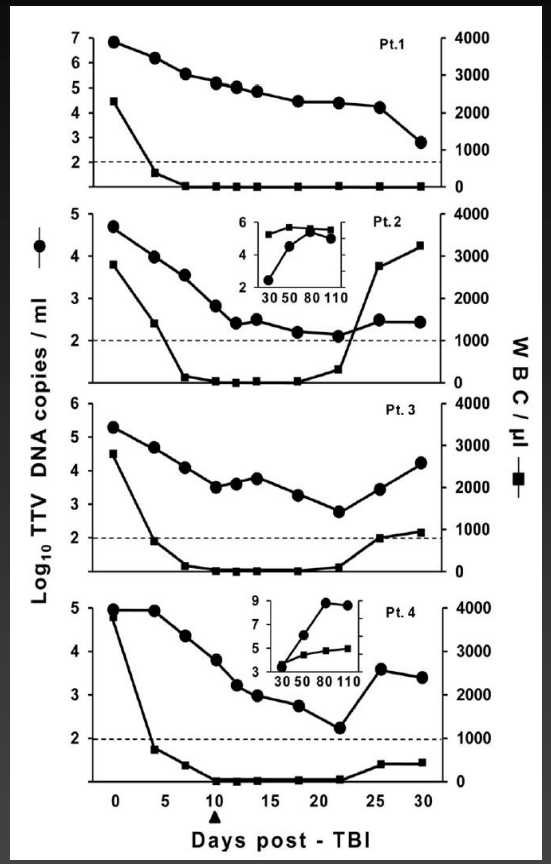
→ Life-long immunosuppression



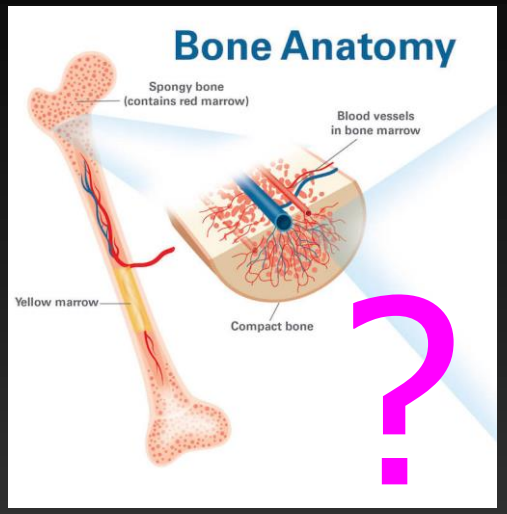


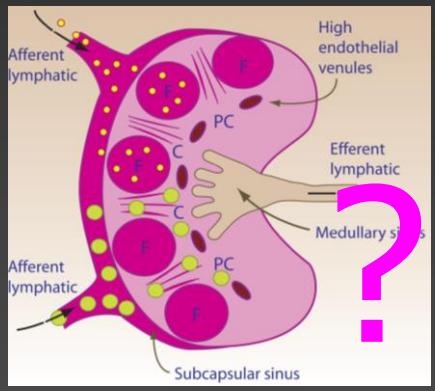
Too much **optimal dose** Too little

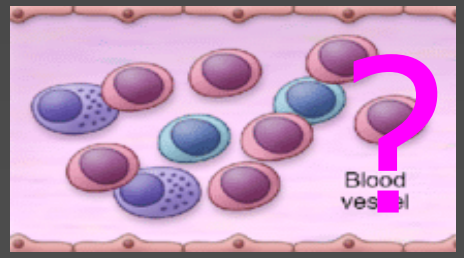




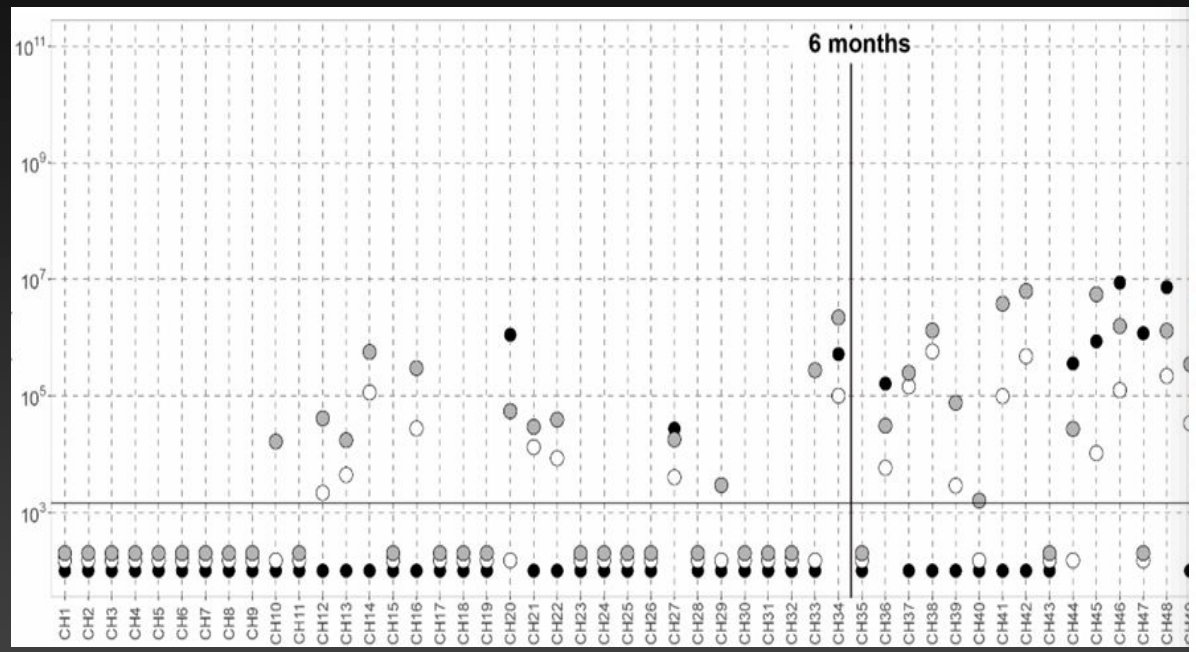
Maggi et al., Journal of Virology. 2010. 1;84(13):6891-3.



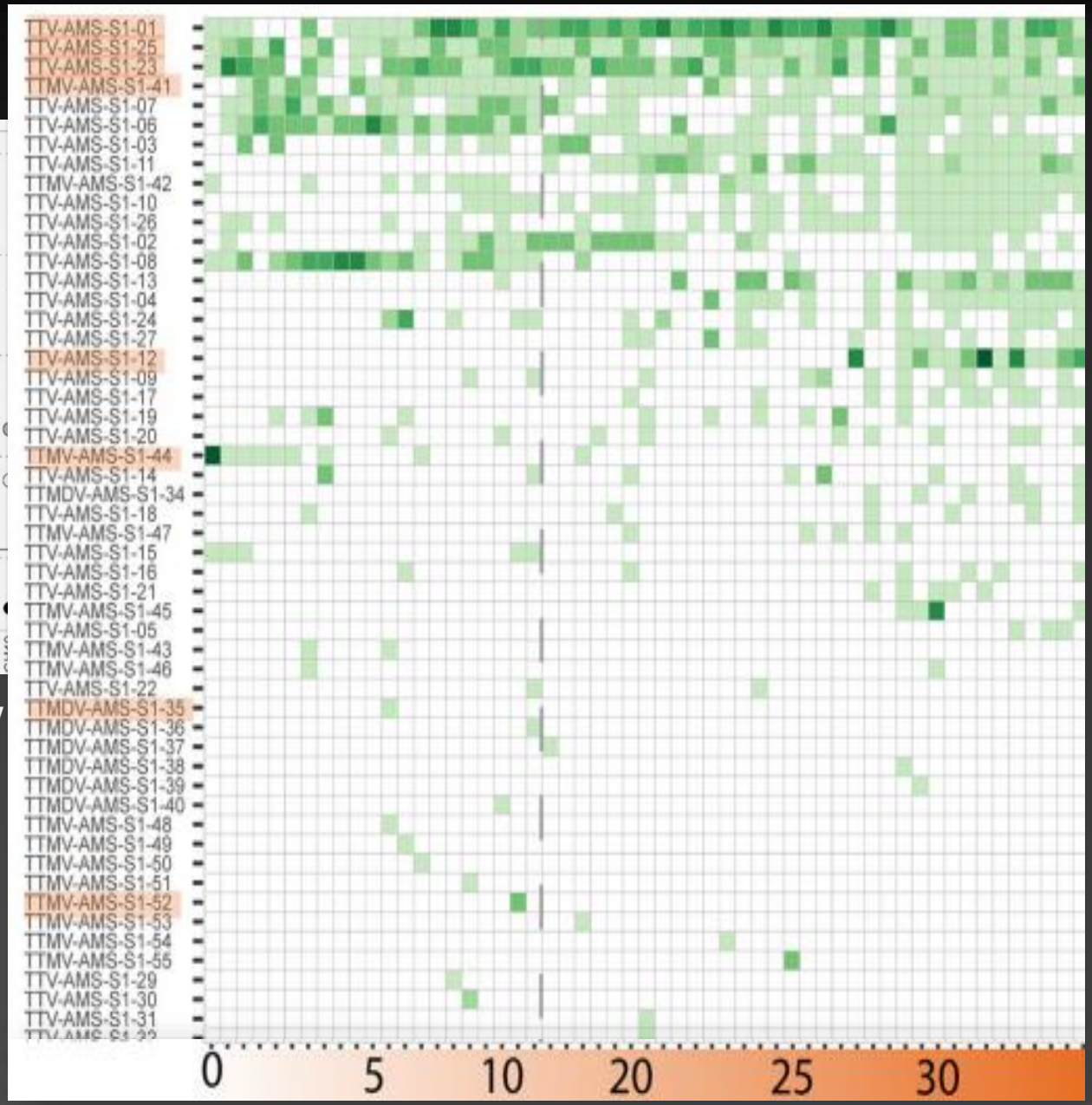




Pyoria et al., Nucleic Acids Res. 2023 ;51(7):3223-3239



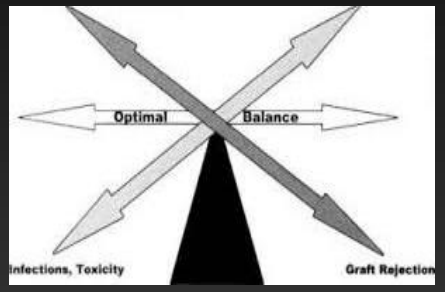
White ● : TTMV (betatorque) | Grey ● : TTMDV



Early-Life Colonization by Anelloviruses in Infants

Joanna Kaczorowska [1,2,*], Aurelija Cicilionytė [1,2], Anne L. Timmerman [1,2], Martin Deijs [1,2], Maarten F. Jebbink [1,2], Johannes B. van Goudoever [3,4], Britt J. van Keulen [3,4], Margreet Bakker [1,2] and Lia van der Hoek [1,2,*]

TTV-immunometer



Questions:

1. Predict complications of immunosupressant under- and overdosing?
2. TTV-load measurement for proper immunosuppressant dosing?

1. Predict complications of immunosupressant under- and overdosing?

515 adult living-related kidney transplant patients Period '03-'12

4 patients transplanted 2x, with different donors

519 renal transplant donor/recipient (D/R) pairs

112 Exclusions

22 No plasma samples availa

53 No serum samples pre-KT

37 1 plasma sample availabl

407 D/R pairs

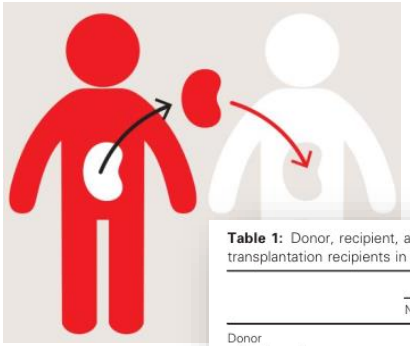
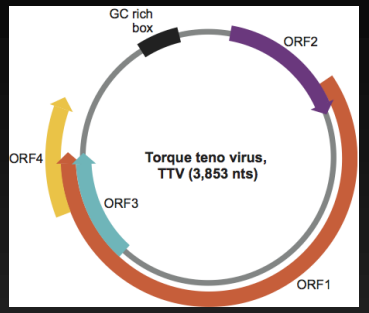


Table 1: Donor, recipient, and transplantation characteristics sorted for BKPyV viremia and BKPyVAN among 407 kidney transplantation recipients in the first year after kidney transplantation

	All recipients (n = 407)			Viremic recipients (n = 111)		
	No BKPyV viremia (n = 296)	BKPyV viremia (n = 111)	p-value[1]	No BKPyVAN (n = 99)	BKPyVAN (n = 12)	p-value[1]
Donor						
Age (years)	53 (11.7)	54 (11.5)	0.354	54 (11.7)	57 (9.6)	0.386
Sex						
Male	119 (40%)	42 (38%)	0.664	37 (37%)	5 (42%)	0.763
Recipient						
Age (years)	50 (13.5)	53 (14.2)	0.080	53 (14.1)	53 (16.1)	0.790
Sex						
Male	177 (60%)	73 (66%)	0.271	65 (66%)	8 (67%)	1.000
Underlying condition[2]						
Inherited	72 (24%)	26 (23%)	0.239	22 (22%)	4 (33%)	0.411
Glomerular	80 (27%)	26 (23%)		23 (23%)	3 (25%)	
Vascular	55 (19%)	32 (29%)		31 (31%)	1 (8%)	
Obstructive	27 (9%)	7 (6%)		6 (6%)	1 (8%)	
Other	62 (21%)	20 (18%)		17 (17%)	3 (25%)	
Dialysis pretransplantation	182 (62%)	64 (58%)	0.482	57 (58%)	7 (58%)	1.000
Duration dialysis (mo)	12 (18.4)	9 (12.1)	0.106	9 (11.6)	12 (15.9)	0.730
PRA pretransplantation						
Nonimmunized[3]	284 (96%)	108 (97%)	0.768	97 (98%)	11 (92%)	0.293
Monoclonal antibody						
Basiliximab	277 (94%)	103 (93%)	0.776	92 (93%)	11 (92%)	1.000
Alemtuzumab	19 (6%)	8 (7%)		7 (7%)	1 (8%)	
Calcineurin inhibitor						
Cyclosporin A	70 (24%)	27 (24%)	0.887	27 (27%)	0 (0%)	0.037
Tacrolimus	226 (76%)	84 (76%)		72 (73%)	12 (100%)	
Proliferation inhibitor						
Azathioprine	0 (0%)	1 (<1%)	0.273	1 (1%)		1.000
Everolimus	1 (<1%)	0 (0%)	1.000	0 (0%)	0 (0)%	n.p.
Mycophenolate mofetil	295 (100%)	110 (99%)	0.472	98 (99%)	0 (0%)	1.000
Corticosteroids	296 (100%)	111 (100%)	n.p.	99 (100%)	12 (100%)	n.p.
Rejection treatment[4]	61 (21%)	31 (28%)	0.116	22 (22%)	9 (75%)	<0.001
Transplantation						
Retransplantation	25 (8%)	11 (10%)	0.650	9 (9%)	2 (17%)	0.339
Year of transplantation						
Before 2007	43 (15%)	18 (16%)	0.671	18 (18%)	0 (0%)	0.209
2007 to present	253 (85%)	93 (84%)		81 (82%)	12 (100%)	
Unrelated donor	144 (49%)	67 (60%)	0.035	58 (59%)	9 (75%)	0.357
Blood group						
Compatible[5]	283 (96%)	104 (94%)	0.341	92 (93%)	12 (100%)	1.000
HLA mismatched						
A, B and DR loci[6]						
0	17 (6%)	6 (5%)	0.888	6 (6%)	0 (0%)	0.437
1–3	143 (48%)	51 (46%)		47 (48%)	4 (33%)	
4–6	136 (46%)	54 (49%)		46 (46%)	8 (67%)	

Wunderink et al., Am J Transplant 2017



PCR target gene UTR product length: 63 bp

Maggi et al., J Virol. 2003; 77:2418-2425

TTV-load measurements

Pre-KTx

Wk ~ -2

T = 0

Wk 6

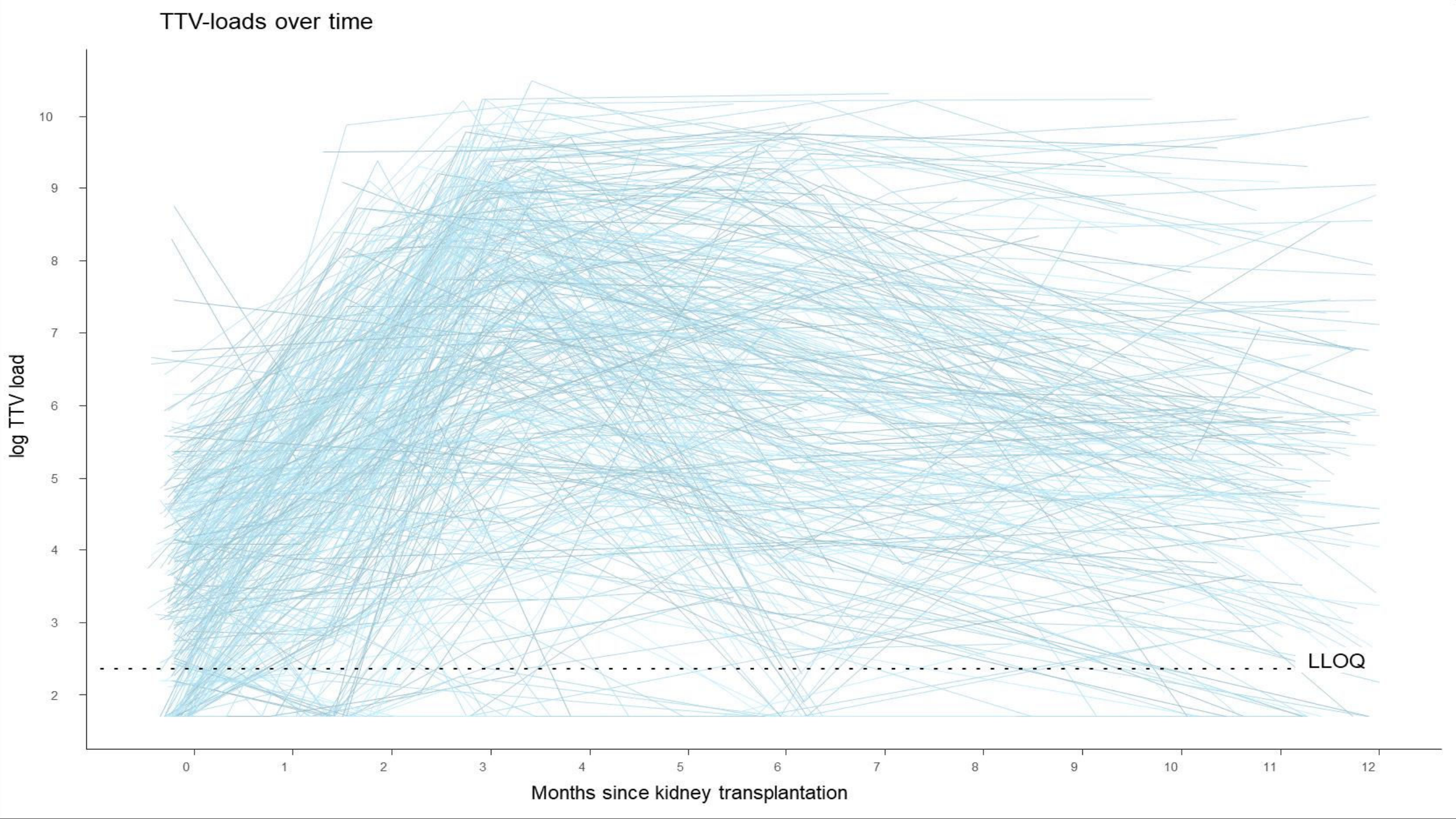
Wk 12

Wk 26

Wk 39

Wk 52

1 year follow-up


TTV-loads over time
log TTV load
10
9
8
7
6
5
4
3
2
LLOQ
0
1
2
3
4
5
6
7
8
9
10
11
12
Months since kidney transplantation

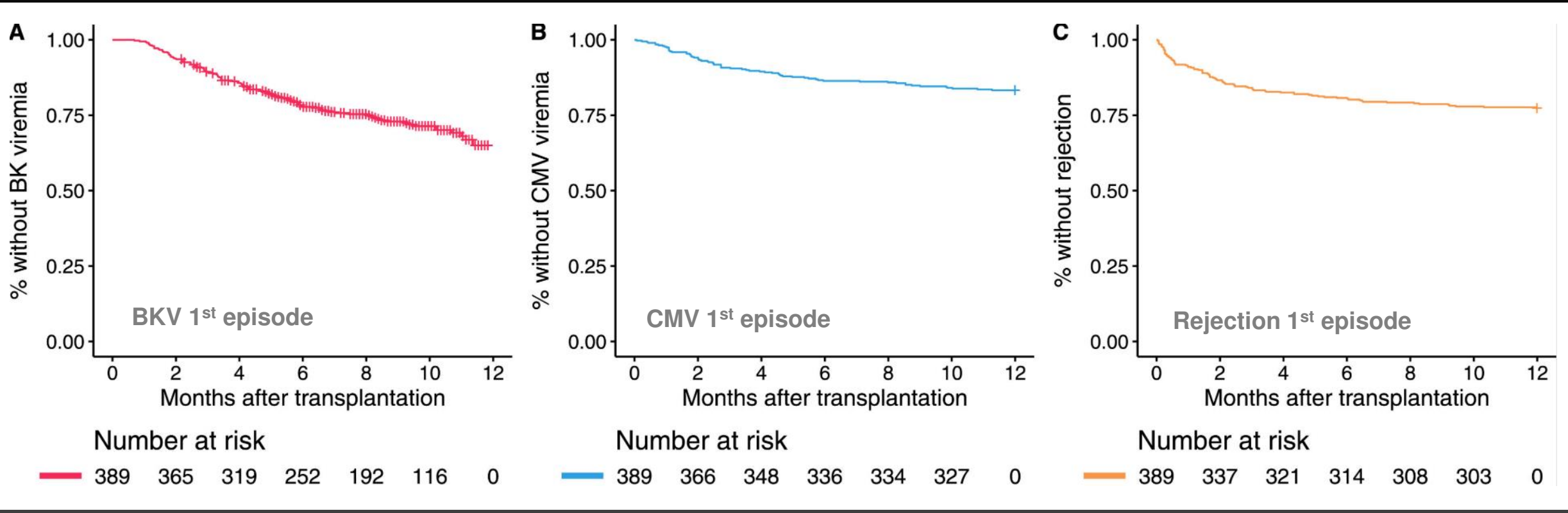


Table 4

Estimated hazard rate for BKPyV viremia and rejection based on changes in TTV load after KTx.

		HR*	95% CI		P value
BKPyV viremia	*TTV load 1 log increase*				
CMV viremia	*TTV load 1 log increase*				
Rejection episode	*TTV load 1 log increase*	0.74	0.71	0.76	<0.001

Kidney allograft rejection (Rejection endpoint)

Allograft rejection was the third endpoint in this study. Allograft rejection was defined as the first initiation of rejection treatment after transplantation. In some patients, rejection treatment was initiated without prior histological confirmation of allograft rejection if clinical suspicion was high and alternative explanations were excluded. Suspicion of rejection included increased serum creatinine levels, low concentration of immunosuppressive medications and allograft biopsy with histological evidence of rejection. First rejection treatment consisted of 1000 mg methylprednisolone intravenously for three days. The median

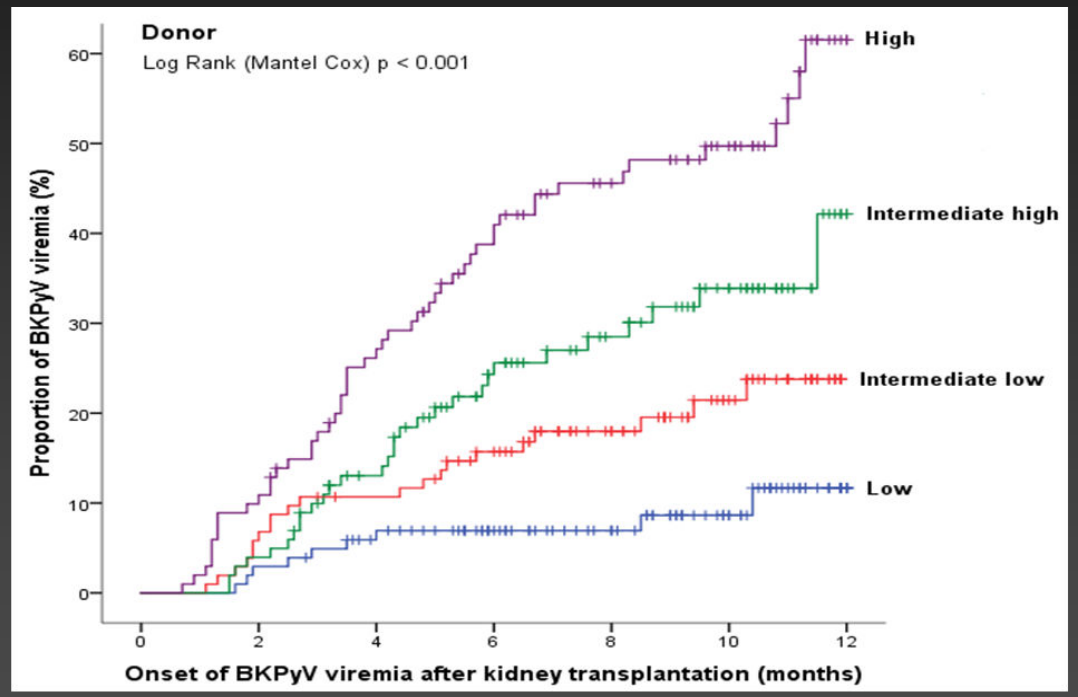
! - D/R CMV-matching
- CMV prophylaxis

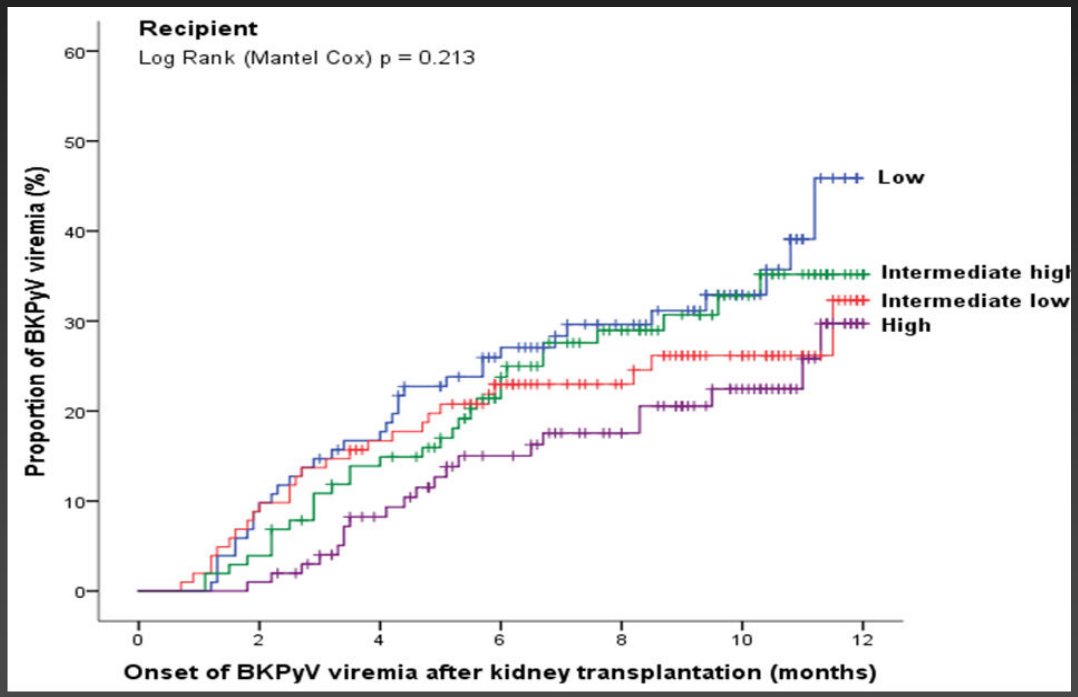
Van Rijn et al., J Clin Virol. 2021 ;140:104871

Van Rijn et al., J Clin Virol. 2021 ;140:104871

Our observation that the risk of BKPyV viremia was not related with TTV-load nor with any of the other covariates, fits with findings from one of our previous studies aimed at identifying risk factors for BKPyV infection [3]. In that study performed within the same cohort, we showed that the risk of BKPyV viremia is primarily governed by the BKPyV infection risk imposed by the donor, which can be estimated based on pre-KTx donor BKPyV IgG seroreactivity, and much less dependent on the immune status of the recipient.

Wunderink et al., Am J Transplant 2017



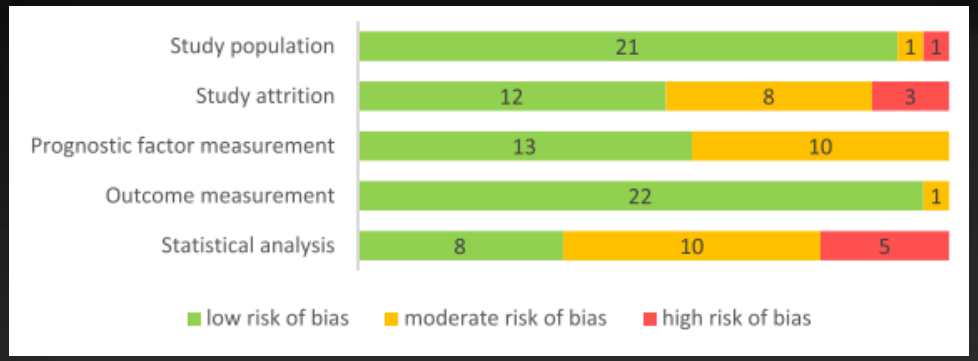


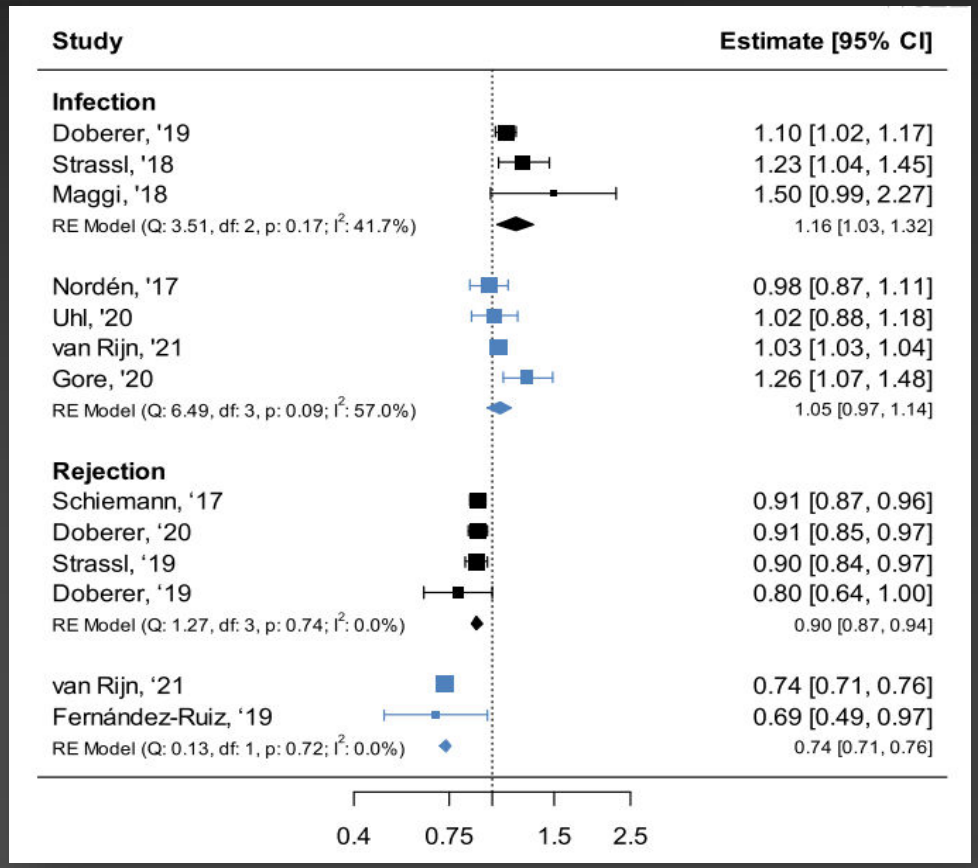
Donor	HR	95%-CI	P-value
Seroreactivity quartile groups			
Q1 Low	**1.0**		< 0.001
Q2 Low intermediate	**2.34**	1.07 - 5.11	0.033
Q3 High intermediate	**3.82**	1.82 - 8.06	<0.001
Q4 High	**6.92**	3.41 - 14.06	<0.001

Recipient	HR	95%-CI	P-value
Seroreactivity quartile groups			
Q1 Low	**1.0**		0.221
Q2 Low intermediate	**0.74**	0.47 - 1.24	0.257
Q3 High intermediate	**0.85**	0.52 - 1.39	0.509
Q4 High	**0.57**	0.33 - 0.98	0.041

Original article				TTV PCR	Reported association[c]	
First author, year	Tx type[a]	Size[b]	Population	Primer set	Infection	Rejection
Blatter, '18	LuTx	57	Pediatric	Maggi et al.[22]		▼
Blatter, '20	LuTx	64	Adults	Maggi et al.		=
Doberer, '19	KTx	386	Adults	Maggi et al.	▲	▼
Doberer, '20	KTx	307	Adults	Maggi et al.		▼
Fernández-Ruiz, '19	KTx	221	Adults	TTV R-GENE®	▲	▼
Fernández-Ruiz, '20	KTx	215	Adults	TTV R-GENE®	▲	
Frye, '19	LuTx	34	n.m.[d]	Maggi et al.	▲	▼
Gore, '20	KTx	666	Adults	TTV R-GENE®	▲	
Görzer, '14	LuTx	31	Both	Maggi et al.	▲	
Görzer, '17	LuTx	20	Adults	Maggi et al.		▼
Handala, '19	KTx	116	Adults	TTV R-GENE®	=	
Herrmann, '18	LiTx	136	Adults	Maggi et al.	▲	
Jaksch, '18	LuTx	143	Adults	Maggi et al.	▲	▼
Maggi, '18	KTx + LiTx	280	Adults	Maggi et al.	▲	
Nordén, '17	LuTx	98	Adults	Maggi et al.	=	=
Ruiz, '19	LiTx	63	Adults	Maggi et al.	▲	▼
Schiemann, '17	KTx	715	Adults	Maggi et al.		▼
Simonetta, '17	LiTx	39	Both	Maggi et al.		▼
Solis, '19	KTx	66	Adults	TTV R-GENE®	▲	▼
Strassl, '18	KTx	169	Adults	Maggi et al.	▲	
Strassl, '19	KTx	113	Adults	Maggi et al.		▼
Uhl, '20	KTx	45	Pediatric	Maggi et al.	=	
Van Rijn, '21	KTx	389	Adults	Maggi et al.	=	▼

Note: ▲ Authors conclude there is an association between high TTV-load and the outcome. ▼ Authors conclude there is an association between low TTV-load and the outcome. =Authors conclude there is no association.





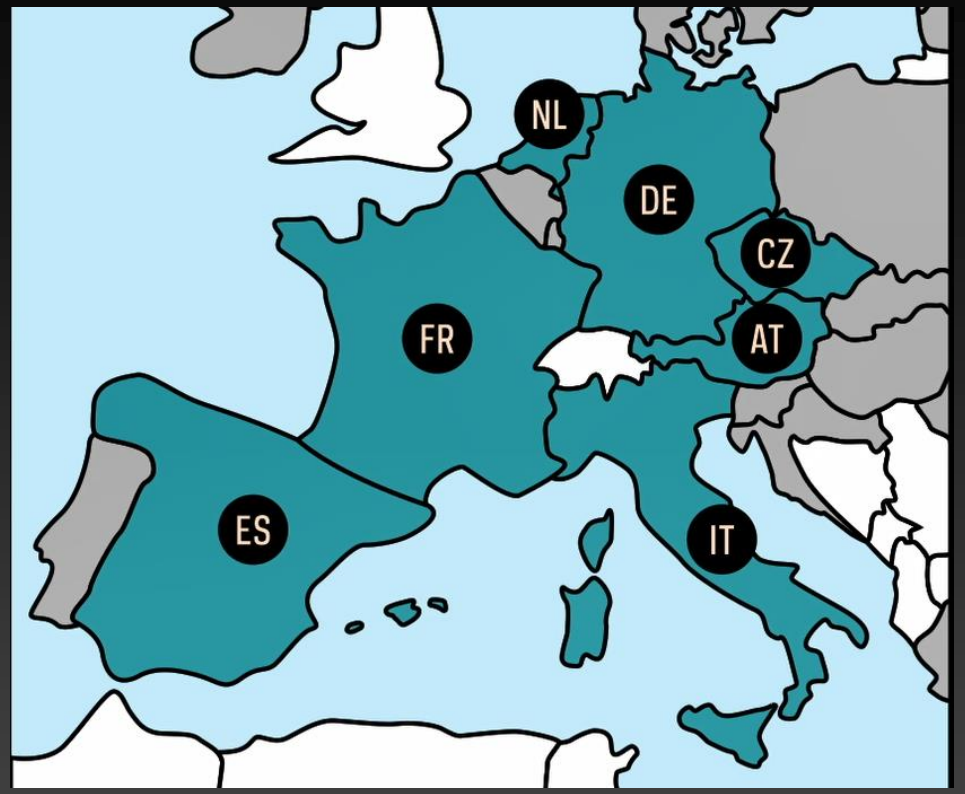
Van Rijn et al., Rev Med Virol. 2023 Jan;33(1):e2393

2. TTV-load measurement to guide immunosuppressant dosing?

TTV-GUIDE-TX intervention trial

TTV GUIDE

Torque Teno Virus Based Immune Monitoring



Consortium

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European Union Funding
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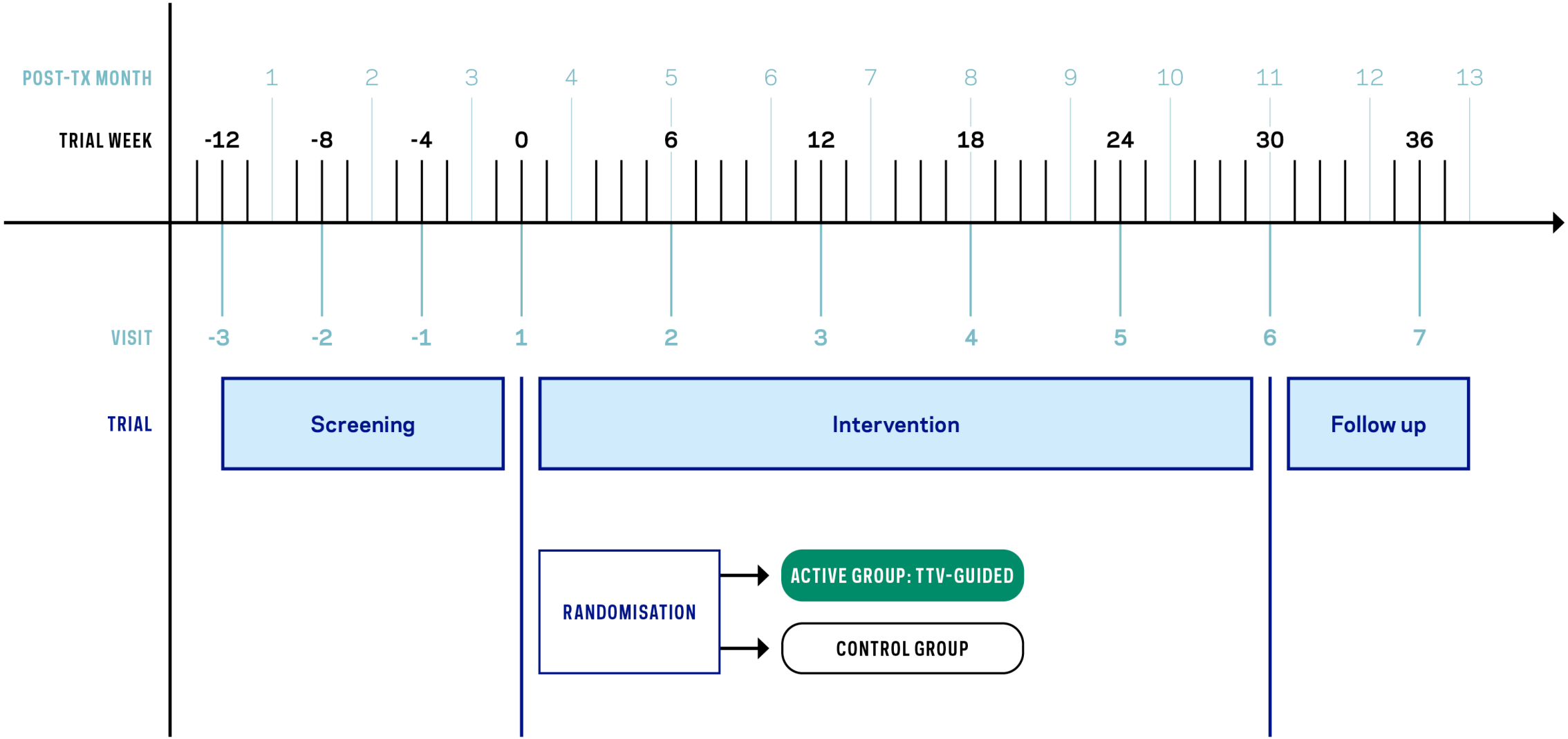
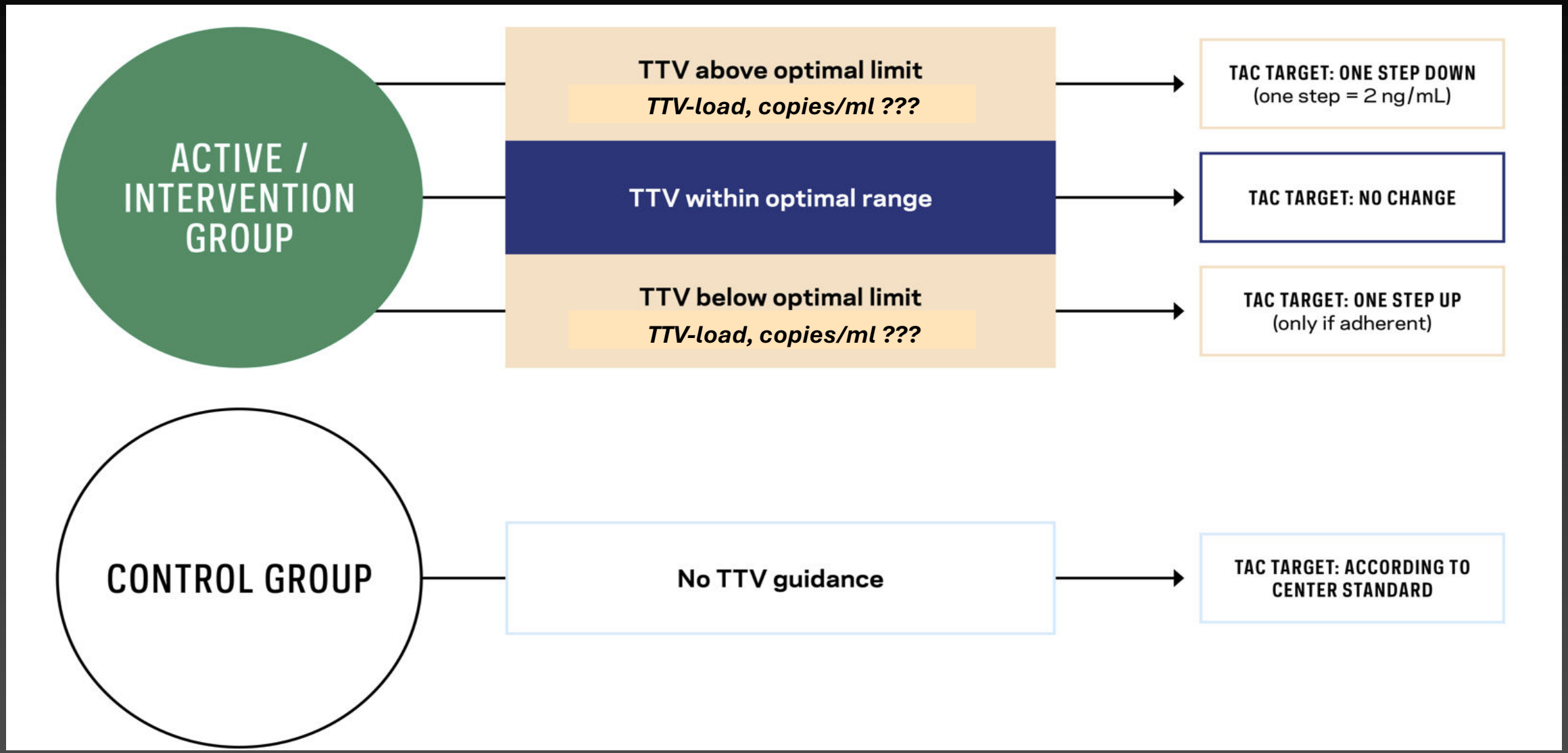
TRANSPLANTATION (TX)





Randomization

1 : 1 (~300 pts)

Measurement

TTV-load

Intervention

[TAC-dosing]

Table 3
Diagnostic accuracy of rejection detection by TTV load applying commercial PCR.

TTV	NPV	PPV	Sensitivity	Specificity
<4.0 log_{10}	0.84	0.67	0.33	0.97
<4.6 log_{10}	0.86	0.53	0.44	0.90
<5.0 log_{10}	0.92	0.62	0.67	0.90
<6.0 log_{10}	0.92	0.42	0.78	0.73
<7.0 log_{10}	0.97	0.31	0.94	0.46
<8.0 log_{10}	0.86	0.22	0.94	0.12

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; TTV, Torque Teno virus.

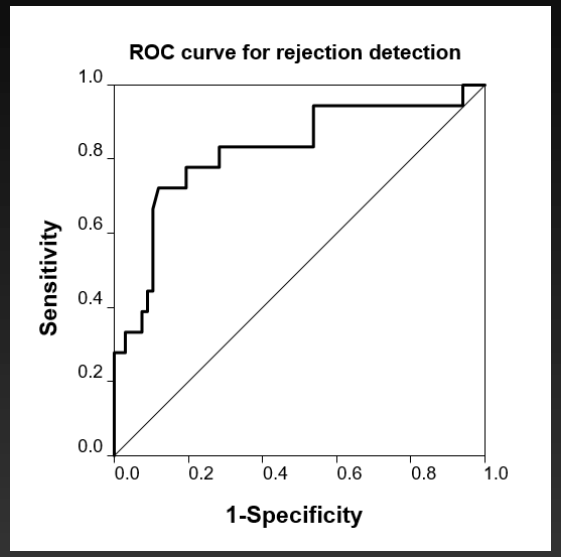
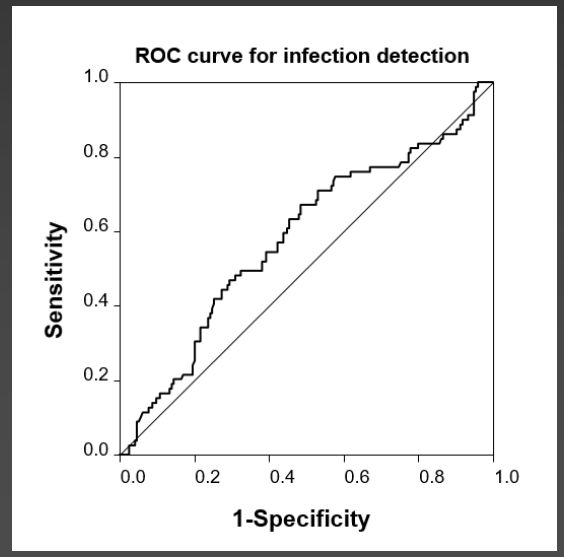


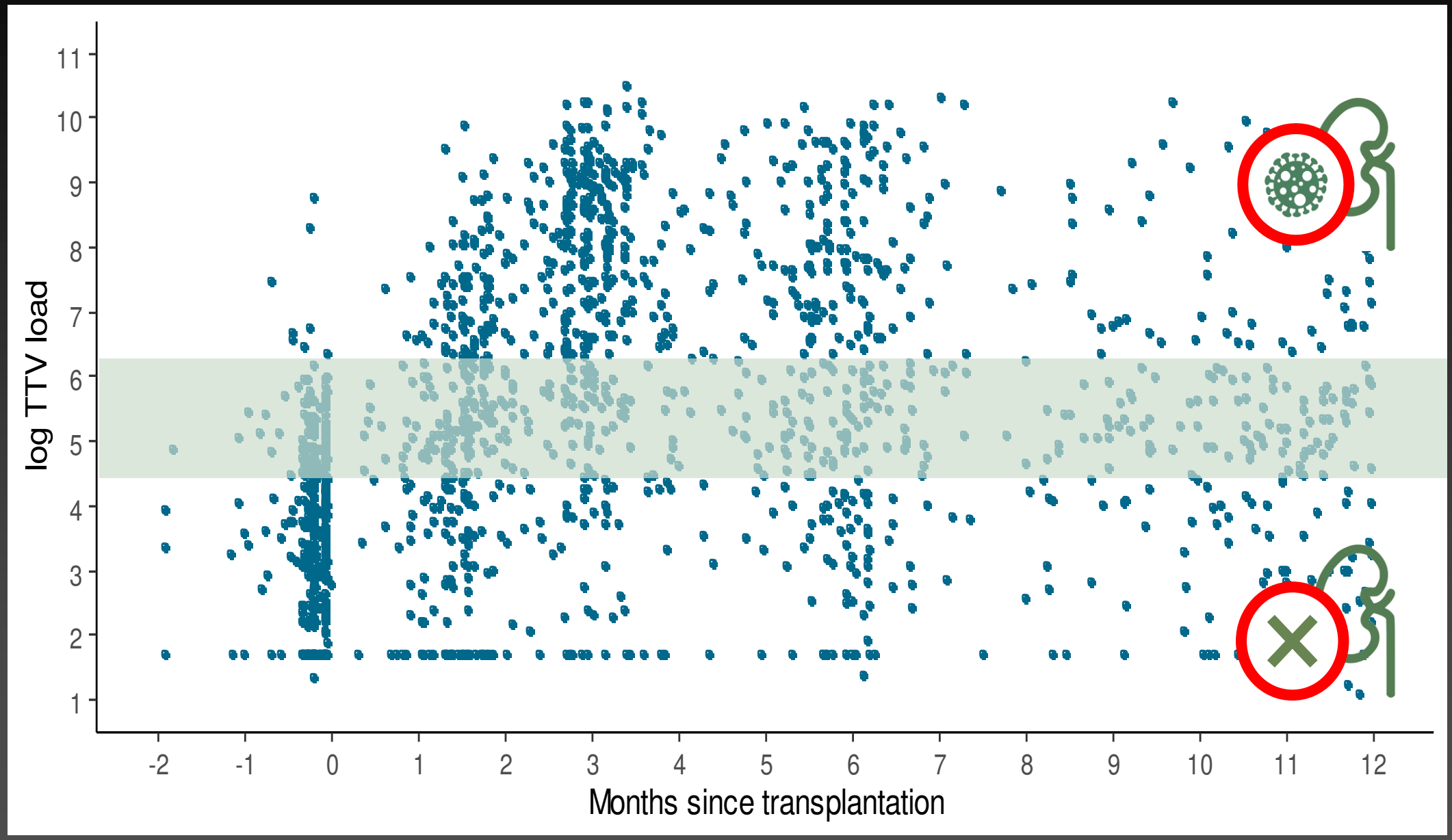
Table 4
Diagnostic accuracy of infection detection by TTV load applying commercial PCR.

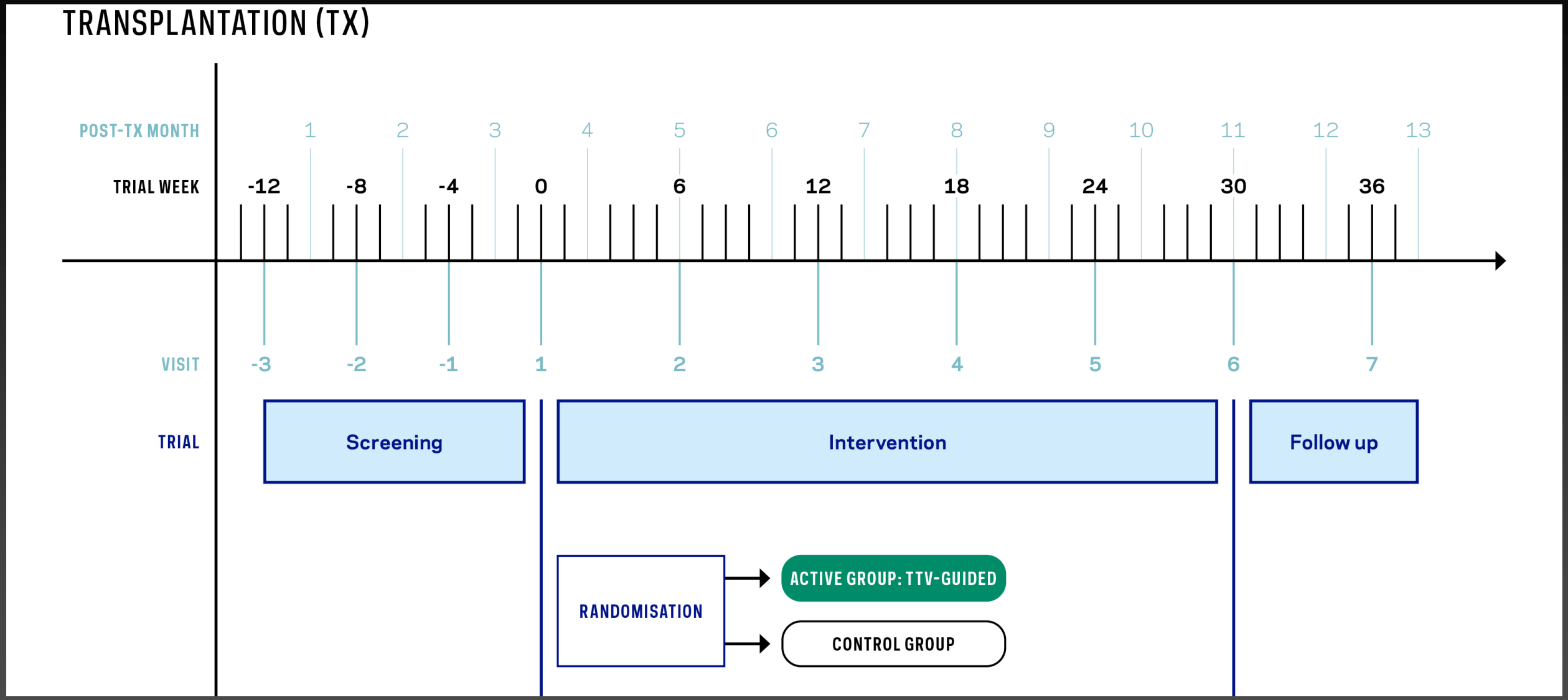
TTV	NPV	PPV	Sensitivity	Specificity
≥4.0 log_{10}	0.65	0.28	0.89	0.09
≥5.0 log_{10}	0.75	0.30	0.77	0.28
≥6.0 log_{10}	0.78	0.34	0.68	0.47
≥6.6 log_{10}	0.77	0.35	0.57	0.58
≥7.0 log_{10}	0.76	0.38	0.49	0.67
≥8.0 log_{10}	0.72	0.38	0.14	0.91

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; TTV, Torque Teno virus.



Gorzer et al., J Clin Virol. 2023; 158:105348


log TTV load
11
10
9
8
7
6
5
4
3
2
1
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
Months since transplantation
6.2 Log10
4.6 Log10



Inclusion almost finalized

First results are expected end of 2025, beginning 2026