TTV as a marker of immune reconstitution/suppresion in allo-HSCT

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Disclosures……..

- ***Funding: Pfizer, Astellas, MSD, Abbott, Roche, Genómica, Biomerieux***
- ***Conferences/advisories: Pfizer, MSD, Abbott, Roche, Qiagen, Biomerieux***

Conflicts of interest…..

None

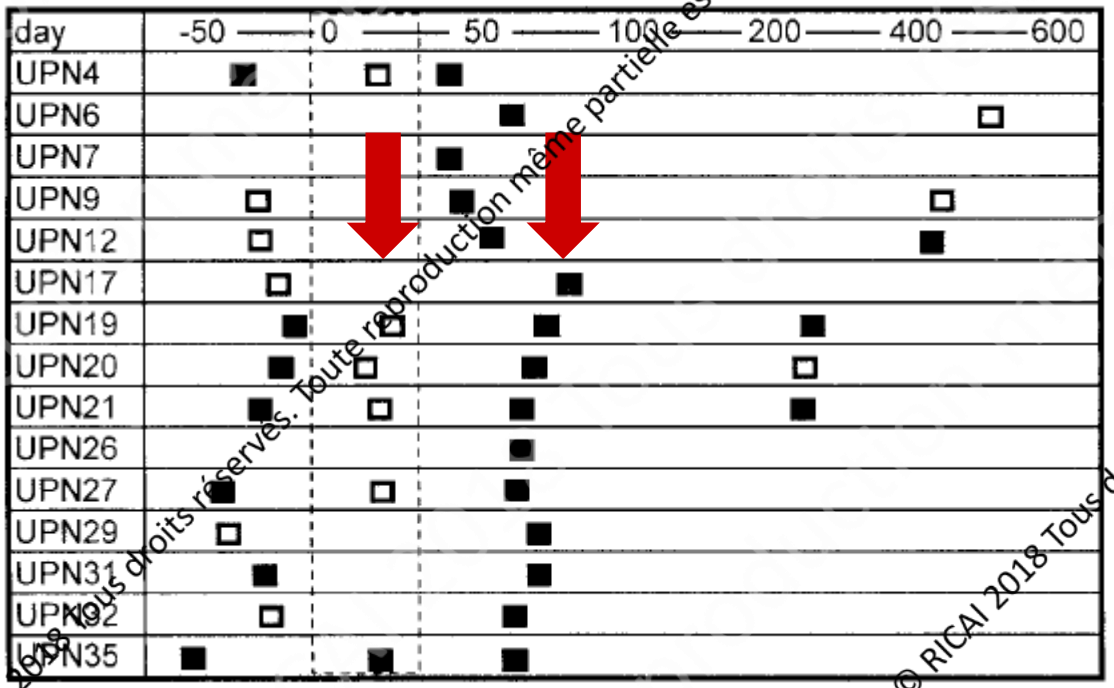
Blood, Vol 93, No 8 (April 15), 1999: pp 2485-2490

TT Virus in Bone Marrow Transplant Recipients

By Yoshinobu Kanda, Yuji Tanaka, Masahiro Kami, Toshiki Saito, Takashi Asai, Koji Izutsu, Koichiro Yuji, Seishi Ogawa, Hiroaki Honda, Kinuko Mitani, Shigeru Chiba, Yoshio Yazaki, and Hisamaru Hirai

Plasma TTV DNA (qualitative seminested –ORF-1 PCR)

■ Pos □ Neg

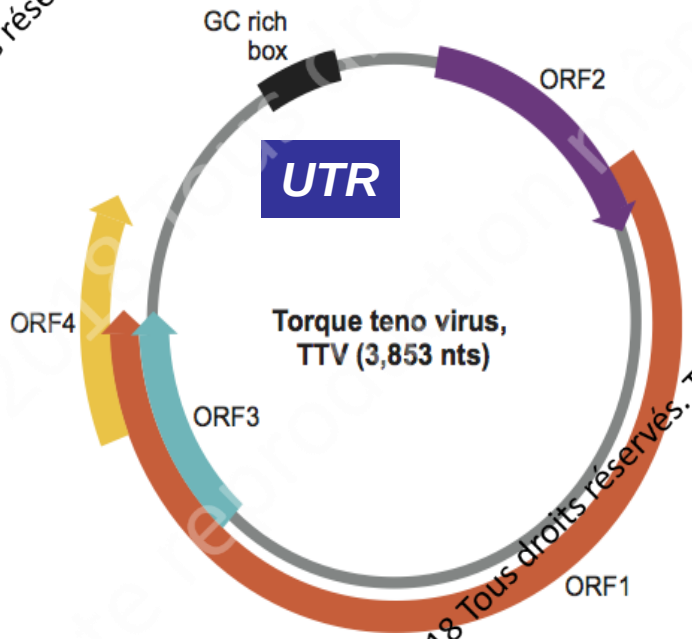


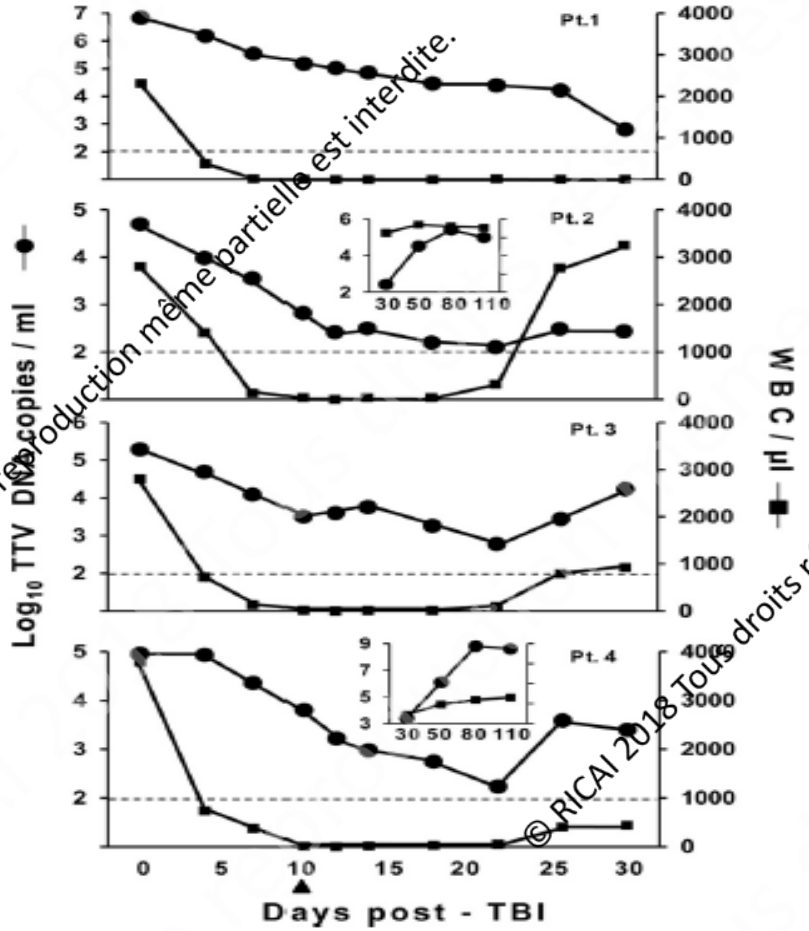
JOURNAL OF VIROLOGY, July 2010, p. 6891–6893
0022-538X/10/$12.00 doi:10.1128/JVI.00273-10
Vol. 84, No. 13

Role of Hematopoietic Cells in the Maintenance of Chronic Human Torquetenovirus Plasma Viremia▽

Fabrizio Maggi,[1]* Daniele Focosi,[2] Melania Albani,[1] Letizia Lanini,[1] Maria Linda Vatteroni,[1] Mario Petrini,[2] Luca Ceccherini-Nelli,[1] Mauro Pistello,[1] and Mauro Bendinelli[1]

qPCR: UTR





Journal of Clinical Virology 94 (2017) 22–28

Contents lists available at ScienceDirect

Journal of Clinical Virology

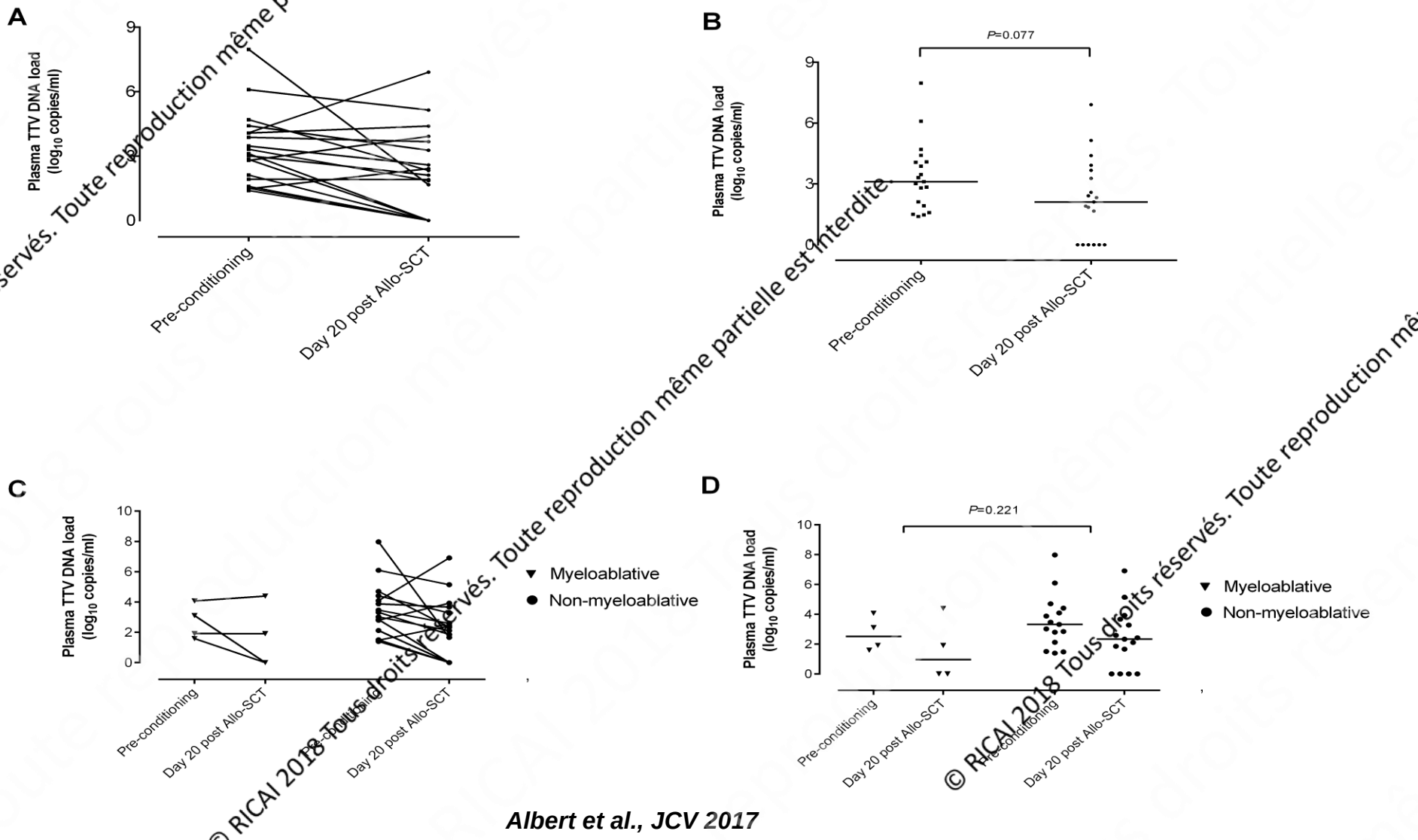
journal homepage: www.elsevier.com/locate/jcv

Dynamics of Torque Teno virus plasma DNAemia in allogeneic stem cell transplant recipients

Eliseo Albert[a], Carlos Solano[b,c], Tania Pascual[a], Ignacio Torres[a], Lisa Macera[d], Daniele Focosi[e], Fabrizio Maggi[d], Estela Giménez[a], Paula Amat[b], David Navarro[a,f,*]

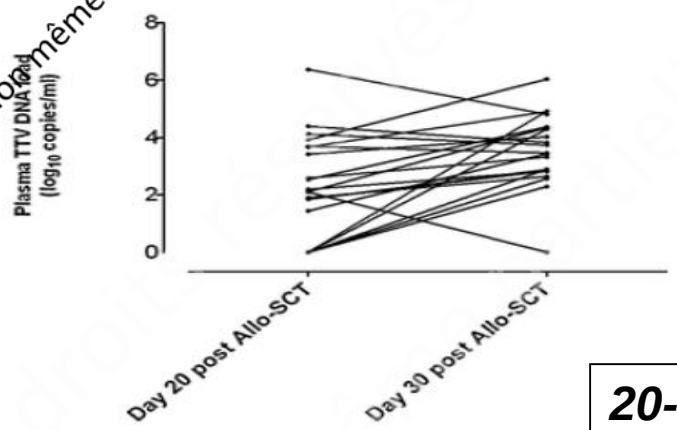
- *72 non-consecutive patients undergoing T-cell replete allo-HSCT*
- *TTV DNA load quantitation (qPCR UTR): pre-transplantation/time of transplantation/ days+20/+30/+60+/90*
- *Study period: 100 days after Allo-HSCT*

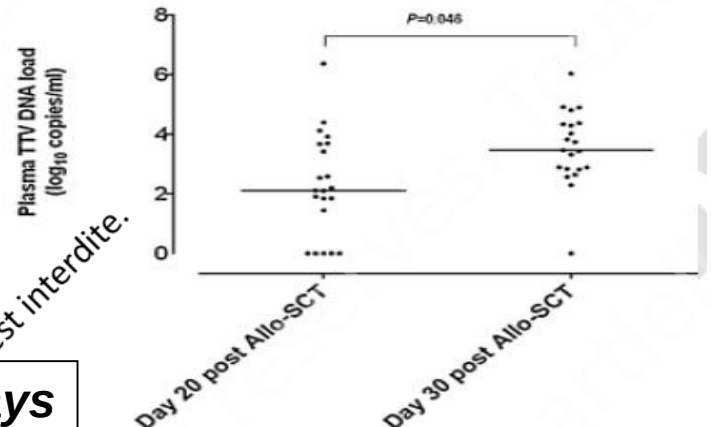
Plasma TTV DNA load decreases following conditioning



Albert et al., JCV 2017

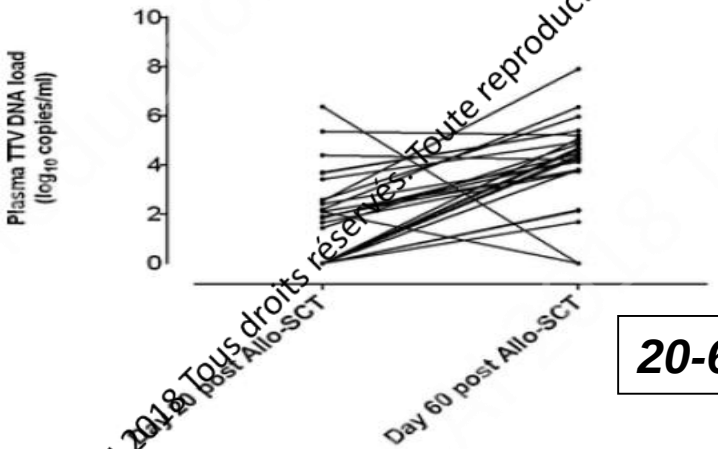
Plasma TTV DNA load increases following engraftment



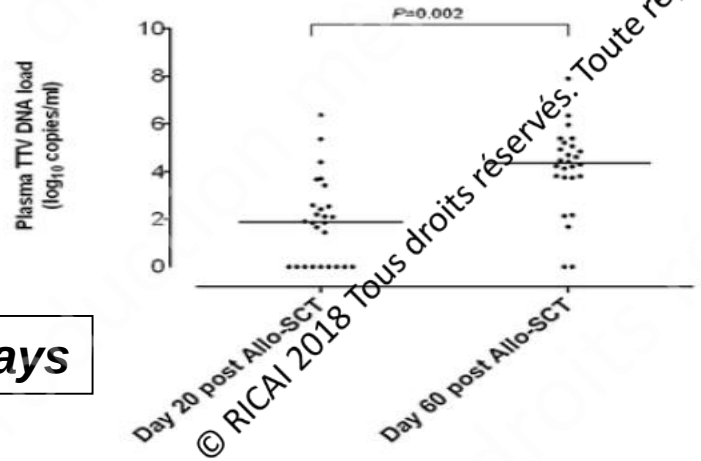


20-30 days

C



D



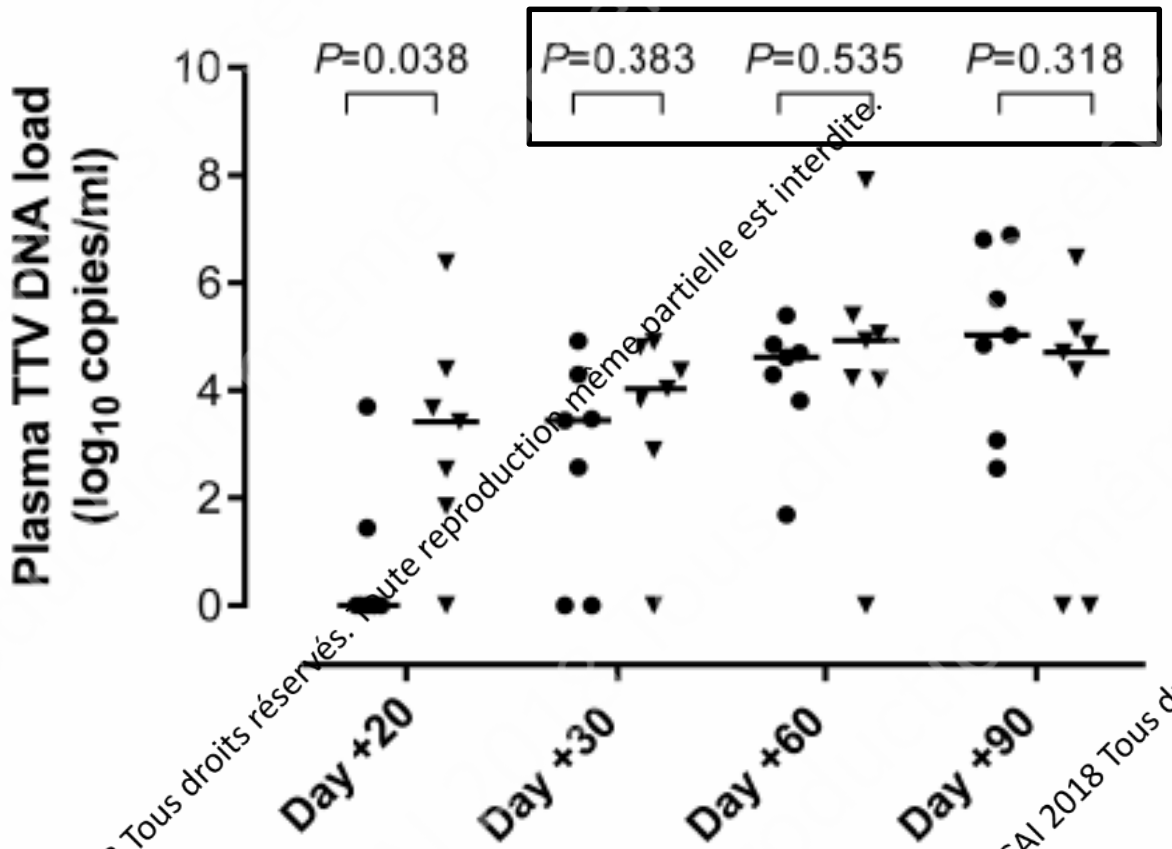
20-60 days

Albert et al., JCV 2017

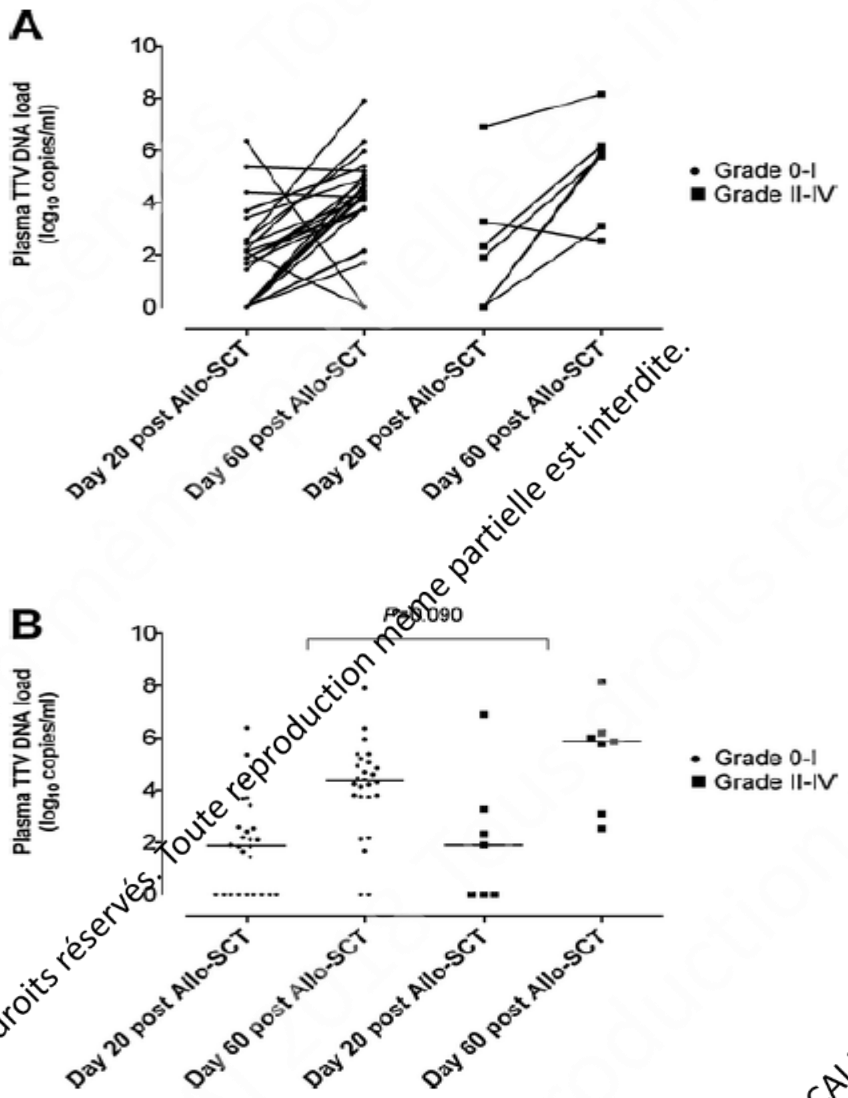
Prophylaxis aGvHD:

▼ Including m-Tor Inhibitors

● Not including m-Tor Inhibitors



Albert et al., JCV 2017



Effect of aGvHD

Albert et al., JCV 2017

Bone Marrow Transplantation (2015), 1–3

www.nature.com/bmt

LETTER TO THE EDITOR

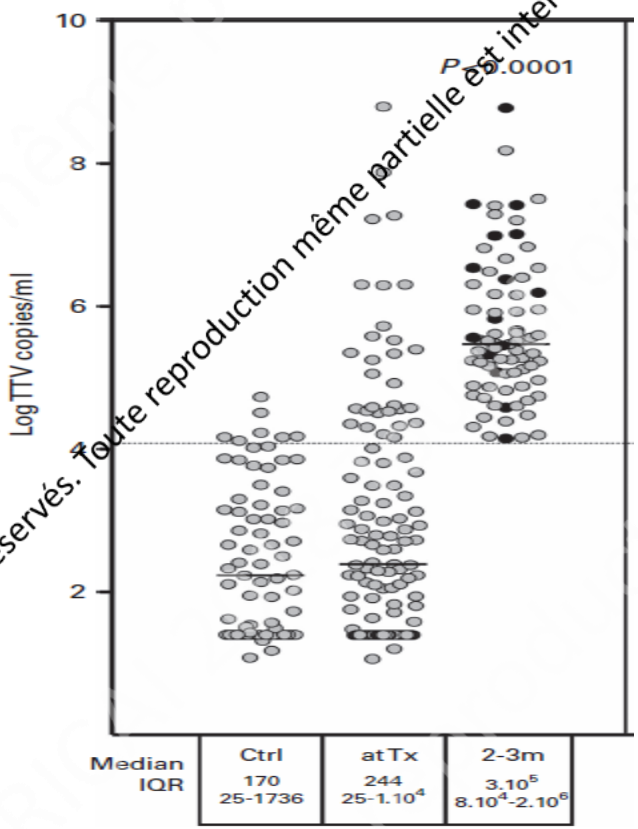
Torque teno virus in patients undergoing allogeneic hematopoietic stem cell transplantation for hematological malignancies

S Masouridi-Levrat[1], A Pradier[2], F Simonetta[1], L Kaiser[3], Y Chalandon[1] and E Roosnek[2]

[1]Stem Cell Transplant Team, Division of Hematology, Geneva University Hospital, Geneva, Switzerland; [2]Division of Hematology, Geneva University Hospital and Geneva Medical School, Geneva, Switzerland and [3]Division of Infectious Diseases, Laboratory of Virology and Division of Laboratory Medicine, University Hospital of Geneva, Geneva, Switzerland

GvHD

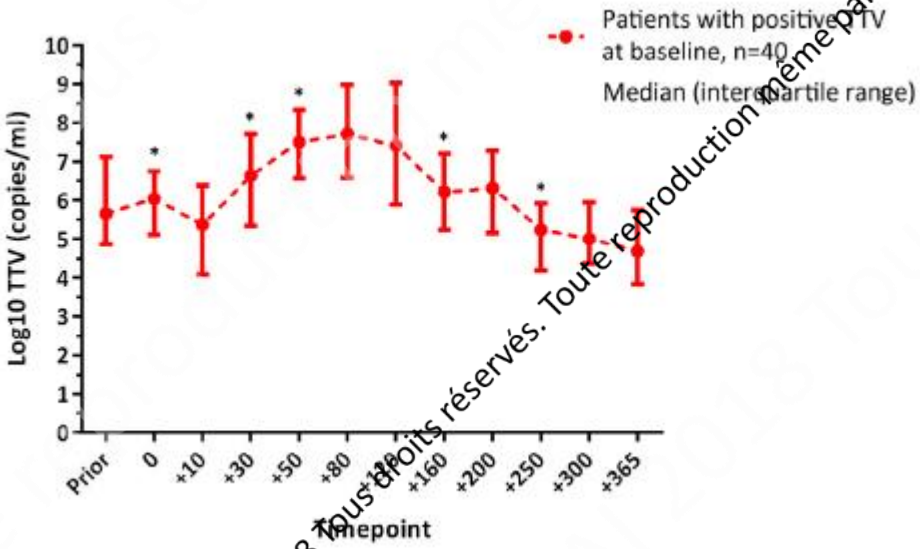
No GvHD

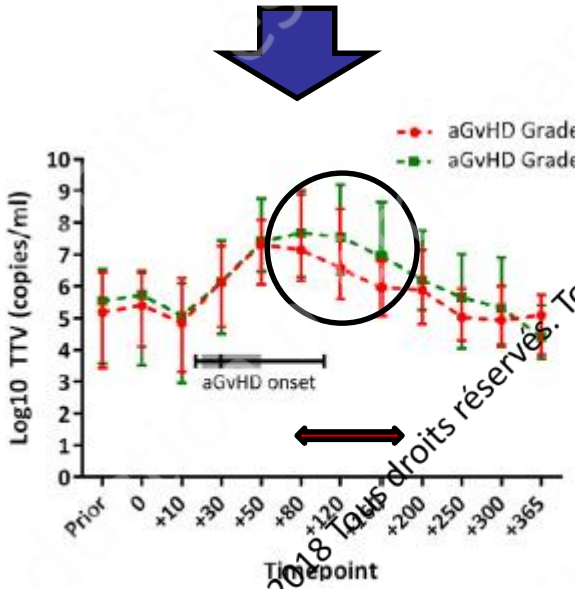


Torquetenovirus Dynamics and Immune Marker Properties in Patients Following Allogeneic Hematopoietic Stem Cell Transplantation: A Prospective Longitudinal Study

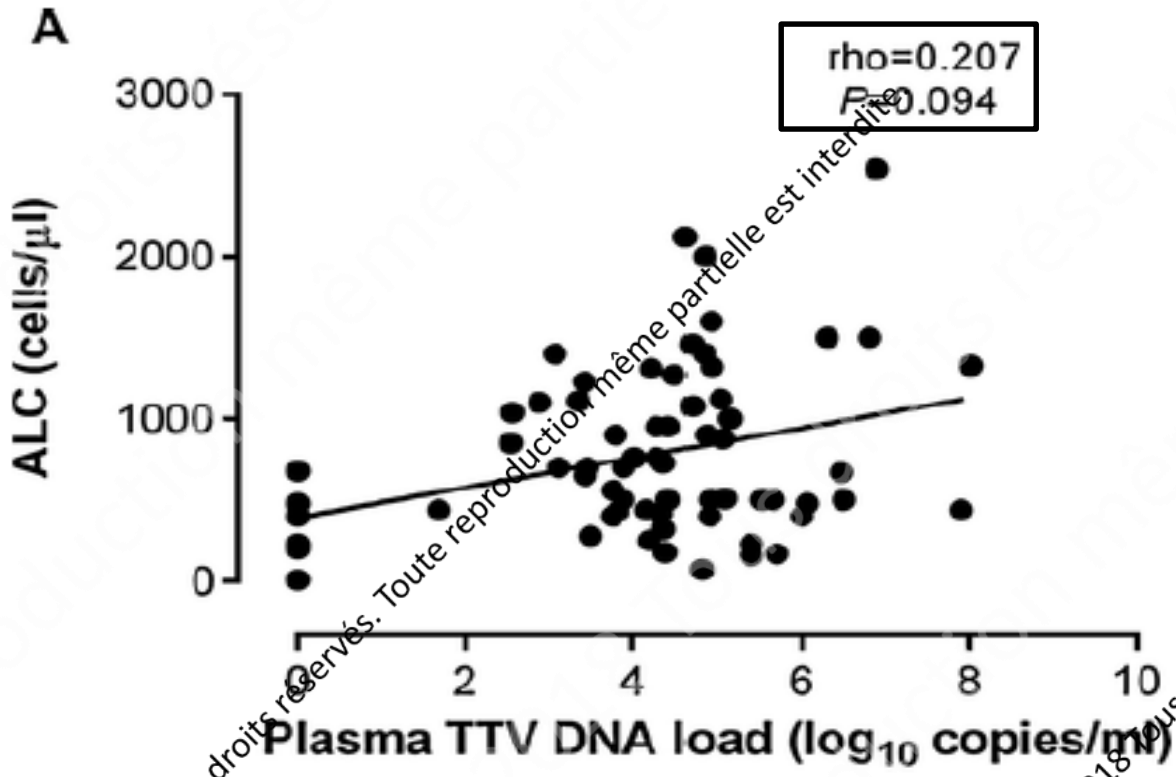
Philipp Wohlfarth [1,*], Michael Leiner [1], Christian Schoergenhofer [2], Georg Hopfinger [1], Irene Goerzer [3], Elisabeth Puchhammer-Stoeckl [3], Werner Rabitsch [1]

[1] Division of Blood and Marrow Transplantation, Department of Medicine I, Medical University of Vienna, Vienna, Austria
[2] Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria
[3] Department of Virology, Medical University of Vienna, Vienna, Austria





Correlation (trend) between TTV DNA loads and ALC counts: days +20/+30/+60/



Albert et al., JCV 2017

Received: 17 February 2018 | Accepted: 2 May 2018

DOI: 10.1002/jmv.25218

RESEARCH ARTICLE

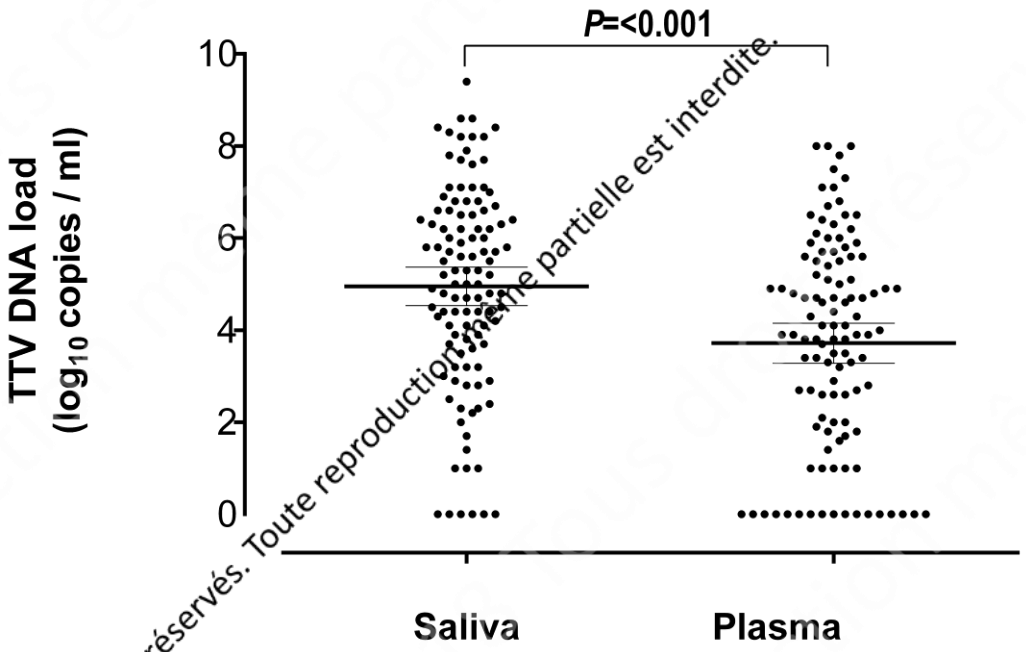
WILEY JOURNAL OF MEDICAL VIROLOGY

Kinetics of torque teno virus DNA load in saliva and plasma following allogeneic hematopoietic stem cell transplantation

Eliseo Albert Pharm.D[1] | Ignacio Torres Pharm.D[1] | Alberto Talaya Pharm.D[1] | Estela Giménez Pharm.D[1] | José Luis Piñana MD[2] | Juan Carlos Hernández-Boluda MD[2] | Daniele Focosi MD[3] | Lisa Macera MD[3] | Fabrizio Maggi MD[4] | Carlos Solano MD[2,5] | David Navarro MD[1,6]

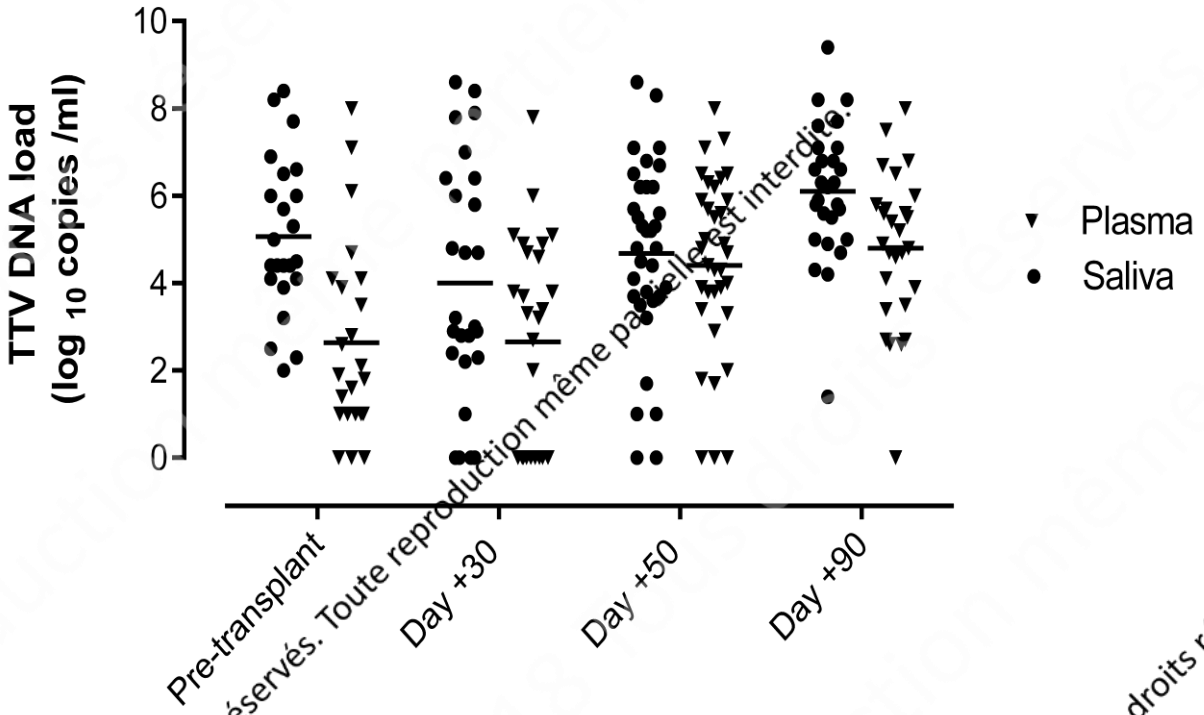
Saliva and plasma specimens were collected at baseline (pretransplant) and at around days +30, +50, and +90 after allo-HSCT. TTV DNA was quantitated in both specimen

- ***TTV DNA is detected more frequently in saliva than in plasma specimens (overall, 94.5% vs. 83.6%) and at higher levels***



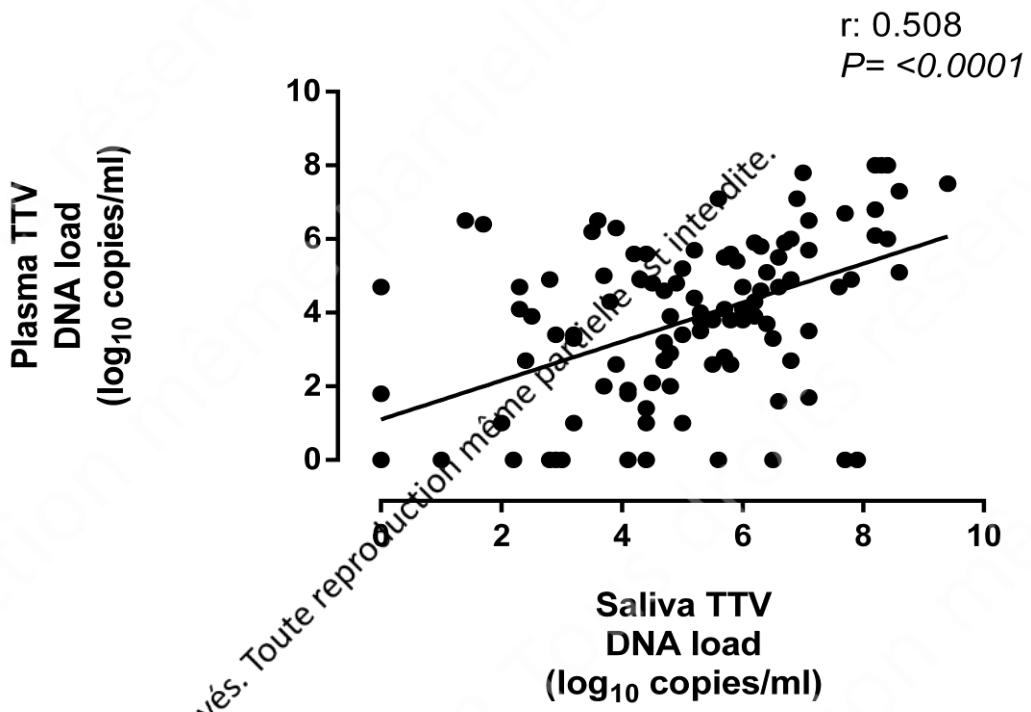
Albert et al., 2018 JMV

- ***TTV DNA is detected more frequently in saliva than in plasma specimens at all time points***
- ***Comparable kinetics in saliva and plasma***

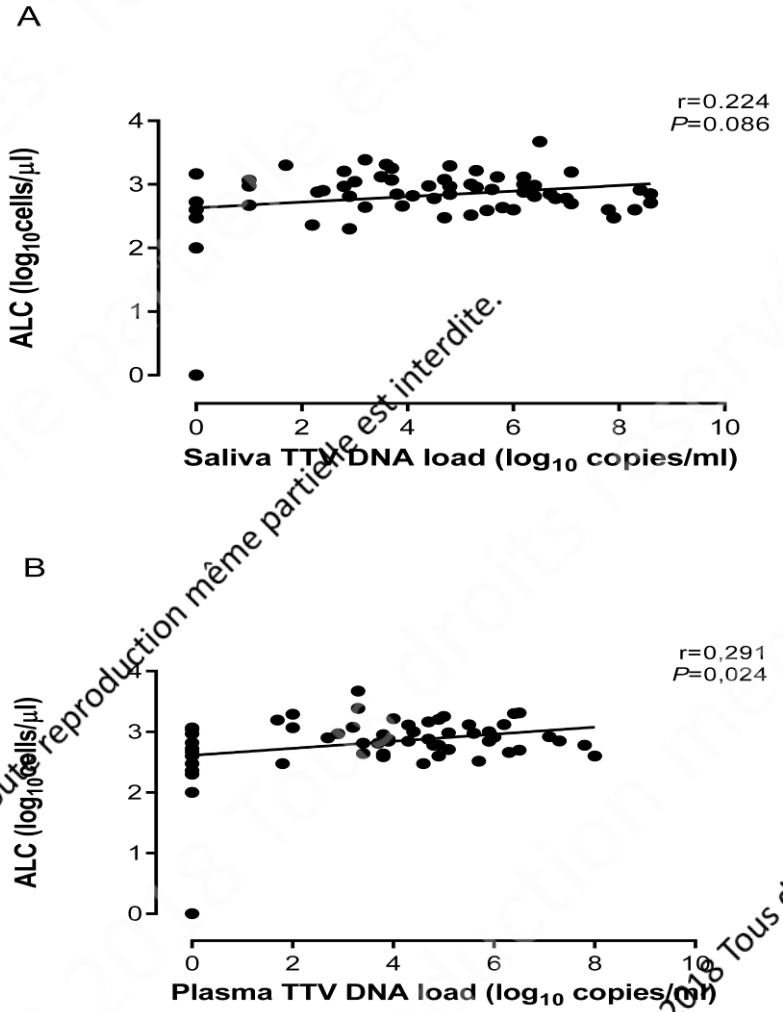


Albert et al., 2018 JMV

- ***TTV DNA in plasma and saliva do correlate significantly***



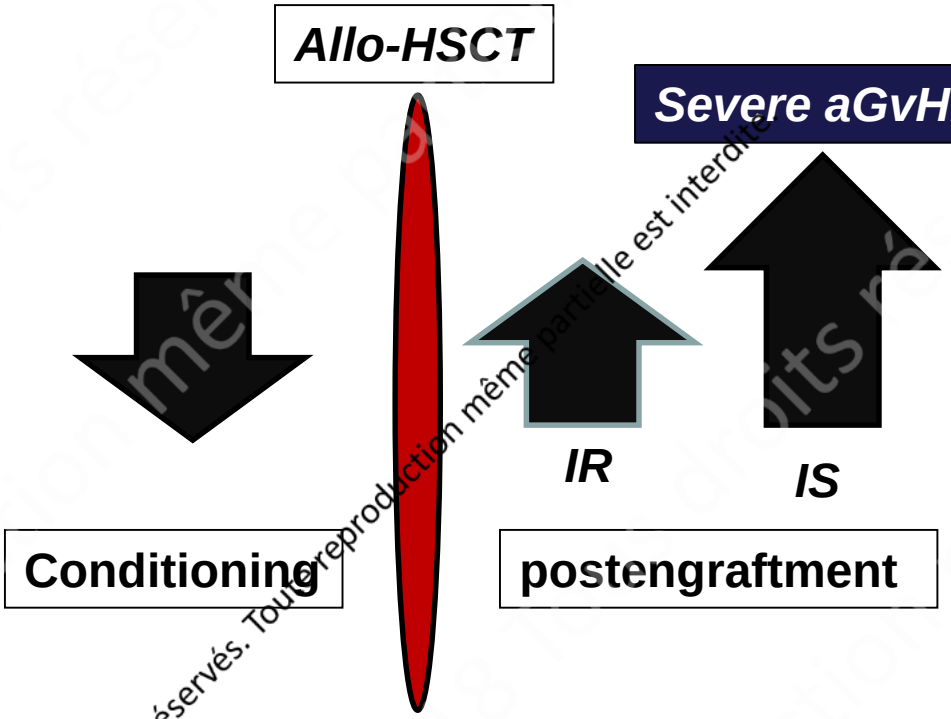
Albert et al., 2018 JMV



Correlation between TTV DNA loads quantified in saliva (A) and plasma (B) specimens and absolute lymphocyte counts (ALCs) following engraftment (between days +30 and +50 after allo-HSCT).

Albert et al., 2018 JMV

✓ Plasma TTV DNA load in allo-HSCT



IS: immunosuppression
IR: Immune reconstitution

Plasma TTV DNA load as a marker of immune competence early after engraftment?

Predicting the risk of CMV and EBV DNAemia

Bone Marrow Transplantation (2018) **53,** 180–187

www.nature.com/bmt

ORIGINAL ARTICLE

The kinetics of torque teno virus plasma DNA load shortly after engraftment predicts the risk of high-level CMV DNAemia in allogeneic hematopoietic stem cell transplant recipients

E Albert[1], C Solano[2,3], F Giménez[1], D Focosi[4], A Pérez[2], L Macera[5], JL Piñana[2], JCH Boluda[2], F Maggi[4] and D Navarro[1,6]

Table 1. Demographic and clinical characteristics of the patients

Parameter	n (%)
Sex	
Male	42 (59.2)
Female	29 (40.8)
Underlying hematological disease	
Hodgkin's lymphoma	3 (4.2)
Non-Hodgkin's lymphoma	21 (29.2)
ALL	6 (8.3)
CLL	6 (8.3)
AML	15 (21.1)
Multiple myeloma	5 (7.0)
Myelodisplastyc syndrome	7 (9.9)
Other	8 (11.3)
Allograft type	
Related	39 (54.9)
Unrelated	32 (45.1)
Matched	50 (70.4)
Mismatched	21 (29.6)
Haploidentical	12 (16.9)
Unrelated	9 (12.7)
Conditioning regimen	
Myeloablative	13 (18.3)
Non-myeloablative	58 (81.7)
Stem cell source	
Peripheral blood	69 (97.2)
Bone marrow	1 (1.4)
Umbilical cord blood	1 (1.4)
GvHD prophylaxis regimen	
Cyclosporine A or tacrolimus ± methotrexate	24 (33.8)
Cyclosporine A or tacrolimus ± mycophenolate mofetil or tacrolimus+sirolimus	29 (40.8)
Regimens including thymoglobulin	4 (5.6)
Regimens including cyclophosphamide	14 (19.7)
CMV serostatus	
D+/R+	41 (57.7)
D+/R−	8 (11.3)
D−/R+	16 (22.5)
D−/R−	6 (8.5)
EBV serostatus	
D+/R+	41 (57.7)
D+/R−	5 (7.0)
D−/R+	3 (4.2)
D/R+[a]	18 (25.4)
D/R−[a]	4 (5.6)

Intermediate risk For CMV and EBV-related morbidity

Higher risk:

- ***Unrelated***
- ***HLA-mismatch***
- ***Non-PB***
- ***CMV D-/R+***
- ***EBV D-/R+***
- ***EBV D+/R-***

CMV

Diagnostic Microbiology and Infectious Disease 75 (2013) 207–209

Contents lists available at SciVerse ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Comparison of the new Abbott Real Time CMV assay and the Abbott CMV PCR Kit for the quantitation of plasma cytomegalovirus DNAemia

María Ángeles Clari [a], Dayana Bravo [a], Elisa Costa [a], Beatriz Muñoz-Cobo [a], Carlos Solano [b], María José Remigia [b], Estela Giménez [a], Omar J. BenMarzouk-Hidalgo [c], Omar Pérez-Romero [c], David Navarro [a,d,*]

LOD: 20 copies/ml (31 IU/ml)
Weekly monitoring

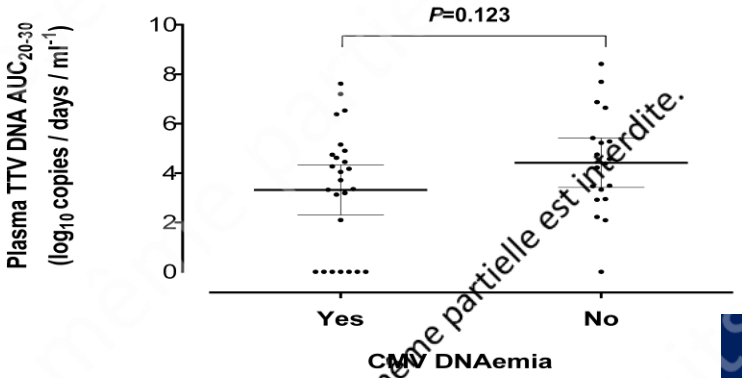
No end-organ disease

Albert et al., BMT 2018

Hypothesis: the magnitude of the area under the curve (AUC) for log_{10} TTV DNA loads, quantified between days **20 and 30** after transplant (TTV DNA load AUC_{20-30}) predicts subsequent CMV DNAemia occurrence

A

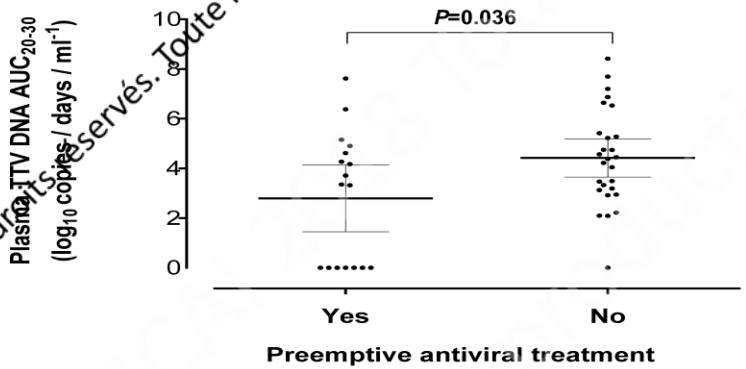
Overall CMV DNAemia



Comparable incidence of Severe aGvHD in both groups

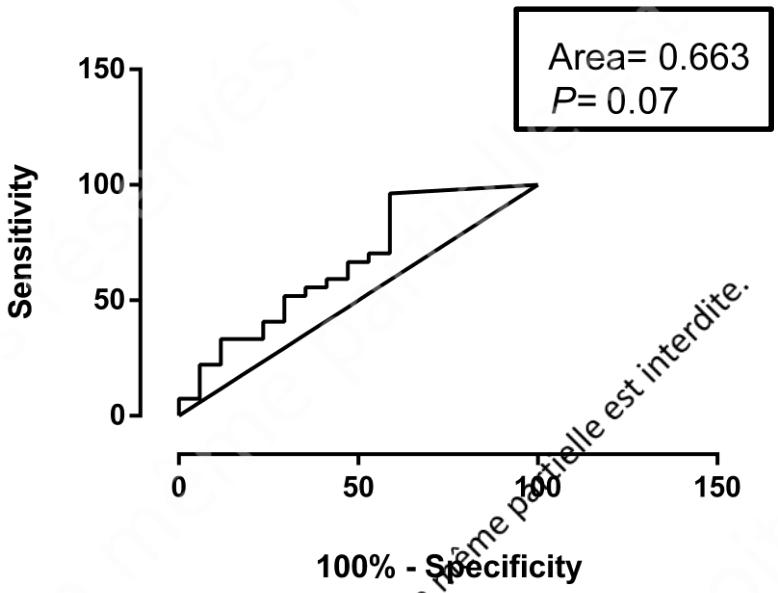
B

High-level CMV DNAemia: requiring PET



1,500 IU/ml

Albert et al., BMT 2018



✓ *$AUC_{20\text{-}30}$ ≤2.8 copiesxday/mL^{-1} best identified patients at risk of developing high-level CMV DNAemia requiring antiviral therapy (PPV:70%)*

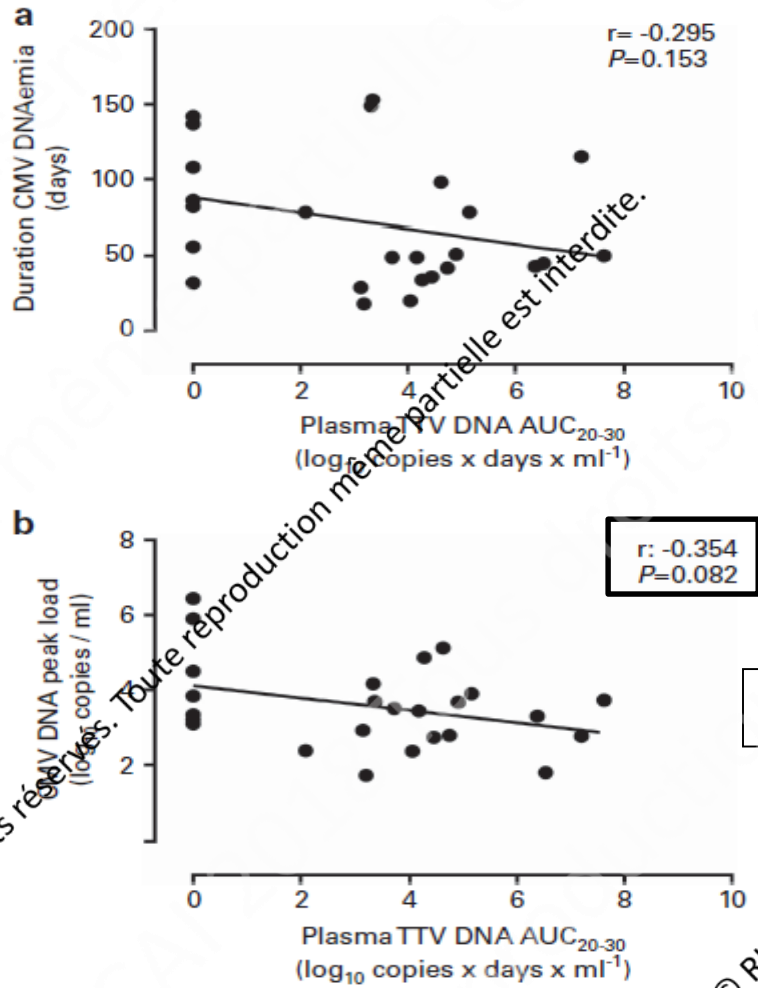
Albert et al., BMT 2018

Albert et al., BMT 2018

Risk factors for CMV DNAemia requiring preemptive antiviral therapy

Variable	*Univariate*		*Multivariate*	
	OR (CI 95%)	*P-value*	*OR (CI 95%)*	*P-value*
Plasma TTV DNA load $AUC_{20\text{-}30} \leqslant 2.8$	4.02 (0.96–16.91)	0.05	5.94 (0.91–38.97)	0.06
Allograft type				
Mismatched vs matched	1.45 (0.514.13)	0.48		–
Related vs unrelated	0.73 (0.47–1.92)	0.52		–
Conditioning regimen (myeloablative vs non-myeloablative)	1.62 (0.48–5.50)	0.46	–	
Conditioning regimen (including ATG vs not including ATG)	1.79 (0.23–13.54)	0.57	–	
aGvHD (grade II–IV vs 0–I)	2.18 (0.76–6.30)	0.14		
Serostatus CMV vs D−/R−				
D+/R+	2.32 (0.24–21.93)	0.46	–	–
D+/R−	1.66 (0.11–24.56)	0.71		
D−/R+	8.33 (0.77–89.47)	0.08		
Serostatus CMV vs D+/R+				
D−/R+	3.59 (1.07–12.00)	0.04	5.84 (0.90–38.97)	0.06
D−/R−	0.43 (0.04–4.06)	0.46		
D+/R−	0.71 (0.127–4.05)	0.70		
aGvHD prophylaxis regimen Including CP vs no CP	2.00 (0.61–6.53)	0.25	–	–

TTV 20-30 AUC and duration of CMV DNAemia: trend towards an inverse relationship

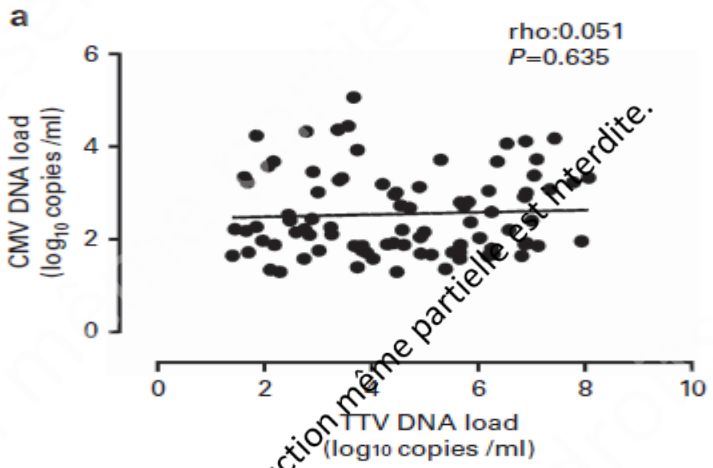


✓ *All episodes*

✓ *Treated episodes*

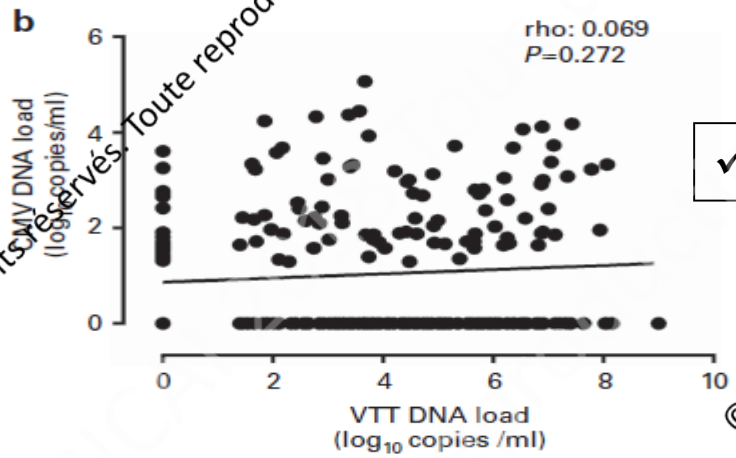
Albert et al., BMT 2018

Correlation between TTV and CMV DNA loads



✓*All specimens*

Albert et al., BMT 2018

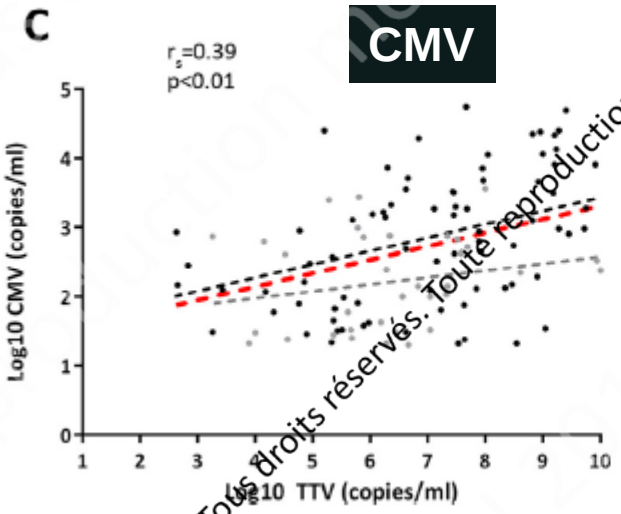


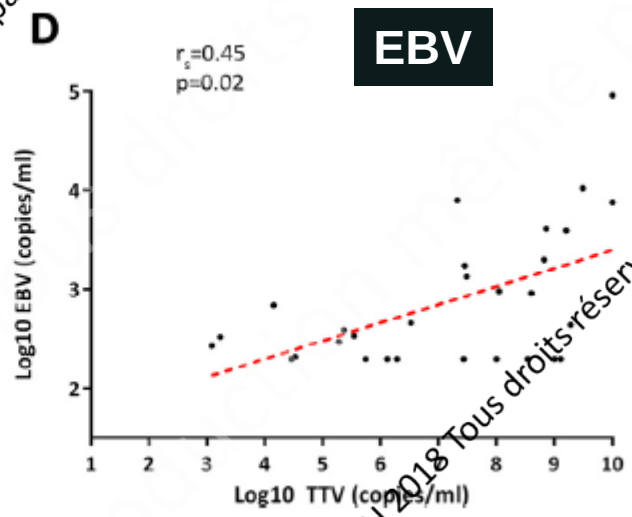
✓*PCR positive specimens*

Torquetenovirus Dynamics and Immune Marker Properties in Patients Following Allogeneic Hematopoietic Stem Cell Transplantation: A Prospective Longitudinal Study

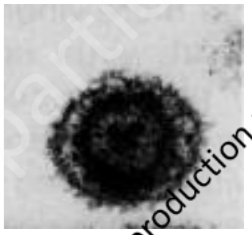
Philipp Wohlfarth [1,*], Michael Leiner [1], Christian Schoergenhofer [2], Georg Hopfinger [1], Irene Goerzer [3], Elisabeth Puchhammer-Stoeckl [3], Werner Rabitsch [1]

[1] Division of Blood and Marrow Transplantation, Department of Medicine I, Medical University of Vienna, Vienna, Austria
[2] Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria
[3] Department of Virology, Medical University of Vienna, Vienna, Austria





✓ Does TTV DNA $AUC_{20\text{-}30}$ correlate with early reconstitution of cytomegalovirus-specific T-cell immunity



pepmix pp65 and IE-1
(1 µg/mL/peptide)
+ CD28/CD49d moAbs

Brefeldin (at 2 h.)

6 h.

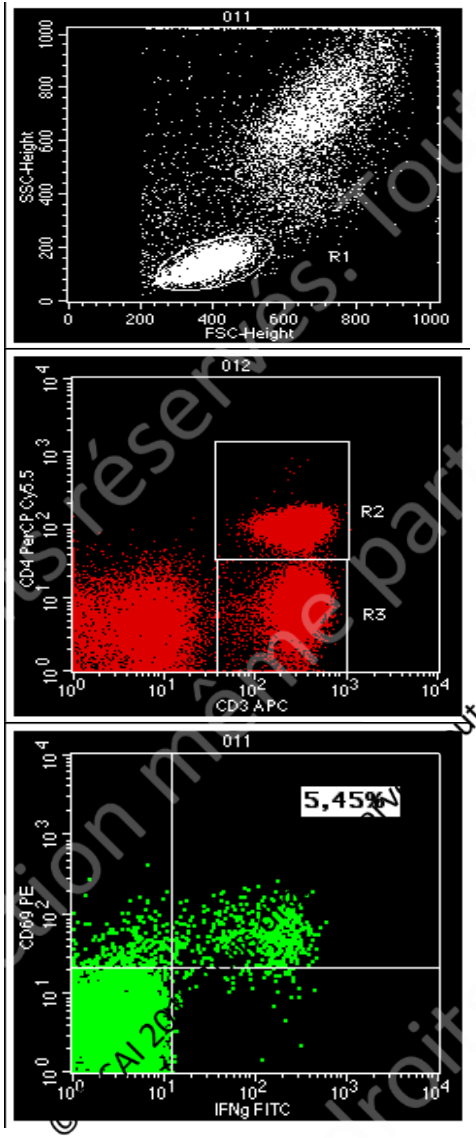
Lysis/Fixation

BD Fastimmune

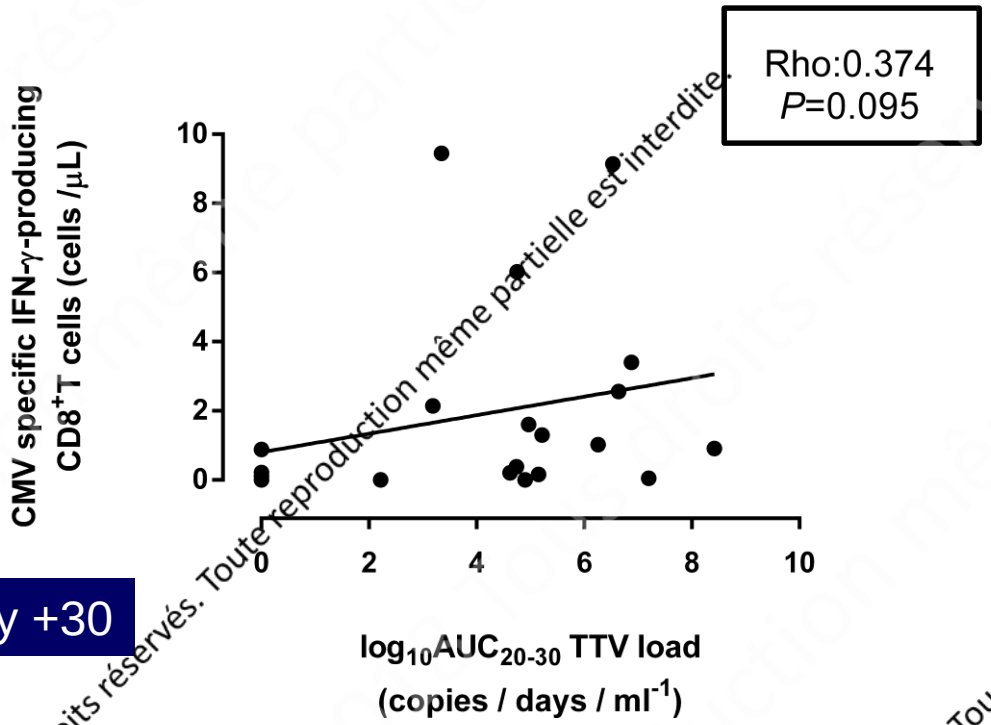
Permeabilization

Staining (CD3⁺/CD4⁺ or CD8⁺/CD69⁺/IFNγ)

Solano et al., Haematologica, 2008



✓ *Kinetics of plasma TTV DNA load and early reconstitution of cytomegalovirus-specific T-cell immunity*



Day +30

Albert et al., BMT 2018

Diagnostic Microbiology and Infectious Disease xxx (2017) xxx–xxx

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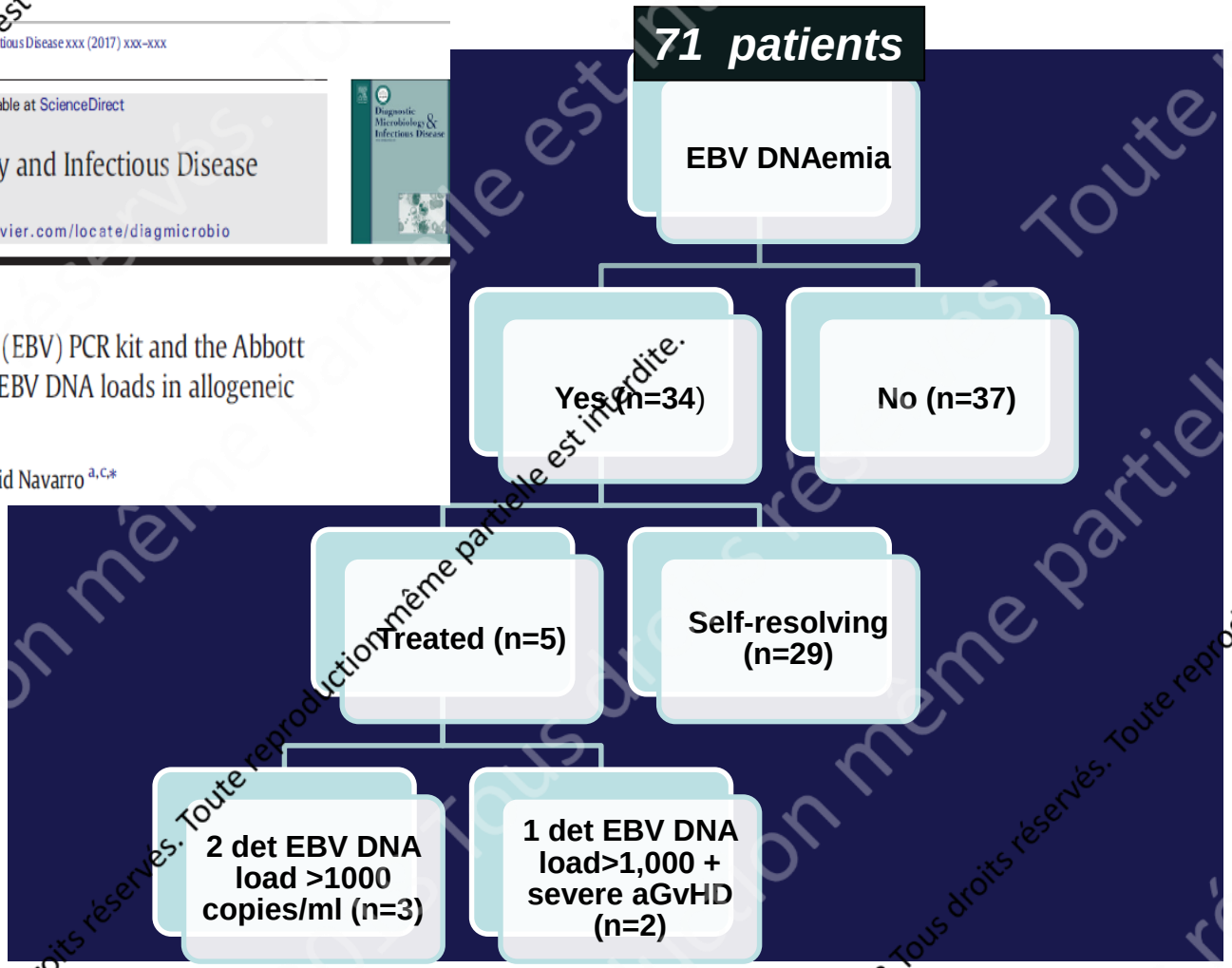
Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Note

Comparison of the artus Epstein–Barr virus (EBV) PCR kit and the Abbott RealTime EBV assay for measuring plasma EBV DNA loads in allogeneic stem cell transplant recipients

Víctor Vinuesa [a], Carlos Solano [b], Estela Giménez [a], David Navarro [a,c,*]

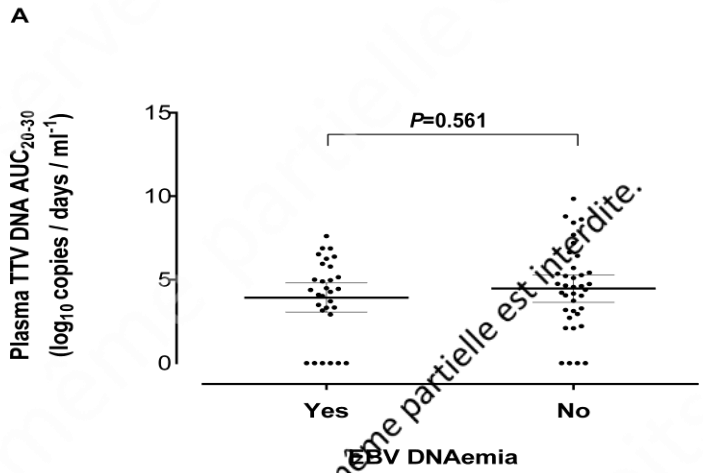


No PTLD

Albert et al., BMT 2018

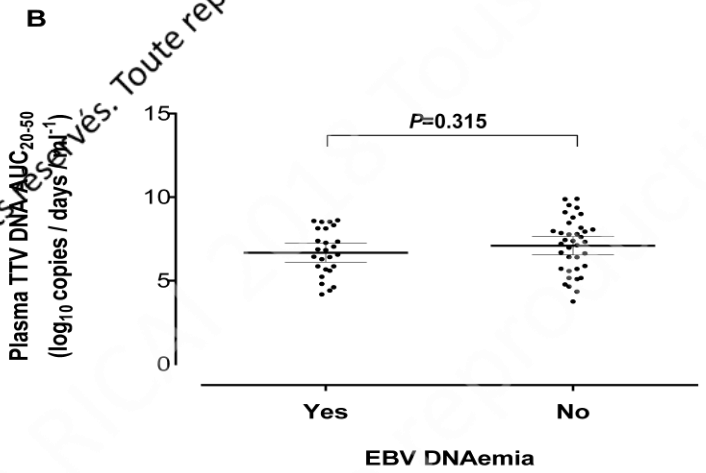
Kinetics of TTV DNA load and the risk of EBV DNAemia :TTV DNA AUC_{20-30} and TTV DNA AUC_{20-50}

Few episodes required PET



20-30 days

Albert et al., BMT 2018



20-60 days

Med Microbiol Immunol
DOI 10.1007/s00430-017-0511-4

ORIGINAL INVESTIGATION

Dynamics of Torque Teno virus viremia could predict risk of complications after allogeneic hematopoietic stem cell transplantation

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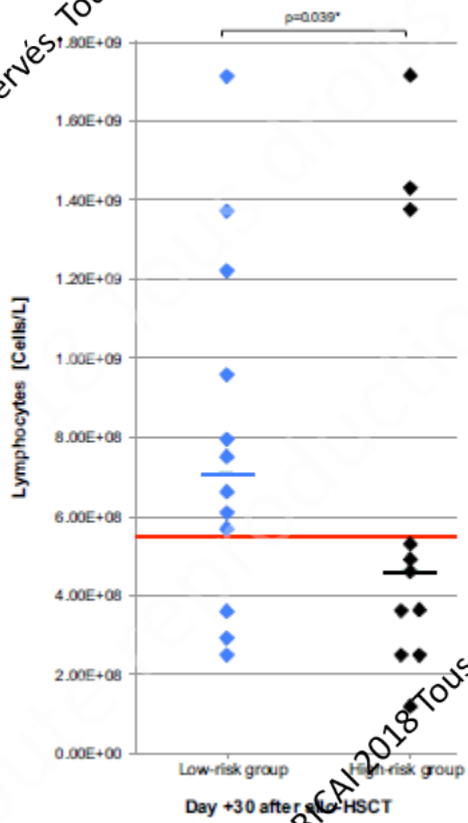
Low-risk group

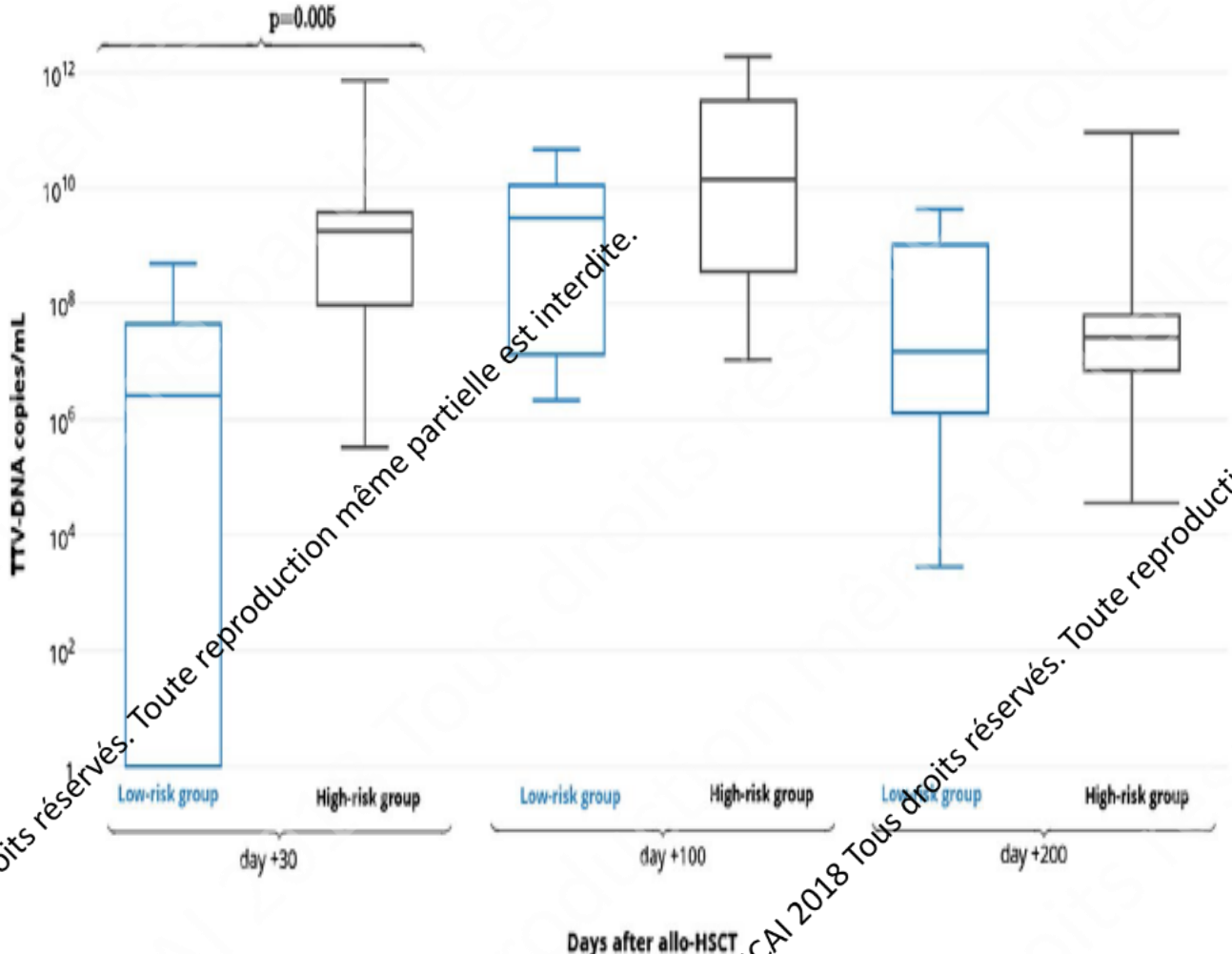
12 patients who did not develop any form of acute GVHD that would have required therapeutic intervention. Furthermore, these patients showed either limited or no CMV, EBV, or/and BKPyV reactivation. Limited CMV or/and EBV infections were defined by the asymptomatic detection of CMV-/EBV-DNA for ≤2 consecutive weeks. Limited BKPyV reactivation was defined by proof of viral DNA in urine only and absence of specific clinical symptoms .

High-risk group

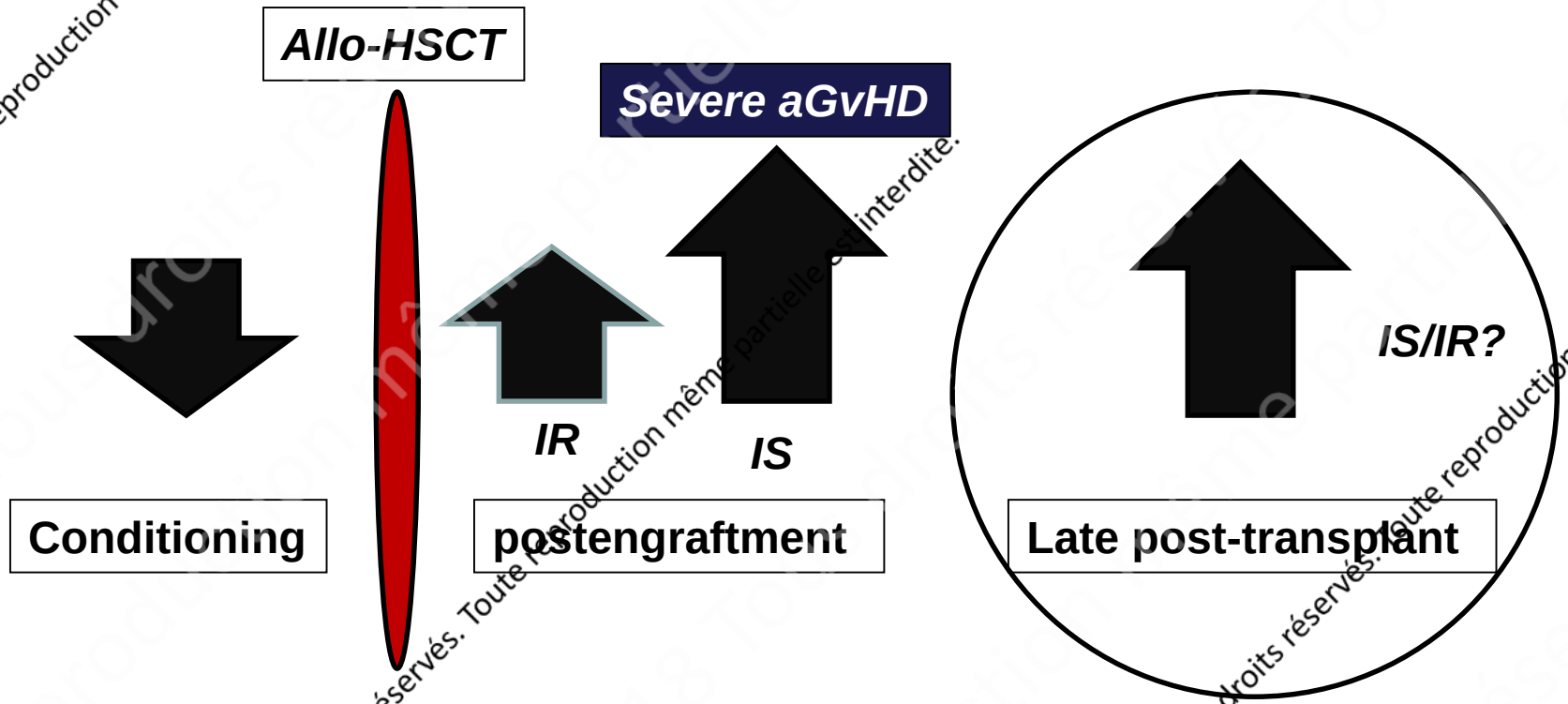
11 recipients who developed acute GVHD requiring escalation of immunosuppression and/or persisting/symptomatic non-TTV viral infections. For CMV and/or EBV reactivation, this was defined by the detection of CMV- and/or EBV-DNA for >2 consecutive weeks. For BKPyV, this was defined by evidence of viral replication in urine and plasma and/or by BKV-associated hemorrhagic cystitis (BKPyV-associated HC).

Fig. 1 Dynamics of TTV-DNA load on days +30, +100, and +200 after allo-HSCT in the low- and high-risk group (color figure online)



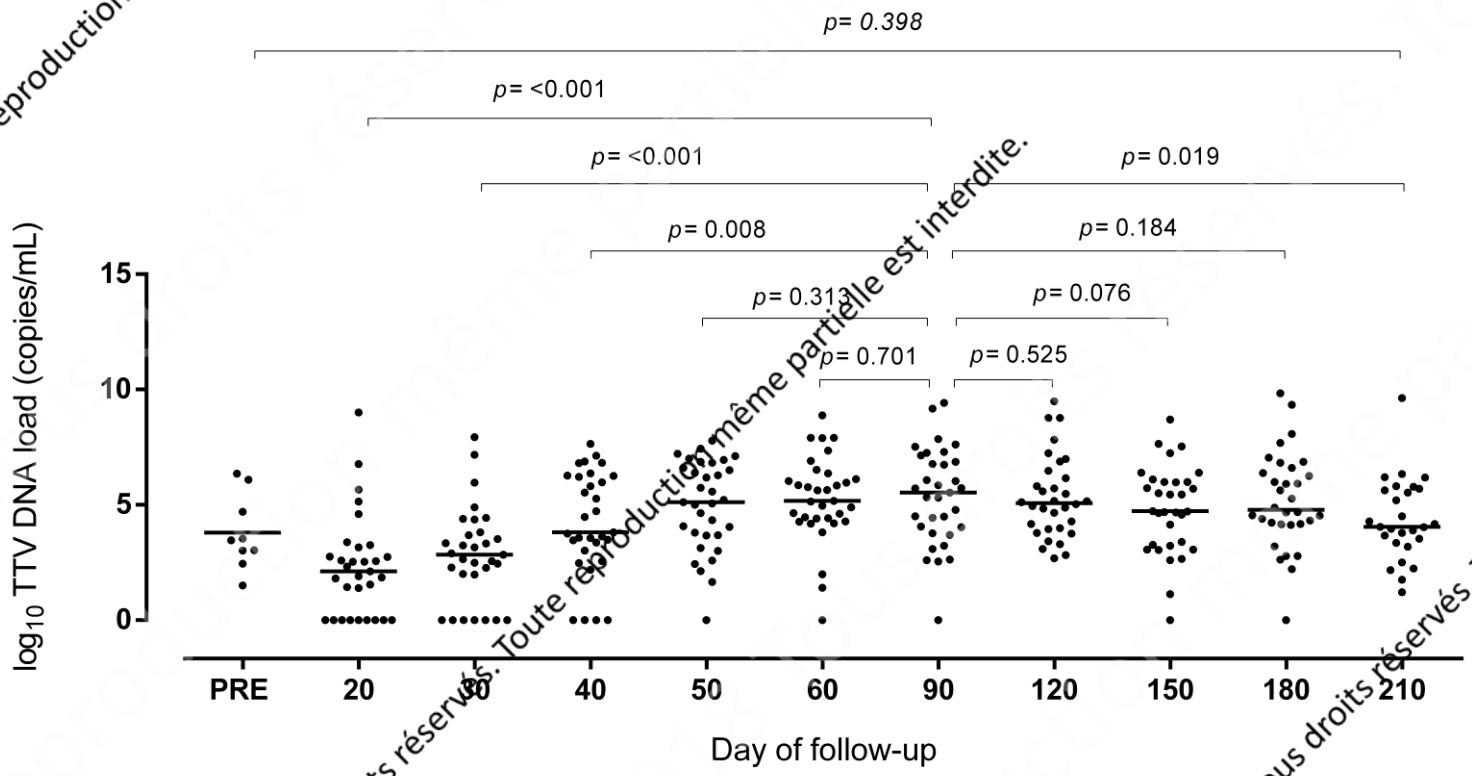


✓ Plasma TTV DNA load in allo-HSCT



IS: immunosuppression
IR: Immune reconstitution

Dnamics of TTV DNAemia in patients undergoing T-cell replete allo-HSCT at late times after transplantation (> day +100)



Albert et al., MMI, 2018 submitted

days +90 and +210

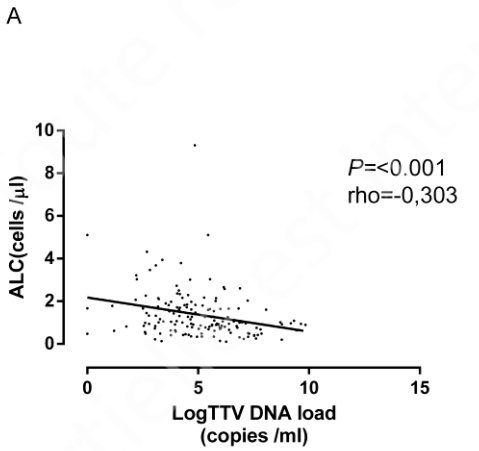
Inverse relationship

days +120 and +210

Inverse relationship

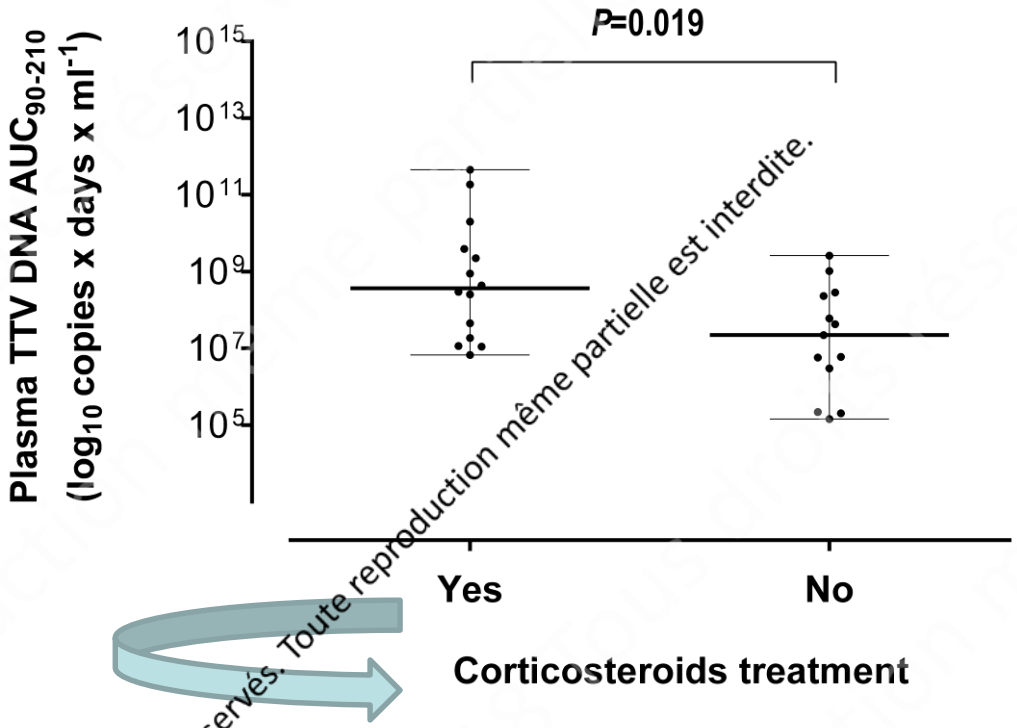
days +20 and +60

Direct relationship



Albert et al., MMI, 2018 submitted

Albert et al., MMI, 2018 submitted

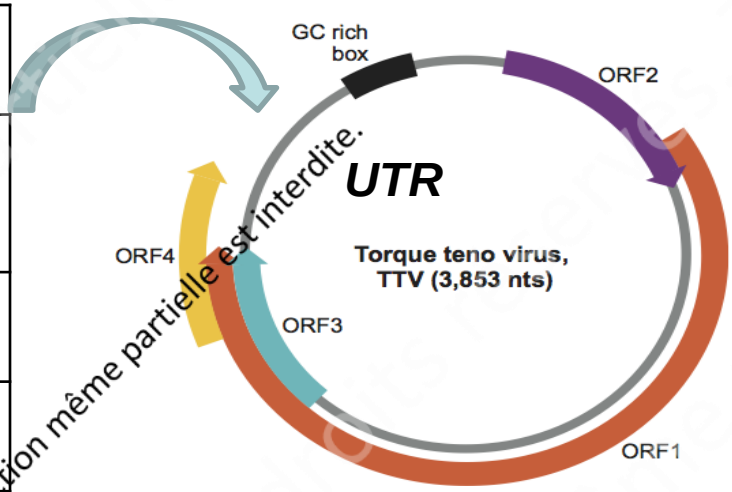


15 Patients: acute GvHD (n=5), chronic GvHD (n=7) or both (n=3

Dynamic changes of Anelloviruses in plasma following Allogeneic Hematopoietic Stem Cell Transplantation

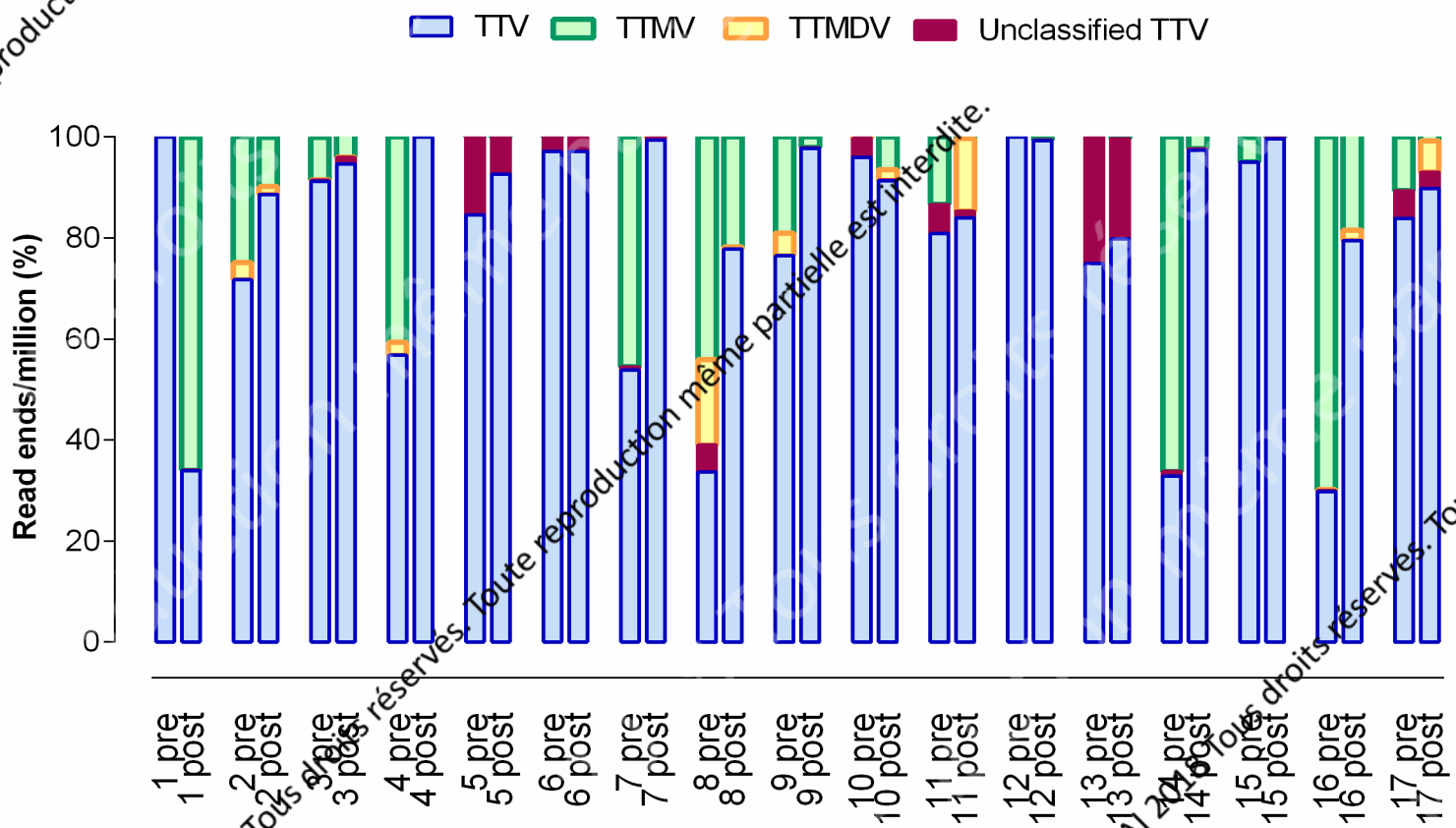
Primer sequences and positions used for amplification of TTV, TTMDV and TTMV				
Primer Sequence[a]	Sense	Nucleotide position TTV[b]	Nucleotide position TTMDV[c]	Nucleotide position TTMV[d]
GGTGRCGAAT GGCTGAGTTT	Forward	99-119	34-54	178-198
GGTGACGAAT GGTAGAGTTT	Forward	99-119	34-54	178-198
ACTTCCGAAT GGCTGAGTTT	Forward	99-119	34-54	178-198
CATGCCCGAR TTGCCCCT	Reverse	257-275	150-168	283-301
CGWGCCCGA ATTGCCCCT	Reverse	257-275	150-168	283-301

Giménez et al. in preparation



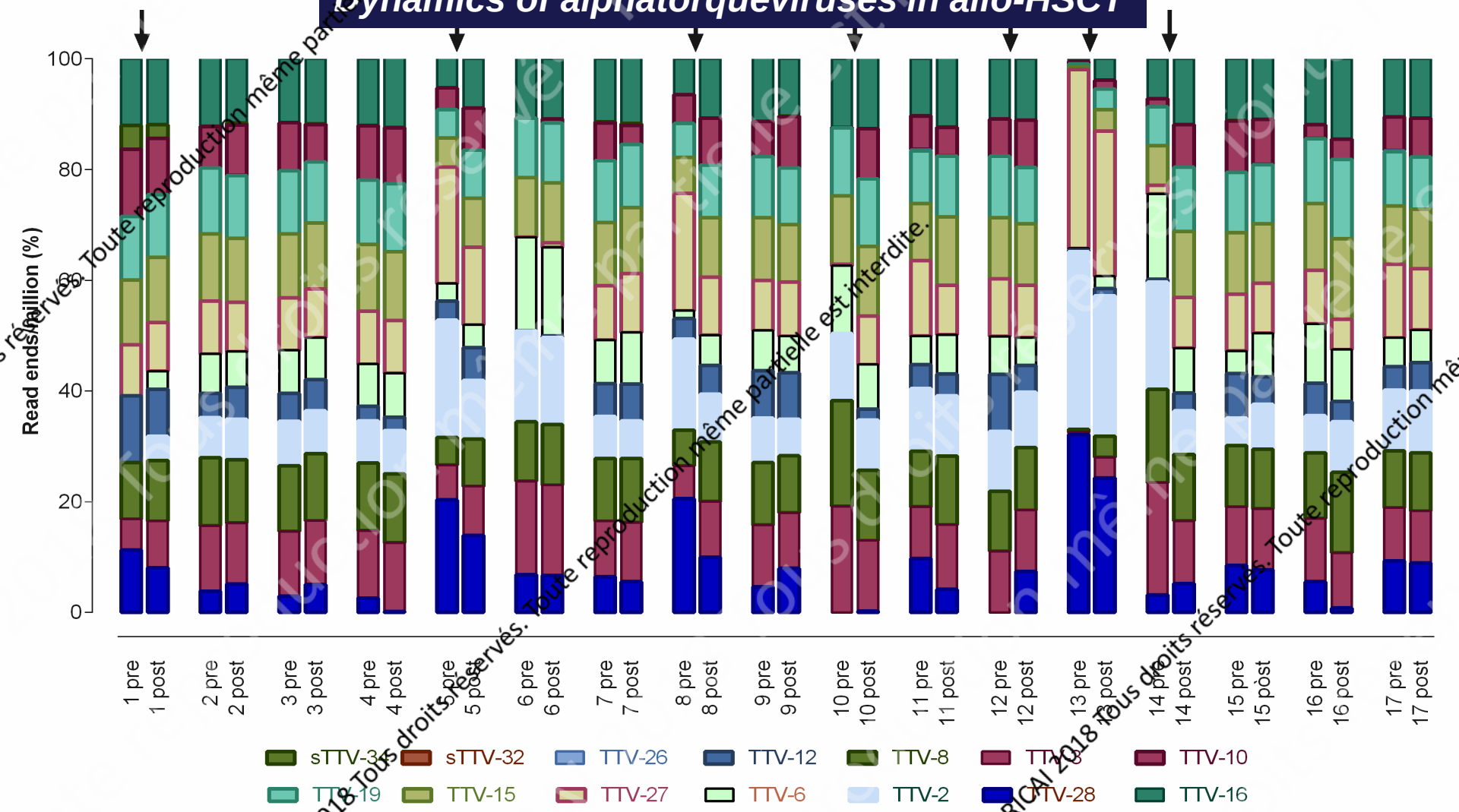
Dynamics of Anelloviruses in allo-HSCT

17 paired plasma specimens (pre-conditioning/post-engraftment)



Giménez et al. in preparation

Dynamics of alphatorqueviruses in allo-HSCT



Giménez et al. in preparation

TTV DNA load in plasma (saliva) is a surrogate marker for Immune reconstitution early after alo-HSCT and for immunosuppression at late times (>day 100)

The use of quantitative real-time PCR assays targeting TTMV and TTMDV in addition to TTV (universal anellovirus PCR) may provide more reliable information on the net state of immunosuppresion or immune competence than TTV-targeted PCR assays employed nowadays?