

Charge virale TTV et greffe quelles applications cliniques ?



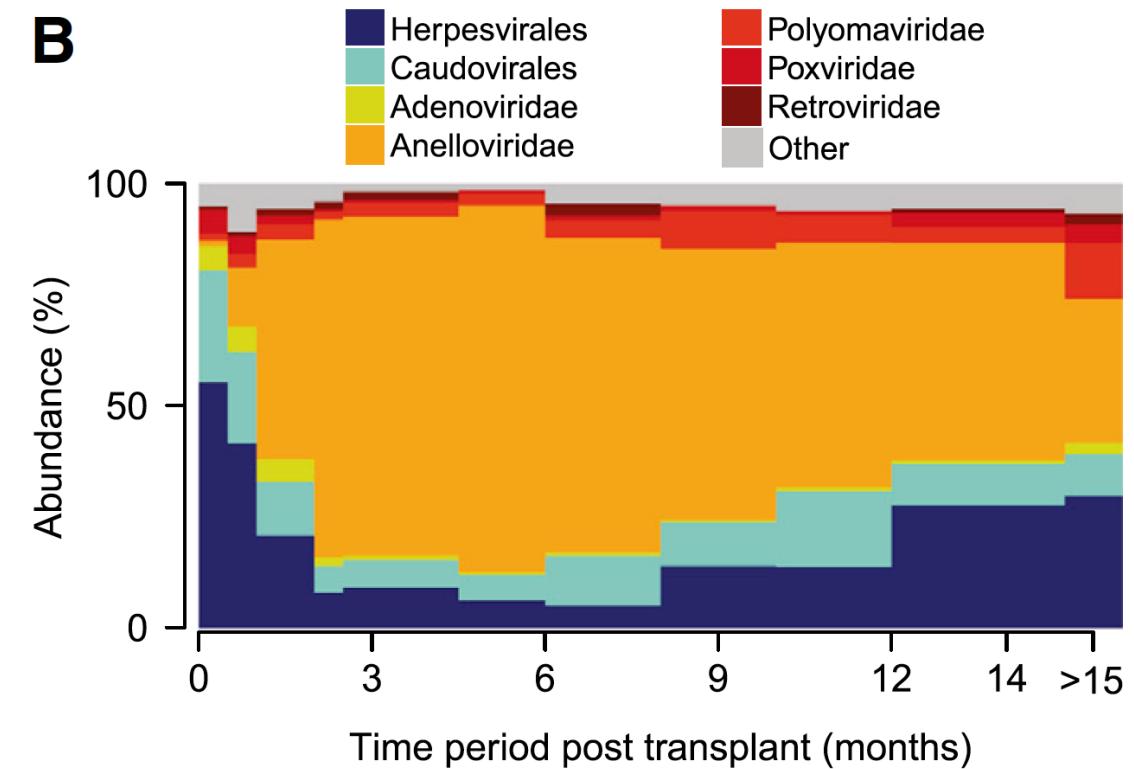
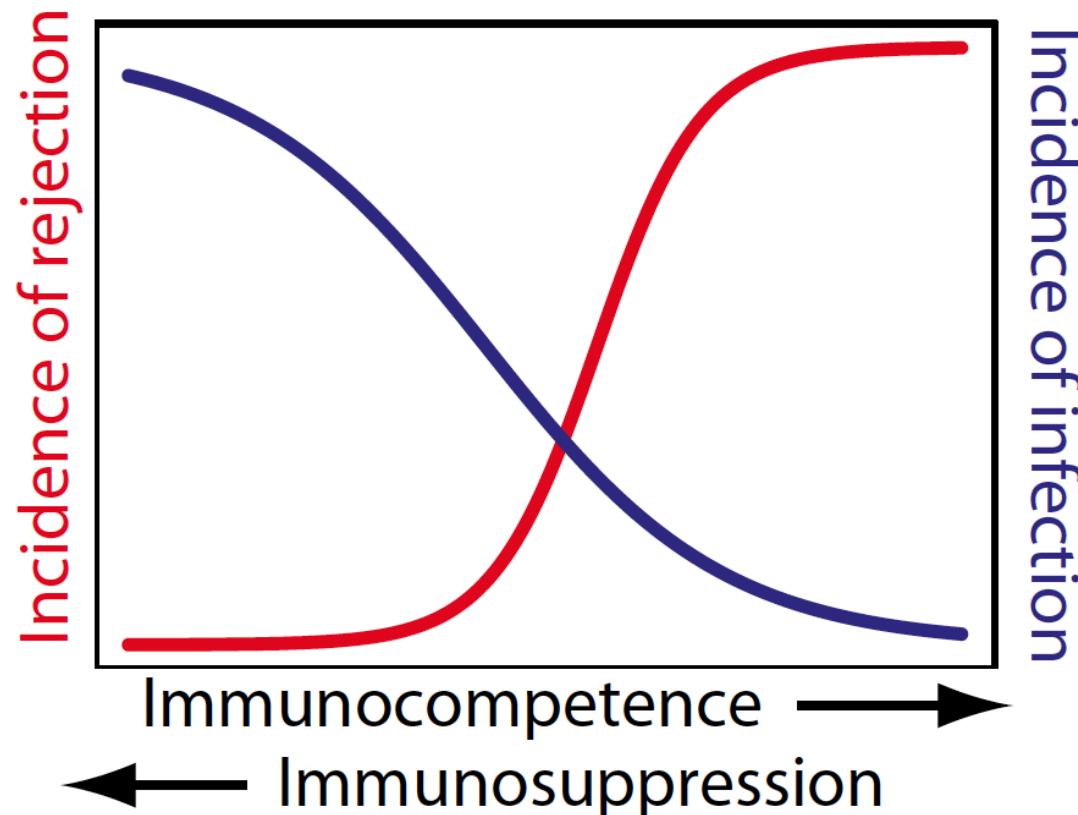
Cohorte/collection biologique
BioSUPORT

Sophie Alain
CNR Herpèsvirus
CHU de Limoges

Congrès OUEST-TRANSPLANT
10 NOVEMBRE 2022



Une relation étroite entre immunosuppression infection et rejet

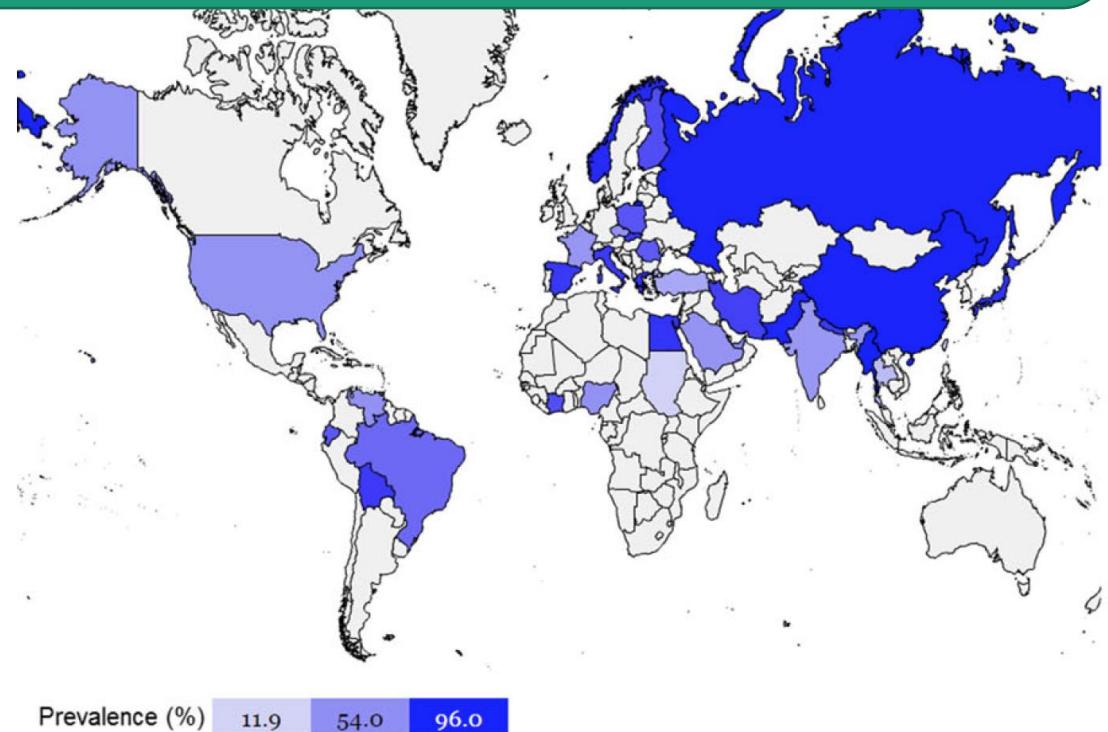


Les atouts de TTV comme biomarqueur de l'immunité

- Distribution ubiquitaire
- Virus nu hautement résistant
- Acquisition précoce dans la vie, par voie respiratoire, digestive, périnatale ...
- Prévalence élevée de détection de l'ADN circulant indépendamment de l'âge, de l'ethnie, du sexe et du statut socio-économique
 - >95% des immunocompétents sont positifs au moins une fois pour l'ADN du TTV
 - Fréquence élevée de détection de l'ADN du TTV dans le plasma des patients immunodéprimés (>> à EBV)
 - 70% cœur-poumon (*De Vlaminck et al., 2013*),
 - 84% poumon (*Gorzer et al., 2014*)
 - 74% foie (*Simonetta et al., 2017*)
 - 83% Kidney (*Kulifaje et al., 2018*)
 - 96% HIV sous ART (*Schmidt et al., 2021*)
- Fluctuations de la charge virale en fonction du niveau d'immunodépression

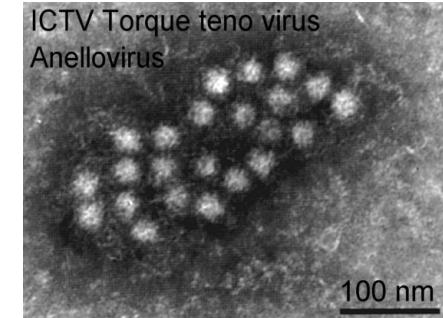
Marqueur de rejet +/- d'infection

pas d'étude interventionnelle à ce jour
=> Programme européen TTV Guide TX



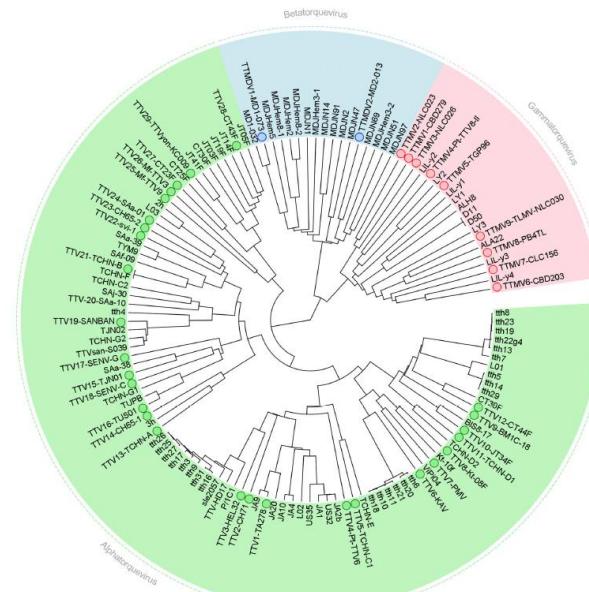
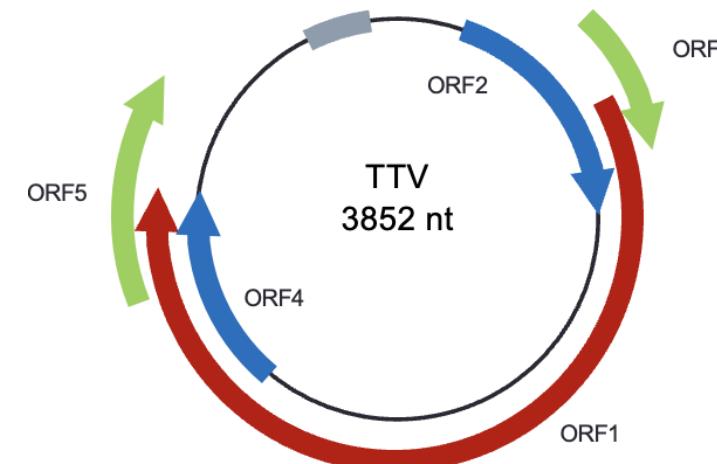
Prévalence de l'ADN TTV dans le plasma
(spandole et al., 2015)

Quantification de la charge virale TTV circulante



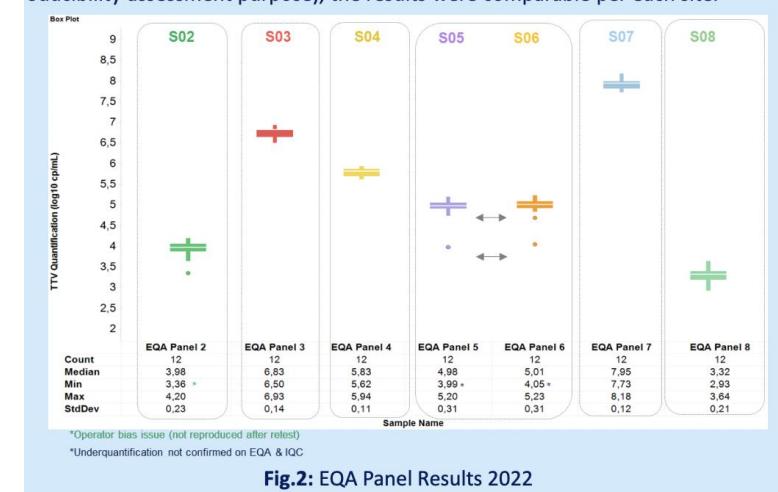
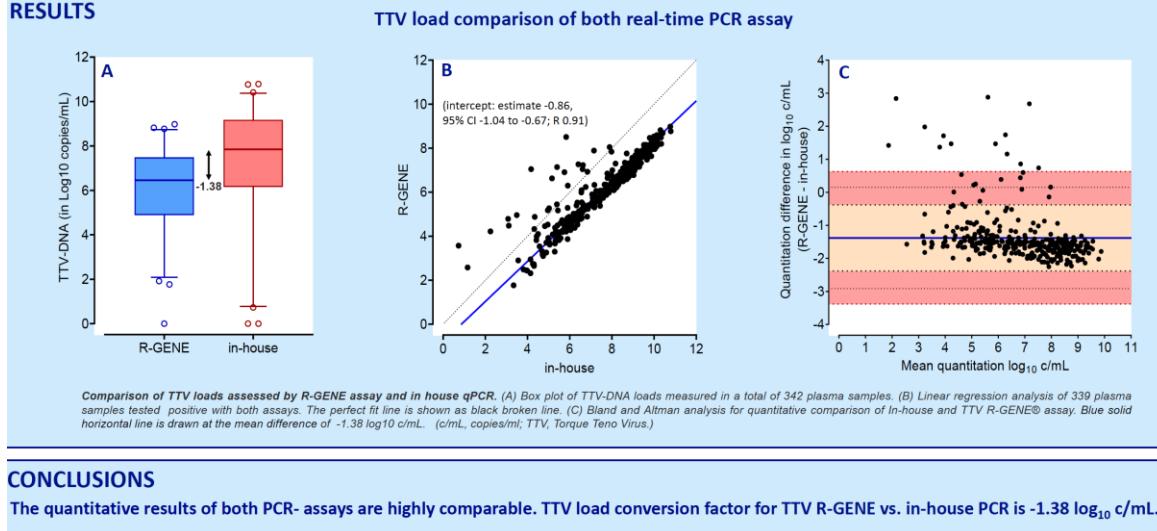
TTV (*Ytoh, BBRC, 2001*)

- 1 qPCR TTV R-GENE® (BioMérieux) CE-IVD : 2-10 log cp/ml
 - 2 qPCRs maison (Vienne/Pise)
 - Ciblent au moins 12 TTV HUMAINS
 - Région 5'non codante, mieux conservée que l'ORF1 (génotypage)
 - Sang total (+/-) ou plasma (++)



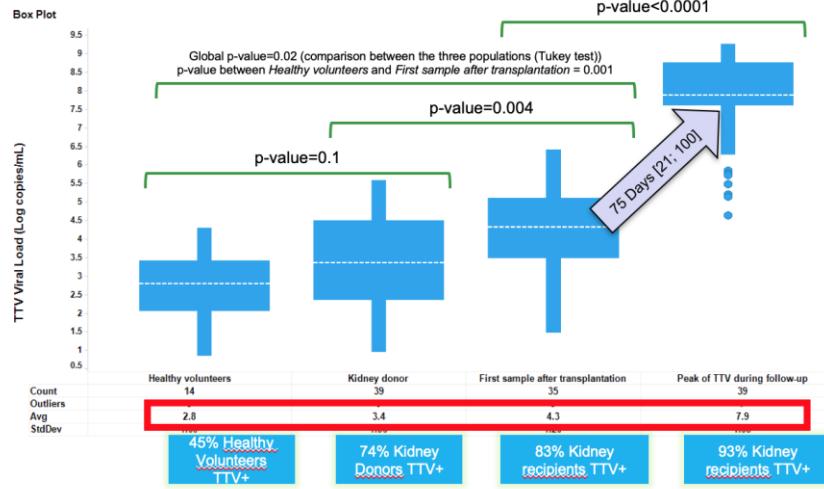
Quelle méthode de mesure de la charge virale TTV ?

- Colinéarité mais différences $> 1 \log$ copies/mL entre PCR maison et PCR CEIVD => Facteur de conversion 1, 38 permettant de comparer les résultats des études **mais standardisation indispensable**
- EQA sur Plasma avec la même PCR (TTV R gene (CEIVD)) sur les 6 laboratoires de TTVGuideTX => résultats homogènes **et colinéaires**



Evolution de la charge virale TTV post greffe

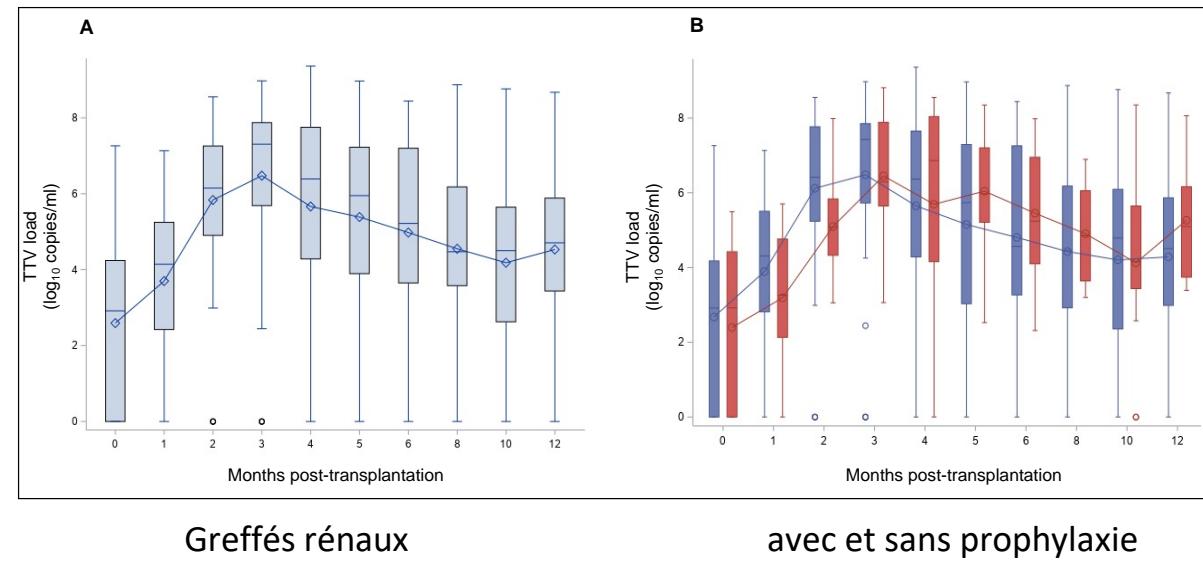
- Une réPLICATION intense : 10^{10} genomes/j, et une élimination rapide du virus du plasma par le système immunitaire
- Des charges virales de 10^2 à 10^9 copies de génome /mL



Kulifaj et al., JCV 2018.

- Non influencée par les traitements antiviraux

Cinétique de la charge virale TTV au cours du suivi :
Résultats du Protocole Quantic R+ (Suivi prospectif. 64 greffés rénaux, multicentrique France) (Mafi et al., en préparation)



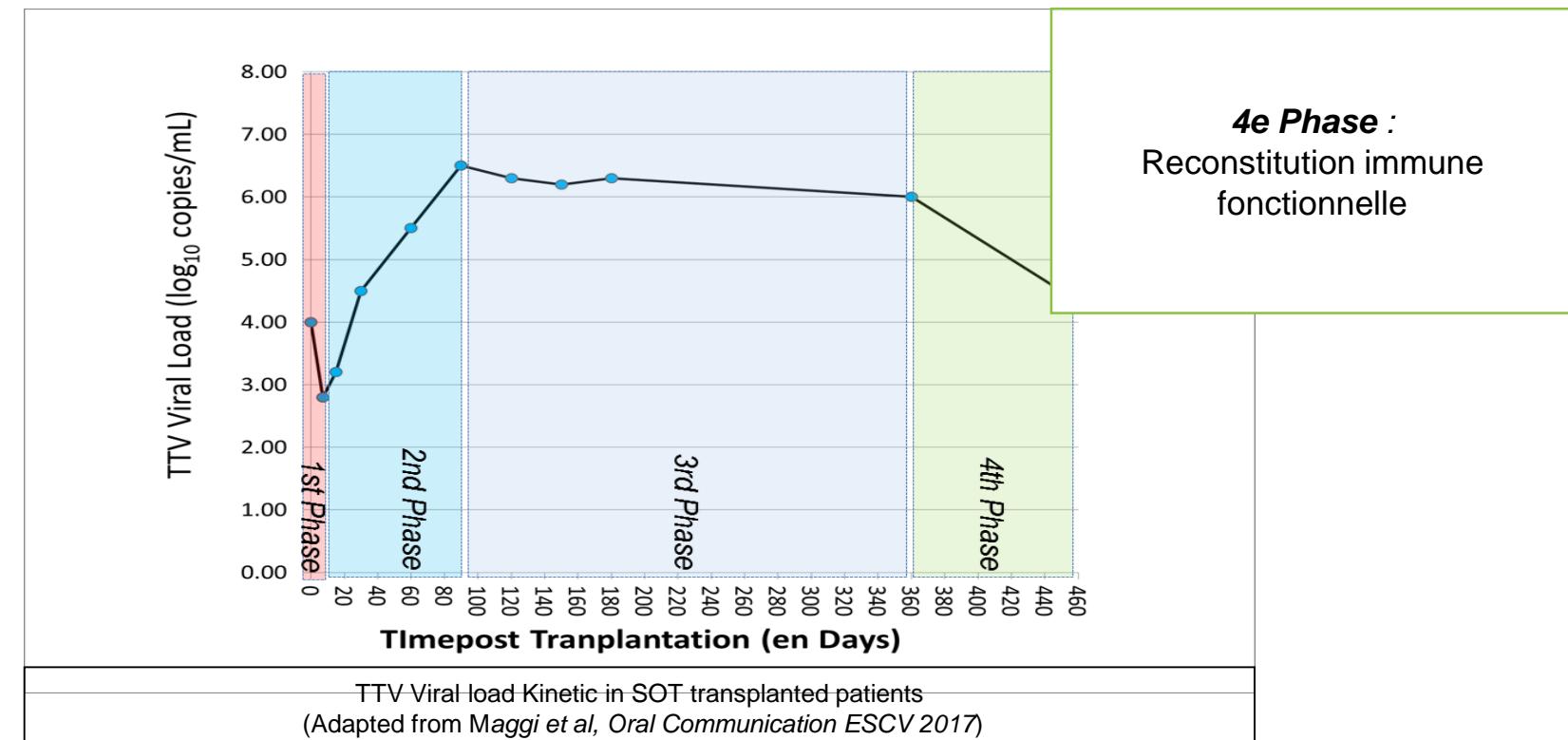
Egalement observé par Vlaminck et al., Cell 2013

Cinétique de charge virale TTV en transplantation d'organe :

- 4 phases (adapté de Maggi et al. ESCV 2017)
 - ≈15 j post-transplantation: diminution
 - ≈15 j-3 mois post-transplantation: augmentation de charge virale 3 à 6-7 \log_{10} copies / mL (rein), 9-10 \log_{10} copies / mL (poumon).
 - ≈3 mois- 1 an post-transplantation: stabilisation
 - >1 an post-transplantation: diminution et retour au niveau basal

La charge virale TTV
au plateau dépend du
type de greffe

Poumon>rein/foie



La charge virale TTV est étroitement associée à la réponse cellulaire en greffe d'organe.

- Corrélation inverse avec :
 - CD3+, p 0,017 at M3 p<0,0001
 - CD4+ p0,015, at M3 p<0,001
 - CD8+ p 0,016
- Pas d'impact du choix du régime immunosupresseur
- Corrélation avec les doses d'immunosupresseurs => futur marqueur?

Valeur prédictive de la charge virale TTV en transplantation d'organe solide ?

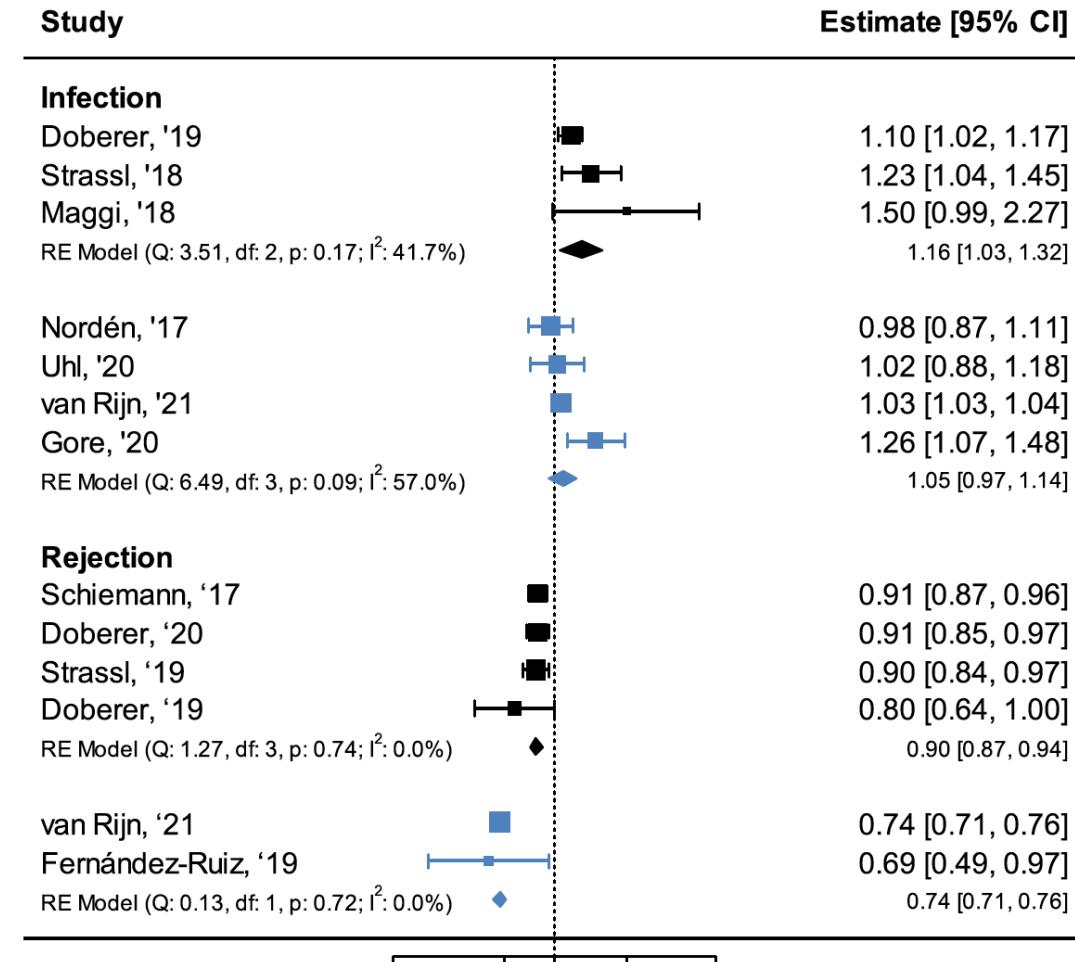
Baseline ou M1

M3 ou > M3

WILEY

VAN RIJN ET AL.

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



TTV et infection?

Intérêt de combiner plusieurs marqueurs pour améliorer la valeur prédictive.

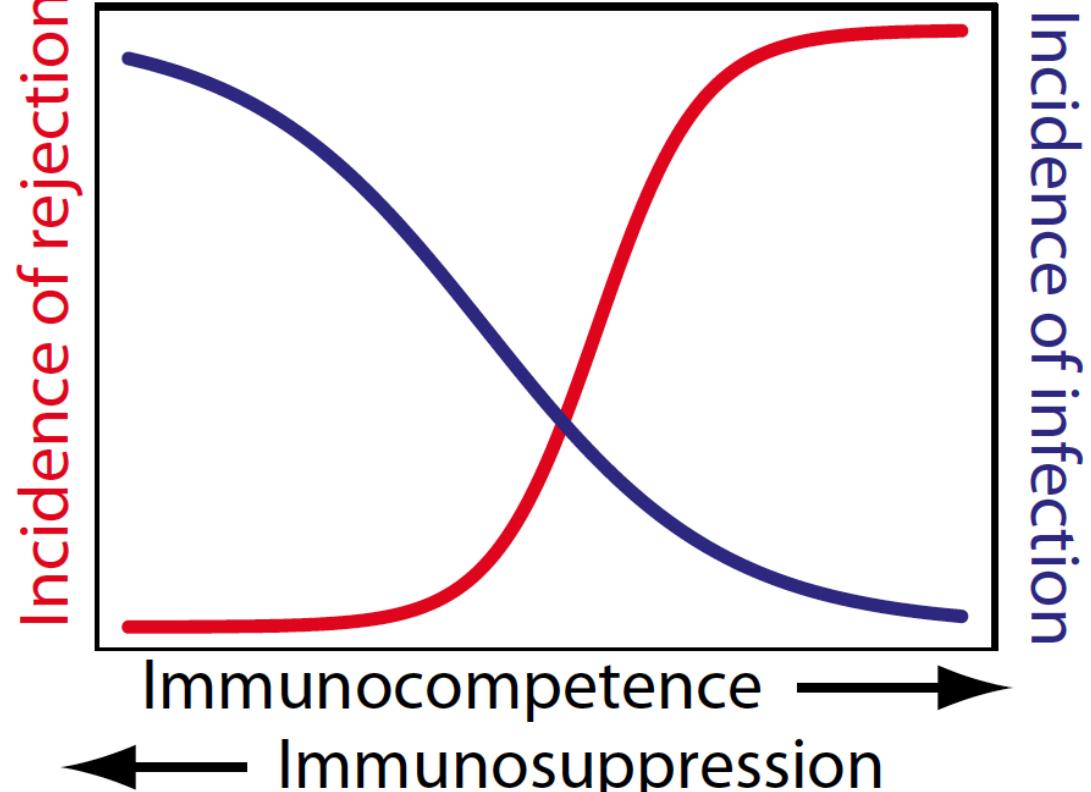


TABLE 2.

Studies that evaluated the association between TTV load and infection in kidney transplant recipients

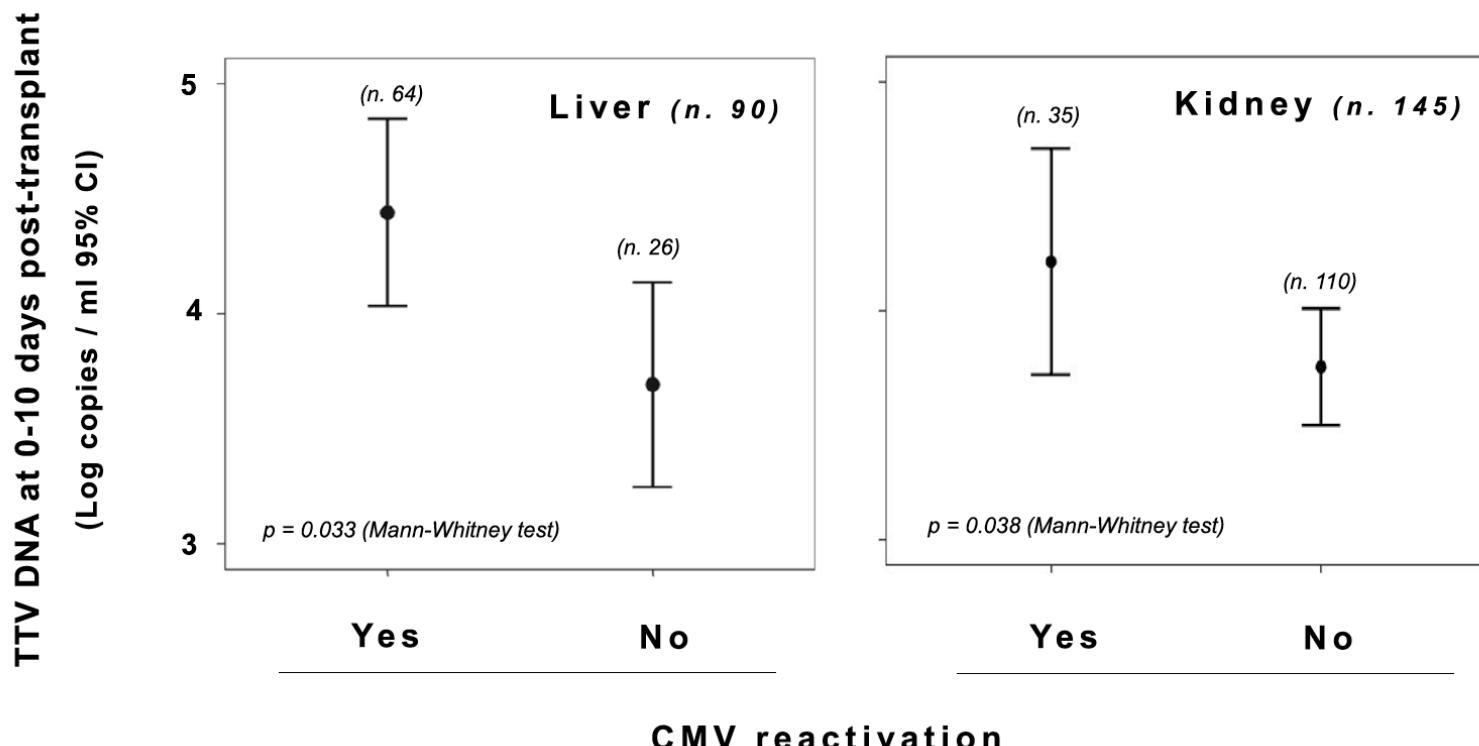
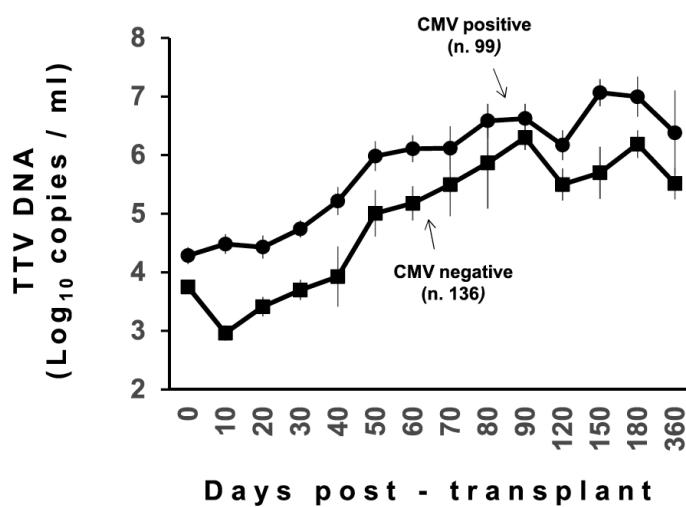
Study design ^a	TX period	Included patients	Endpoint; timing	Patients with event; infectious events				Limitations ^b
				PCR	Main association			
Cohort ⁸⁰	2016	71	Infection leading to medical measure; months 4–12 post-TX	22; 41	IH	TTV 1 mo before event–infection		Interim analysis; secondary endpoint
Cohort ⁷⁴	2014–2016	221	Infection leading to medical measure/opportunistic infection + malignancy; <12 mo post-TX	51; 65	C	TTV 1 mo post-TX–subsequent event		Two main endpoints; multiple testing; missing information on model design/some major determinants of TTV not included
Cohort ⁸¹	2015–2016	116	BKV viremia; <12 mo post-TX	24; 24	C	NA		Multiple testing; no effect size adjustment
Cohort ⁷⁵	2016–2018	274	Infection leading to medical measure; months 4–12 post-TX	127; 193	IH	TTV 1 mo before event–infection		Secondary endpoint
Case-control ^{82,c}	2011–2016	145	CMV viremia; <4 mo post-TX	35; 35	IH	TTV days 0 to 10 post-TX–CMV		Possible selection bias; main analyses include LTX; multiple testing; no effect size adjustment
Case-control ⁷⁹	2012–2014	66	BKV viremia; <2 y post-TX	50; 50	C	TTV–BKV month 6 post-TX		Possible selection bias; multiple testing; no effect size adjustment
Case-control ⁸³	2014–2016	215	BKV viremia; <12 mo post-TX	47; 47	C	TTV 1 mo post-TX–subsequent BKV		No data on subject selection; multiple testing; missing information on model design/some major determinants of TTV not included
Case-control ²¹	2003–2013	389	BKV and CMV viremia; <12 mo post-TX	182; 105/77 ^d	IH	TTV kinetic–time to infection		CMV secondary endpoint

^aThe studies are listed according to their design and date of their online publication.^bAll studies followed a noninterventional and single-center design.^cKidney and liver transplant recipients.^dOne hundred five BKV and 77 CMV.

BKV, BK polyomavirus; C, commercial; CMV, cytomegalovirus; IH, in-house; LTX, liver transplantation; NA, not available; PCR, polymerase chain reaction; TTV, torque teno virus; TX, transplantation.

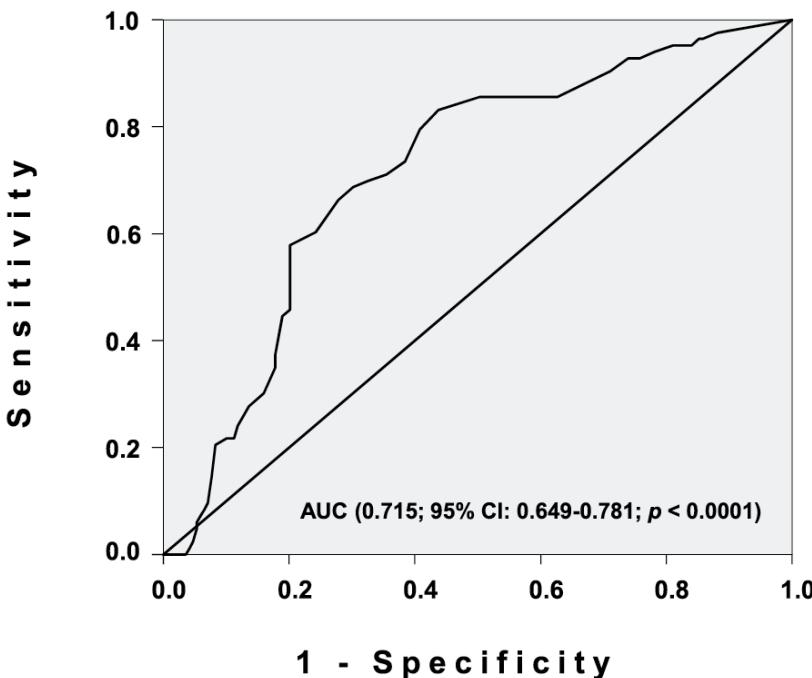
Infection à CMV et charge virale TTV en greffe rénale

- 280 receveurs de rein et de foie, étude prospective



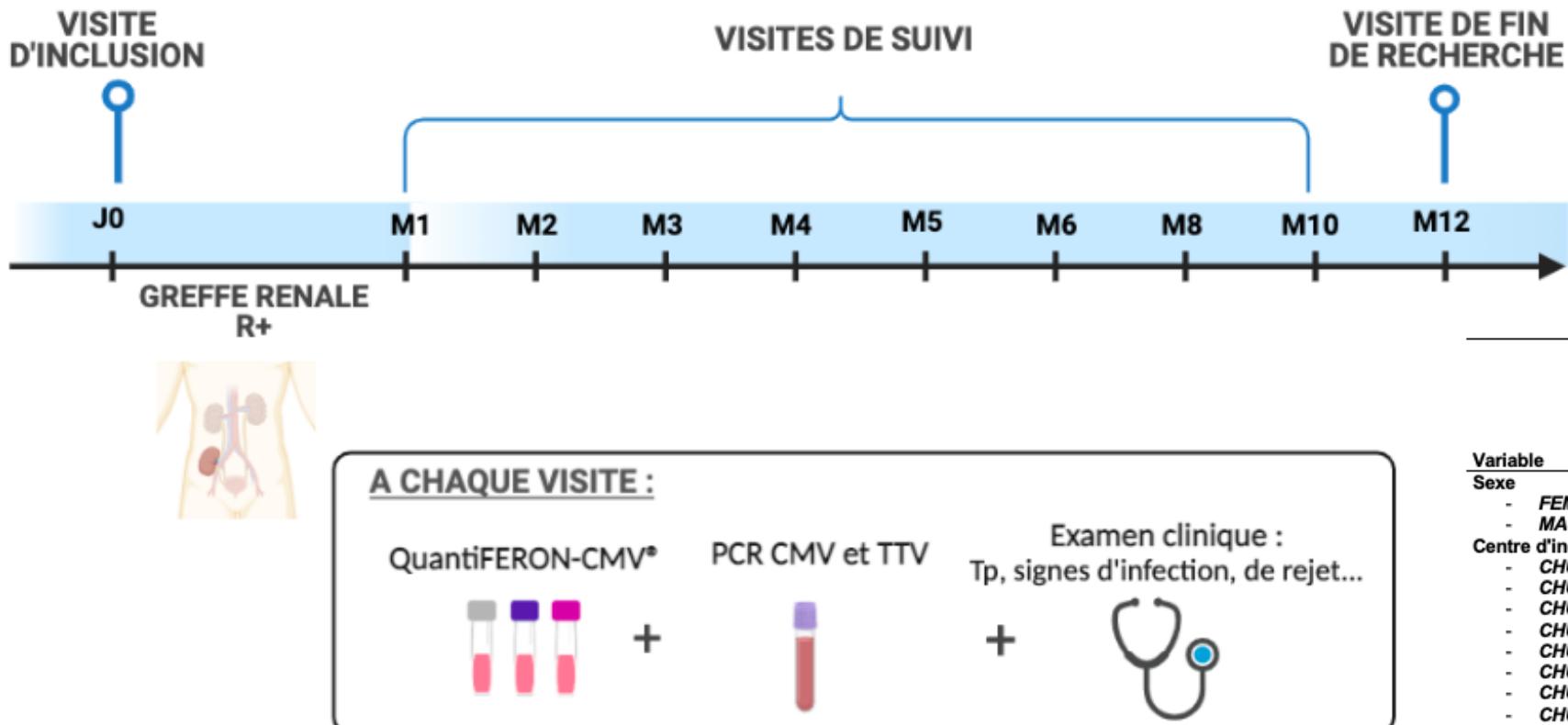
Infection à CMV et charge virale TTV (2)

TTV plasmatique > **3.45** log DNA copies/ml dans les 10 premiers jours post-transplant est corrélée à la survenue d'une infection dans les 4 mois post-greffe



Variable	OR	OR (95% CI)	<i>p</i> value
TTV loads at day 0–10 post-transplant	1.5	1.0–2.3	0.039
Use of anti-CMV prophylaxis	0.4	0.1–1.2	NS
CMV negative serostatus	0.8	0.2–3.1	NS
Mean Tacrolimus levels at month 1 post-transplant	1.0	0.8–1.3	NS

Etude Quantic R+



Variable	Global (n = 64)	n (%)	mean +/- std	n [Min ; Max]	median (Q1 ; Q3)
Sexe					
- FEMININ	22 (34.4%)				
- MASCULIN	42 (65.6%)				
Centre d'inclusion					
- CHU de Caen	7 (10.9%)				
- CHU de Clermont-Ferrand	1 (1.6%)				
- CHU de Grenoble	1 (1.6%)				
- CHU de Lille	6 (9.4%)				
- CHU de Limoges	19 (29.7%)				
- CHU de Nantes	4 (6.3%)				
- CHU de Reims	9 (14.1%)				
- CHU de Rennes	17 (26.6%)				
	54.4 +/- 13.5				
Age (ans)	(N = 64) [25 ; 78]				
	58 (45.5 ; 65.5)				

Quantic R+

INCLUSION (J0) :

- 73 patients greffés rénaux R+ inclus entre 2013 et 2017
- 9 centres : Limoges (n=20), Clermont-Ferrand (n=1), Grenoble (n=1), Reims (n=10), Rennes (n=17), Lille (n=8), Caen (n=8), Nantes (n=4), Besançon (n=1)

EXCLUSION (n = 6)

- Rejet de greffe, n = 1
- Arrêt fonctionnel du greffon, n = 1
- Détransplanté, n = 1
- Décès, n = 1
- Refus de poursuivre l'étude, n = 2
- Données incomplètes, n = 3

SUIVI (M1-M12) : n = 64 patients

- Infections (>3log UI/ml): n=19 (29,7%); Sous Prophylaxie 13/45 (28,9%) délai 119j (63-244)

Caractéristiques de la population étudiée (n = 64)

PARAMETRE	RESULTAT
Age, (moyenne +/- SD)	54,4 ans +/- 13,5 [25; 78]
Sexe :	
Homme	42 (66%)
Femme	22 (34%)
Statut sérologique :	
D+/R+	28 (44%)
D-/R+	36 (56%)
Prophylaxie CMV	45 (70,3%)
Durée de la prophylaxie (moyenne +/- SD)	103,5 [86; 147,5]

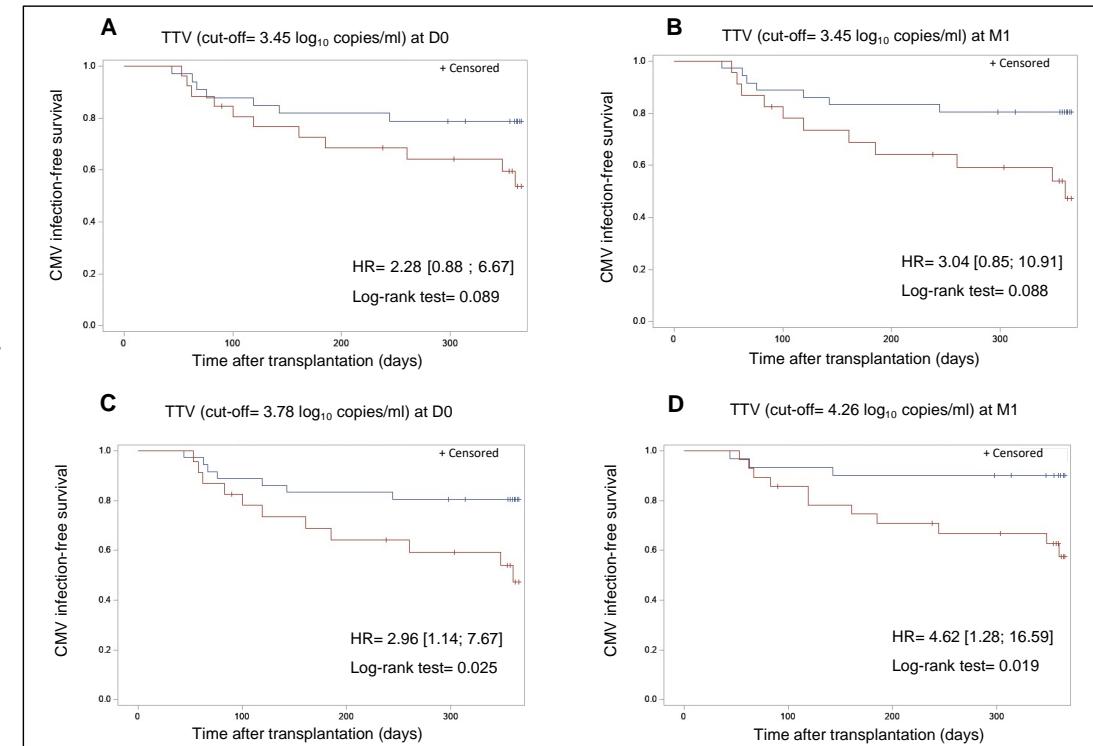
Impact du seuil choisi sur les valeurs prédictives d'infection à CMV

A : seuil défini par Maggi et al., appliqué à la population de QuanticR+

Time point	CMV reactivation	Cut-off (\log_{10} copies/ml)	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]
D0	D0-M12	≥ 3.45	63.2 [38.4; 83.7]	65.0 [48.3; 79.4]	46.2 [26.6; 66.6]	78.8 [61.1; 91.0]
M1	M1-M12		78.6 [49.2; 95.3]	50.0 [34.6; 65.4]	33.3 [18.0; 51.8]	88.0 [68.8; 97.5]

B : seuil adapté des courbes ROC sur la population de QuanticR+

Time point	CMV reactivation	Cut-off (\log_{10} copies/ml)	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]
D0	D0-M12	> 3.78	63.2 [38.4; 83.7]	72.5 [56.1; 85.4]	52.2 [30.6; 73.2]	80.6 [64.0; 91.8]
M1	M1-M12	> 4.26	78.6 [49.2; 95.3]	61.4 [45.5; 75.6]	39.2 [21.5; 59.4]	90.0 [73.5; 97.9]
D0 to M1	M1-M12	> 0.75	78.6 [49.2; 95.3]	48.7 [32.4; 65.2]	35.5 [35.5; 19.2]	86.4 [65.1; 97.1]

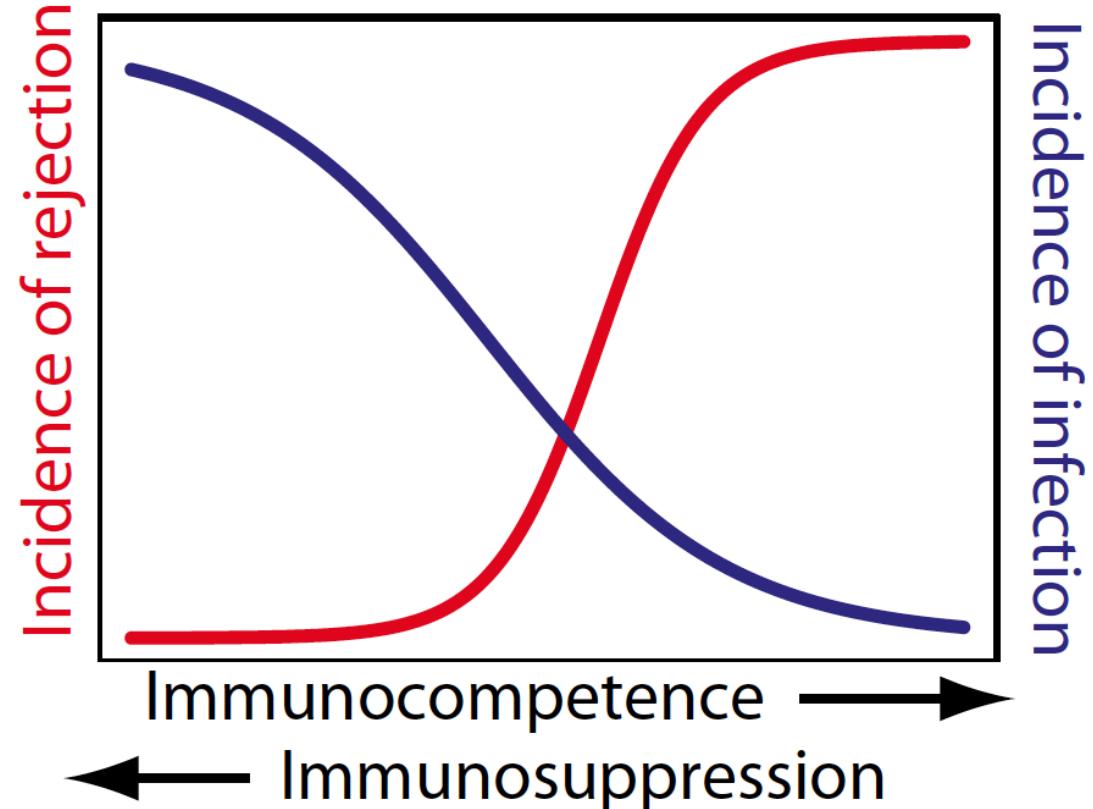


Intérêt de combiner TTV avec d'autres marqueurs? QuantiferonTM CMV+CV TTV à M1

Time point	CMV reactivation	Cut-off (QF-CMV: IU/ml, TTV: \log_{10} copies/ml)	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]
M1	M1-M4	QF-Ag < 2.23 and TTV ≥ 4.26	87.5 [47.3 ; 99.7]	26.5 [14.9 ; 41.1]	16.3 [6.8 ; 30.7]	92.9 [66.1 ; 99.8]
M1	M1-M6	QF-Ag < 9.12 and TTV ≥ 4.26	90.9 [58.7 ; 99.8]	12.8 [4.8 ; 25.7]	19.6 [9.8 ; 33.1]	85.7 [42.1 ; 99.6]
M1	M1-M12	QF-Ag ≤ 2.48 and TTV ≥ 4.26	85.7 [57.2 ; 98.2]	27.9 [15.3 ; 43.7]	27.9 [15.3 ; 43.7]	85.7 [57.2 ; 98.2]
M1	M1-M4	QF-Mg < 1.29 and TTV ≥ 4.26	100	36 [22.9 ; 50.8]	20 [9.0 ; 35.6]	100 [81.5 ; 100]
M1	M1-M6	QF-Mg < 1.29 and TTV ≥ 4.26	72.7 [39.0 ; 94.0]	33.3 [20.4 ; 48.4]	20 [9.0 ; 35.6]	84.2 [60.4 ; 96.6]
M1	M1-M12	QF-Mg ≤ 1.27 and TTV ≥ 4.26	100 [78.2 ; 100]	40.9 [26.3 ; 56.8]	35 [20.6 ; 51.7]	100 [81.5 ; 100]

QF Ag : réponse spécifique CMV seuil du fabricant 0,4 U/mL ; QF Mg : réponse au mitogène (globale) seuil Fabricant 0,5 U/mL

TTV et rejet?



La charge virale TTV a été très tôt associée au risque de rejet

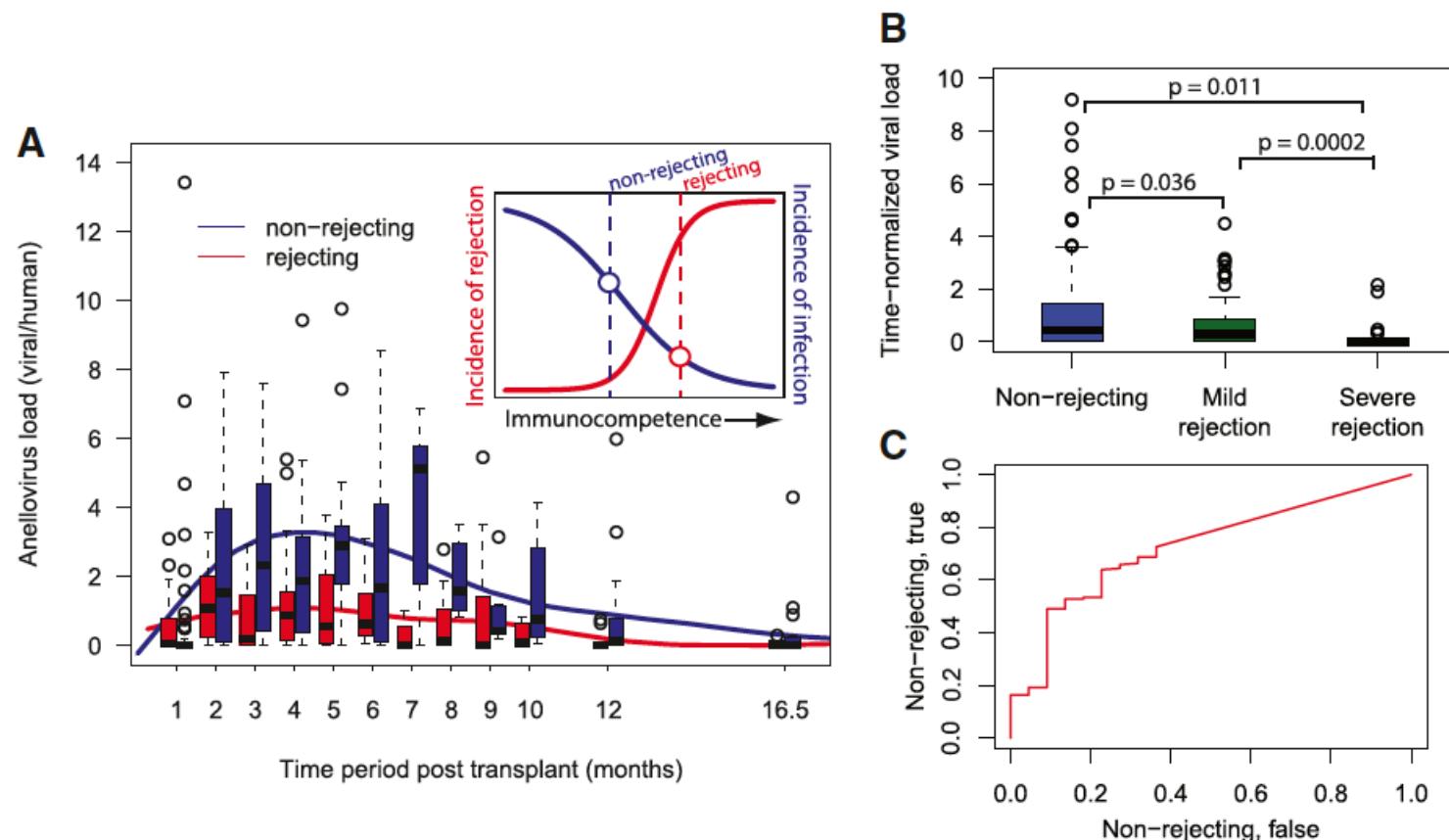


TABLE 1.

Studies that evaluated the association between TTV load and allograft rejection in kidney transplant recipients

Study design ^a	TX period	Included patients	Endpoint; timing	Total BX; BX proven rejection	PCR	Main association	Limitations ^b
Cohort ⁷⁴	2014–2016	221	Clinically overt rejection; <3 mo post-TX	10 ^c	C	TTV at TX–rejection	Secondary endpoint; BX not mandatory; multiple testing; missing information on model design/some major determinants of TTV not included
Cohort ⁷⁵	2016–2018	37	Rejection (iBX); months 4–12 post-TX	39; 11	IH	TTV 2 wk before BX–TCMR, AMR, mixed	Limited number of events
Cohort ⁷⁶	2016–2018	82	Rejection (pBX); month 12 post-TX	82; 19	IH	TTV at BX–TCMR, AMR	High loss to follow-up
Cross-sectional ⁷⁷	1973–2014	715	Rejection (pBX); 6 y post-TX	86; 46	IH	TTV at BX–AMR	Cross-sectional design; possible selection bias due to missing BX in DSA-positive subjects
Case-control ⁷⁸	2012–2017	113	Rejection (iBX); months 4–12 post-TX	113; 33	IH	TTV 1 mo before BX–TCMR, AMR	Case-control design
Case-control ⁷⁹	2012–2014	63	Rejection (iBX); <2 y post-TX	12 ^d	C	TTV pre-TX–TCMR, AMR, mixed	Possible selection bias; nonrejection not BX proven; multiple testing; no effect size adjustment
Case-control ²¹	2003–2013	389	Clinically overt rejection; <12 mo post-TX	80; 54 ^e	IH	TTV kinetic–time to rejection	Secondary endpoint; BX not mandatory; possible misclassification of rejection: nonrejection in BX categorized as rejection

^aThe studies are listed according to the design and date of their online publication.^bAll studies followed a noninterventional and single-center design.^cThe total number of biopsies was not stated; 11 events were scored as rejection.^dThe total number of biopsies was not stated; 14 biopsies were available for the posttransplant month 1 evaluation.^eEighty-eight events were scored as rejection.

AMR, antibody-mediated rejection; BX, biopsy; C, commercial; DSA, donor-specific antibody; iBX, indication biopsy; IH, in-house; pBX, protocol biopsy; PCR, polymerase chain reaction; TCMR, T cell–mediated rejection; TTV, torque teno virus; TX transplantation.



La charge virale TTV précoce est un marqueur prédictif de rejet en greffe d'organe

Torquenovirus viremia for early prediction of graft rejection after kidney transplantation

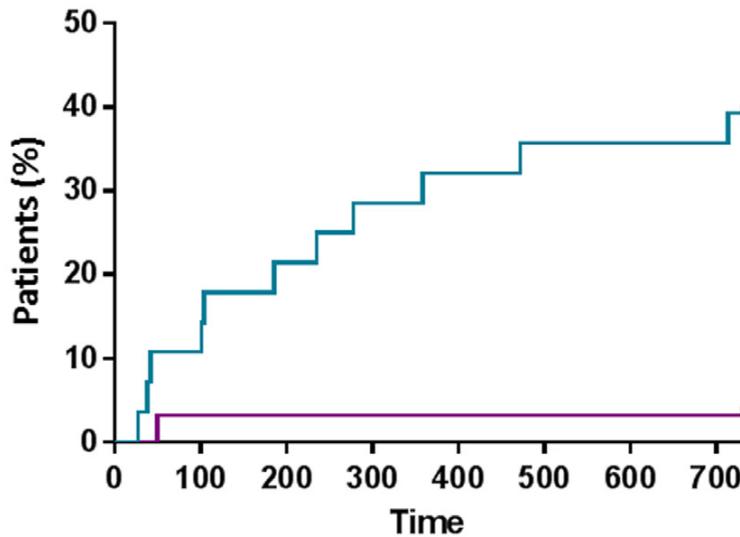
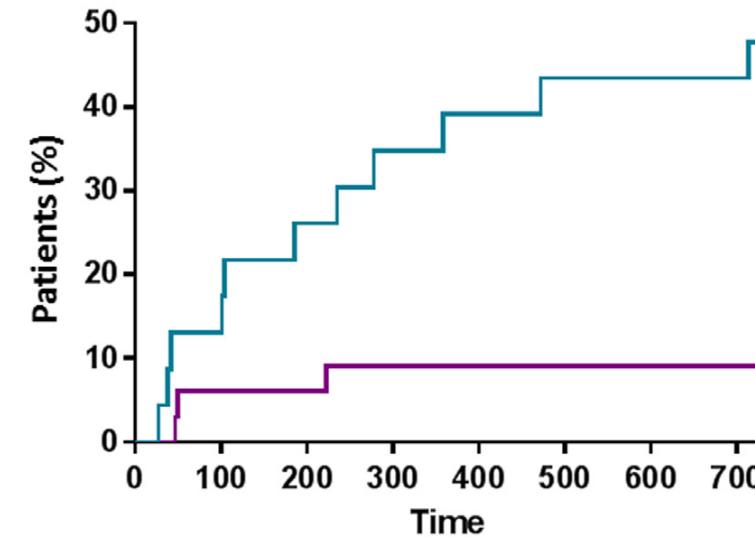
M. Solis^{a,b}, A. Velay^{a,b}, P. Gantner^{a,b}, J. Bausson^a, A. Filipputto^a, R. Freitag^a, B. Moulin^{b,c}, S. Caillard^{b,c}, S. Fafi-Kremer^{a,b,*}

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JO

A**Graft rejection****M1****Graft rejection**

TTV < 3,4 log ₁₀ cp/ml	28	25	22	20	19	18	18	17
TTV > 3,4 log ₁₀ cp/ml	31	30	30	30	30	30	30	30

- TTV load < 3.4 log₁₀ copies/ml
- TTV load > 3.4 log₁₀ copies/ml

TTV < 4,2 log ₁₀ cp/ml	23	20	17	15	14	13	13	12
TTV > 4,2 log ₁₀ cp/ml	33	31	31	30	30	30	30	30

- TTV load < 4.2 log₁₀ copies/ml
- TTV load > 4.2 log₁₀ copies/ml

TTV et rejet : suivre l'augmentation de la charge virale

- **Schiemann et al. 2017** : Cross sectional study AMR vs CV TTV Chez 715 receveurs de rein
 - Augmentation du risque de rejet **RR 0.94 par log TTV** (95%CI 0.90-0.99; P=0.02).
- **Ruiz et al. 2018** : Etude prospective.
 - Seul marqueur en analyse multivariée Augmentation du risque de rejet **RR 0.69 par log TTV** (0,49-0,97 95% CI,p = 0,030)
- **Solis et al. 2018** : suivi 72 greffés rénaux **seuil prédictif de rejet J0 3,4 logs** et à **M1 4,2 log copies/mL plasma**
 - Corrélation avec taux de Lymphocytes TCD8, pas avec le TT Immunosuppresseur, ni la survenue d'infection
- **Doberer et al., 2020** : 318 receveurs de rein suivis 12 mois en charge virale TTV. Analyse à **M3** : Charge virale optimale 1×10^6 - 1×10^8 copies/mL de plasma
 - Chaque log au dessus diminue le risque de rejet de 22% (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.62-0.97; P = .027) et augmente le risque d'infection de 11% (OR 1.11, 95% CI 1.06-1.15; P < .001).

Bilan des seuils prédictifs d'infection et de rejet en transplantation rénale

TABLE 3.

Proposed plasma TTV load cutoff values determined in kidney transplant recipients for the risk prediction of allograft rejection and infection, respectively

Citation	Event; timing	Predictor	TTV cutoff ^a	AUC	Sensitivity	Specificity	PPV	NPV
Rejection								
77	AMR (pBX); 6 y post-TX	TTV at BX	<3.6 log10	NA	NA	NA	NA	NA
79	Rejection; <2 y post-TX (iBX)	TTV pre-TX/TTV 1 mo post-TX	<3.4 log10 <4.2 log10	NA 0.73	NA 0.36	NA 0.89	0.63 0.56	0.92 0.77
75	Rejection (iBX); months 4–12 post-TX	TTV 2 wk before BX	<4.6 log10	0.73	0.36	0.89	0.48	0.92
76	Rejection (pBX); month 12 post-TX	TTV at BX	<4.6 log10	NA	0.63	0.51	0.27	0.82
Infection								
82	CMV viremia; <4 mo post-TX	TTV days 0 to 10 post-TX	>3.8 log10	0.72	0.83	0.56	NA	NA
74	Infection/opportunistic infection or malignancy; <12 mo post-TX	TTV 1 mo post-TX	>3.2 log10 >4.6 log10	0.62 0.70	0.90 0.76	0.31 0.66	0.54 0.41	0.77 0.90
83	BKV viremia; <12 mo post-TX	TTV 1 mo post-TX	>5.0 log10	0.75	0.77	0.75	0.31	0.96
84	Death due to infectious cause	TTV 5 y post-TX	>3.4 log10	NA	0.55	0.67	NA	NA
75	Infection; months 4–12 post-TX	TTV 1 mo before infection	>6.6 log10	0.62	0.41	0.76	0.36	0.80

^aTo facilitate comparison of the proposed TTV cutoffs, values have been converted to values that correspond to the commercial PCR.

AMR, antibody-mediated rejection; AUC, area under the curve; BKV, BK polyomavirus; BX, biopsy; CMV, cytomegalovirus; iBX, indication biopsy; NA, not available; NPV, negative predictive value; pBX, protocol biopsy; PPV, positive predictive value; TTV, torque teno virus; TX, transplantation.

Des seuils variables selon le moment du test TTV ou la population de l'étude

Rejet seuils au plateau ≠ infection seuils précoces J0 à M1, ou plus tardifs, au plateau

TTV et transplantation pulmonaire: des études essentiellement menées à partir de M3 post greffe

TABLE 4.

Studies of lung transplant recipients' evaluations of association between TTV load detected by in-house PCR and allograft rejection and infection, respectively

Study design ^a	TX period	Included patients	Endpoint; timing	Number of events	Main association	Limitations ^b
Rejection						
Cohort ⁸⁹	2013–2015	143	CLAD/AR (iBX); month 6–y 5 post-TX	22 CLAD 11 AR	TTV 3 mo before event–rejection	Three endpoints; some major determinants of TTV not included in the effect size adjustment
Case-control ⁸⁸	2003–2013	47	CLAD; month 4–y 3 post-TX	20	TTV at event–rejection	Possible selection bias; rejection not BX proven; no effect size adjustment
Case-control ⁹⁰	2006–2015	34	AR (pBX); months 4–12 post-TX	13	TTV before event–rejection	Possible selection bias; 2 endpoints; 3 suspected rejection episodes in the control group; no effect size adjustment
Infection						
Cohort ⁶⁹	2008	31 ^c	Infectious events; month 4–y 2 post-TX	13	TTV before event–infection	Insufficient definition of outcome; no effect size adjustment
Cohort ⁸⁹	2013–2015	143	Infections requiring hospitalization; month 6–y 5 post-TX	28	TTV 3 mo before event–infection	Three endpoints; some major determinants of TTV not included in the effect size adjustment
Case-control ⁹⁰	2006–2015	34	Infection leading to medical measure; months 4–12 post-TX	19	TTV months 4 to 12 post-TX–infection	Possible selection bias; 2 endpoints; no effect size adjustment

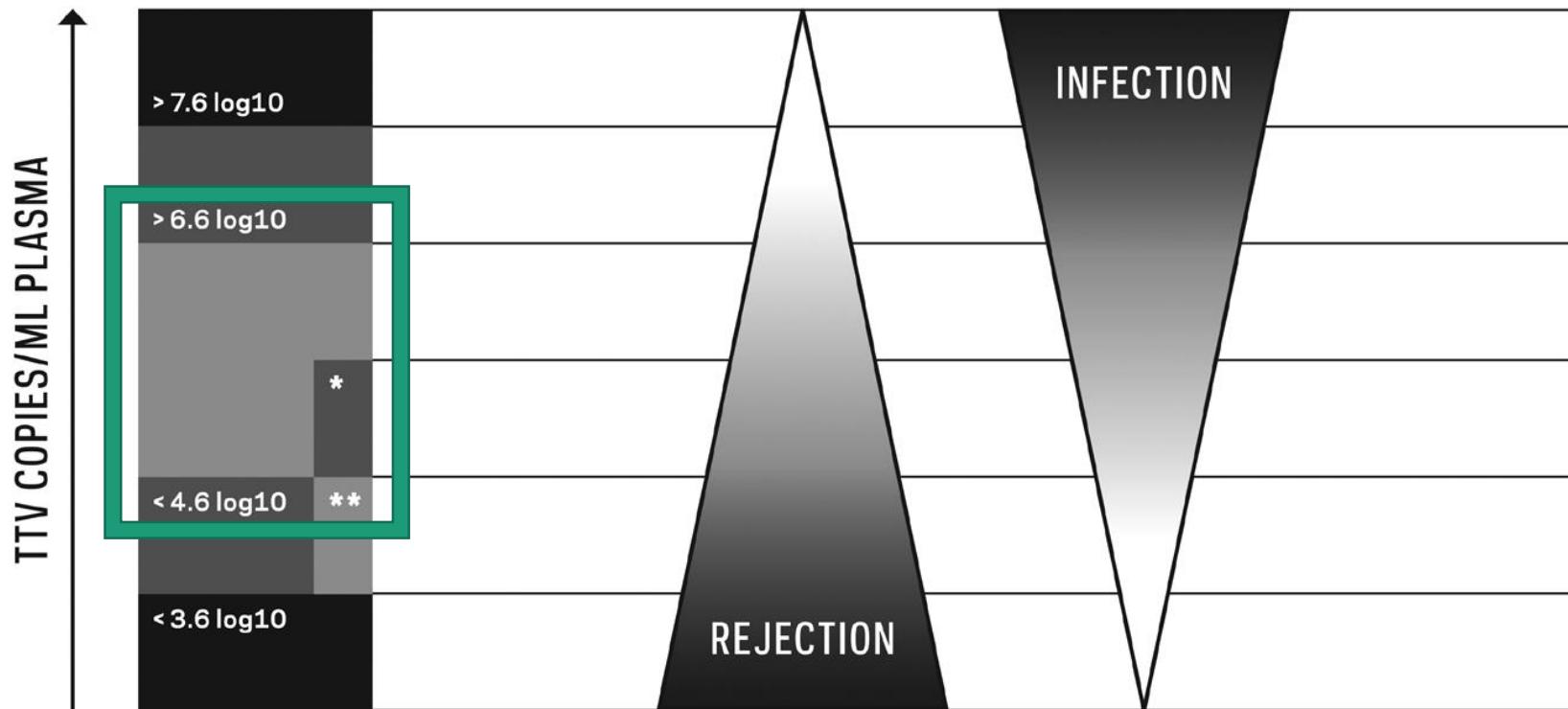
^aThe studies are listed according to their design and date of their online publication.

^bAll studies followed a noninterventional and single-center design.

^cA total of 24 patients analyzed.

AR, acute rejection; BX, biopsy; CLAD, chronic lung allograft dysfunction; iBX, indication biopsy; pBX, protocol biopsy; PCR, polymerase chain reaction; TTV, torque teno virus; TX, transplantation.

Seuils de charge virale significatifs au cours du suivi post-greffe (> M3)



Synthèse des seuils identifiés dans la littérature, rapportés à la PCR CEIVD R gene
(Jacksh et al., revue, Transplantation, Oct 2022)

Encore très peu d'études en greffe hépatique

TABLE 5.

Studies in liver transplant recipients' evaluations of association between TTV load detected by in-house PCR and allograft rejection and infection, respectively

Study design ^a	TX period	Included patients	Endpoint; timing	Events	Main association	Limitations ^b
Rejection						
Cohort ⁹¹	NA	39	BX proven rejection; <12 mo post-TX	13 ^c	TTV pre-TX-rejection	Possible selection bias; insufficient endpoint definition; multiple testing; possible model overfitting
Infection						
Cohort ⁹²	2014–2017	63	CMV viremia/ disease; <12 mo post-TX	26 ^d	TTV at event-CMV viremia/ disease	Two endpoints; no effect size adjustment
Cross-sectional ⁹³	1982–2016	136	BKV events; 10 y post-TX	23	TTV at event–urinary BKV	Possible selection bias; missing data on sampling; multiple testing; no effect size adjustment
Case-control ^{82,e}	2011–2016	90	CMV viremia; <4 mo post-TX	64	TTV days 0 to 10 post-TX–CMV viremia	Possible selection bias; main analysis includes KTX; multiple testing; no effect size adjustment

- Seuil 5,6 log copies/mL plasma et rejet : Sens 100%, spé 77%, NPV 100%, PPV 38%,
- Pas de lien évident à ce jour avec un seuil prédictif d'infection
- Etude de la Valeur prédictive de rejet et d'infection en cours dans le cadre de la cohorte BioSuport de la FHU Suport

Autres indications potentielles de
la charge virale TTV

La charge virale TTV plasmatique prédit la reconstitution immune sous ART chez les patients HIV

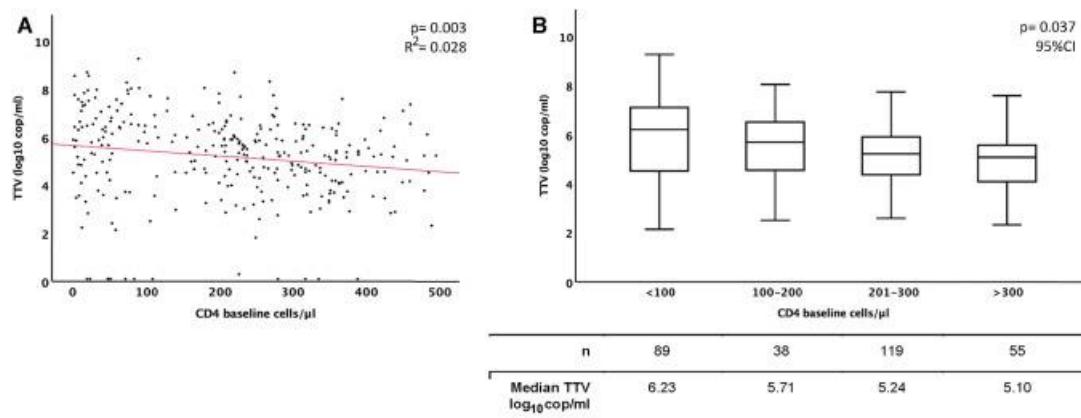
Infection (2021) 49:501–509
https://doi.org/10.1007/s15010-020-01573-7

ORIGINAL PAPER

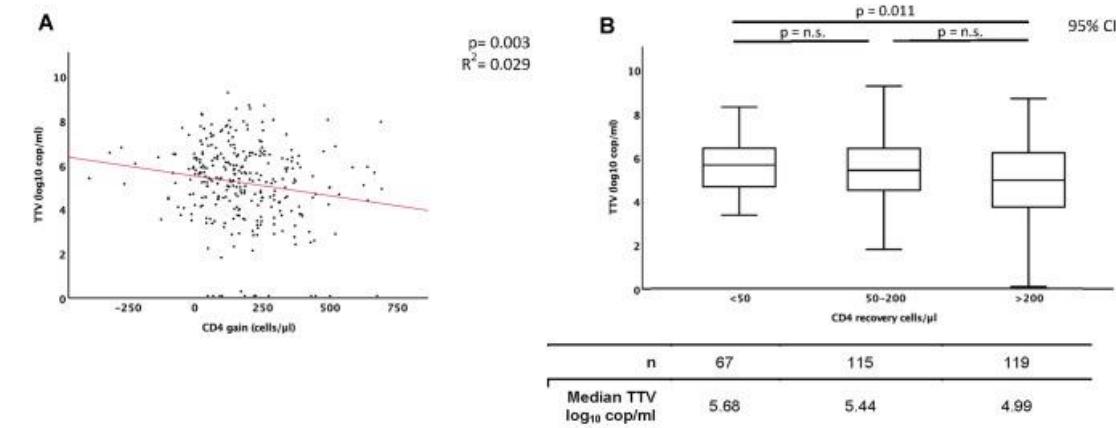
Torque Teno Virus plasma level as novel biomarker of retained immunocompetence in HIV-infected patients

L. Schmidt¹ · B.-E. O. Jensen²  · A. Walker¹ · V. Keitel-Anselmino² · V. di Cristanziano³ · M. Böhm³ · E. Knops³ · E. Heger³ · R. Kaiser³ · A. de Luca⁴ · M. Oette⁵ · D. Häussinger² · J. Timm¹ · A. Fuchs⁶ · N. Lübke¹

TTV et taux de CD4/mm³ à l'inclusion dans la cohorte



TTV et reconstitution CD4 dans les 12 mois de suivi



Seule la charge virale TTV est corrélée à la reconstitution immune en analyse multivariée

Univarié

Variable	N	Univariate analysis	
		OR (95% CI)	p value
Total participants	301		
CD4 ⁺ cell count at baseline (cells/ μ l)			
< 100	89	0.383 (0.190–0.773)	0.006*
100–200	38	1.262 (0.579–2.750)	0.559
201–350	119	0.729 (0.414–1.285)	0.275
> 350	55	3.554 (1.903–6.639)	<0.001*
Sex			
Male	234	0.915 (0.816–1.107)	0.499
Female	67	1.184 (0.732–1.915)	0.503
CMV DNA positive	35	1.282 (0.506–3.252)	0.600
EBV DNA positive	74	1.019 (0.527–1.968)	0.956
HHV-8 DNA positive	29	0.790 (0.320–1.950)	0.608

multivarié

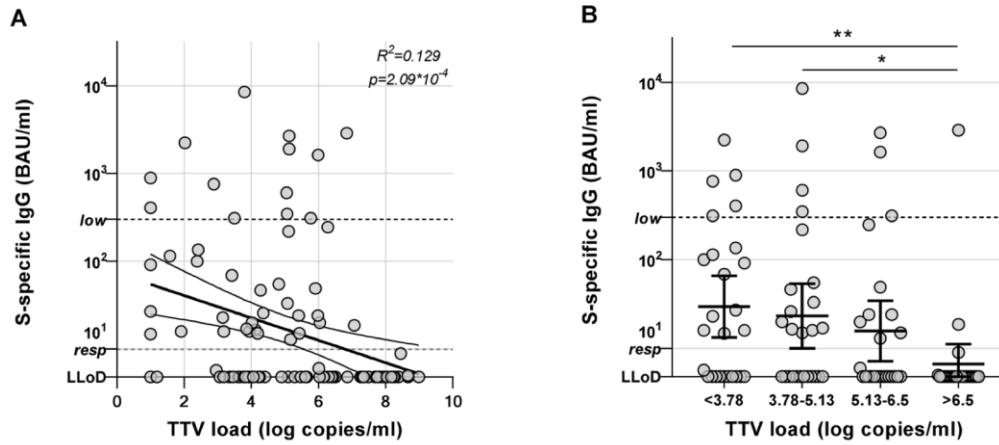
Multiple linear regression analysis for parameters associated with CD4 ⁺ cell recovery within the first year of cART					
	B	SD	β	p value	Cumulative adjusted R ²
TTV DNA (\log_{10} cop/ml)	-19.271	5.550	-0.203	0.001*	
HIV RNA (cop/ml)	-8.449E-7	< 0.001	-0.003	0.953	
CD4 ⁺ cell count at baseline (cells/ μ l)	-0.203	0.073	-0.165	0.006*	
Sex	4.337	23.493	0.011	0.854	
Age	0.091	0.843	0.006	0.914	
Cumulative adjusted R ²					0.042

Intérêt pour prédire la réponse thérapeutique chez d'autres patients ? Notamment en cas de résistance ?

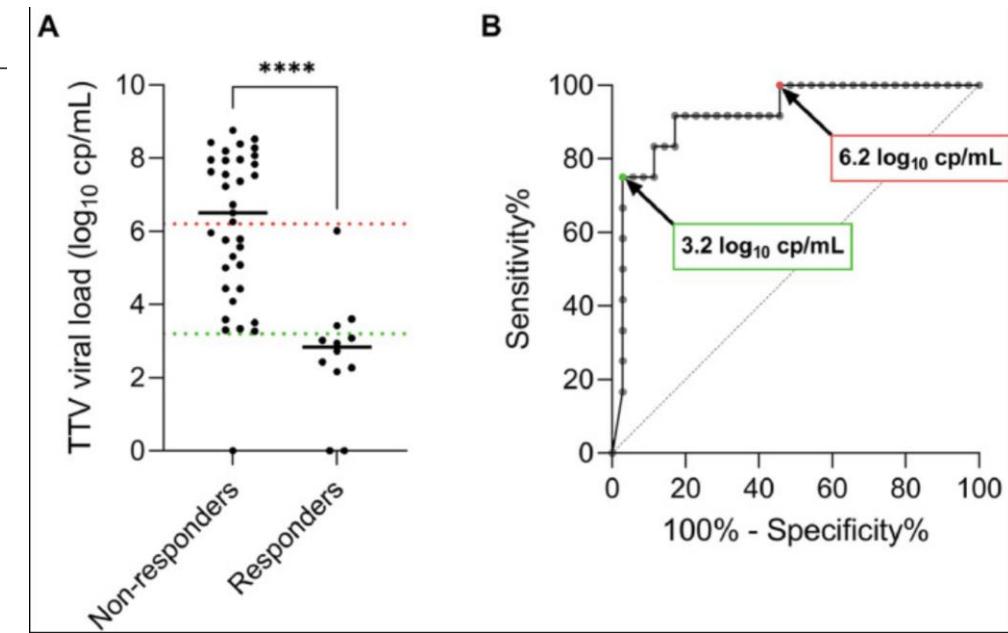
TTV et prédiction d'efficacité vaccinale des vaccins SARS – CoV2 en TX Pulmonaire

Avant la première dose de vaccin

Hoek et al. High torque tenovirus (TTV) load before first vaccine dose



Avant la troisième dose de vaccin

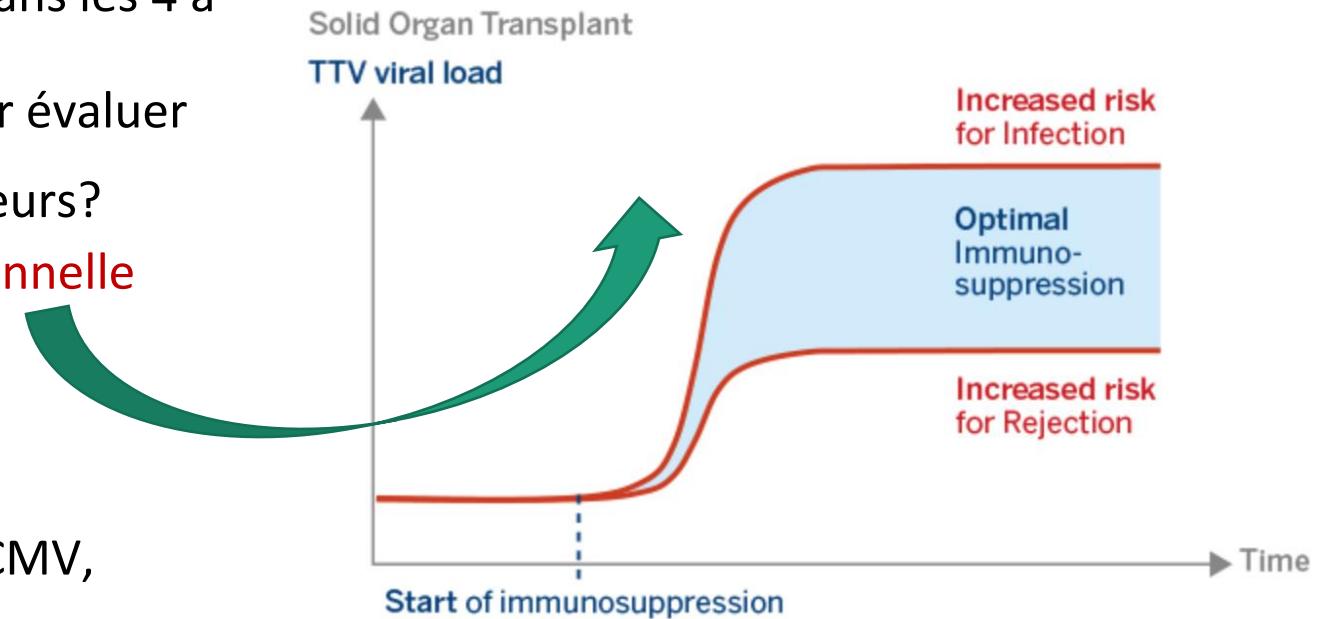


Conclusion : la charge virale TTV est un marqueur d'immunosuppression globale

Comment utiliser la charge virale TTV ?

- A J0-J10-M1 : pour la prédition précoce du rejet et des infections à CMV, BK? dans les 4 à 12mois
- A partir de M3 (tous les mois ?) Pour évaluer le niveau d'immunosuppression Et ajuster/doser les immunosupresseurs?
- **MAIS : Absence d'étude interventionnelle**
- Chez les non répondeurs au tt anti CMV, intégré à l'évaluation globale?
- Pour prédire l'efficacité vaccinale?

Projet européen TTV-guide TX : modulation du tt immunosupresseur





Remerciements :

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Investigateurs cliniciens et virologues de l'étude QuanticR+ et de la cohorte BioSuport

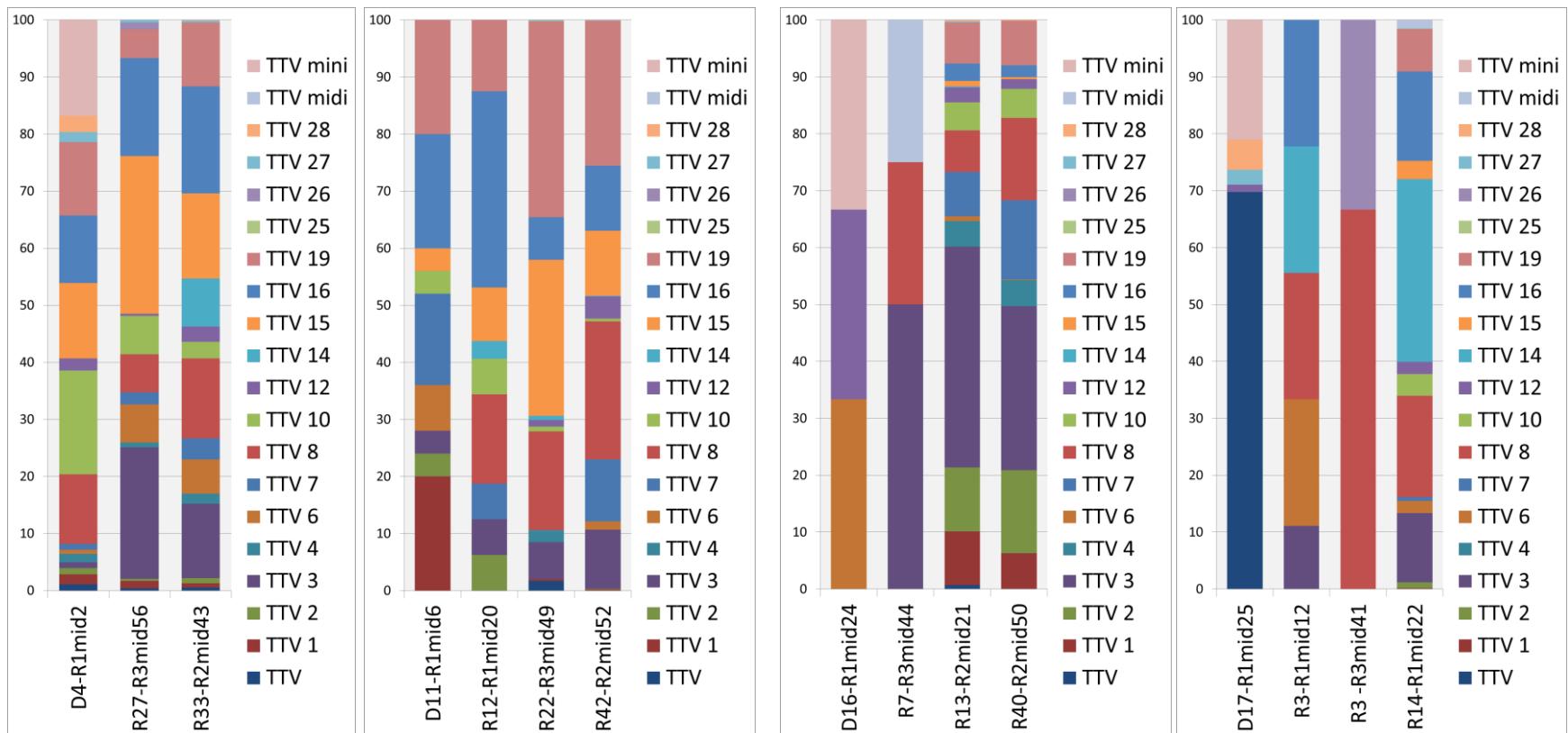
CNR Herpesvirus

BioMérieux

Cohorte/collection biologique
BioSUPORT



- Métagénomics in kidney transplantation Donors and recipient paired samples : les souches du donneur et des receveurs sont différentes et la population virale évolue au cours du temps



- No particular TTV genotyping profile between donors and recipients