Supplement Table S1: TERMINOLOGY AND DEFINTIONS

Term	Definition
BKPyV infection	Specific serological/immunological or virological or molecular evidence of BKPyV exposure after which replication-competent BKPyV genomes are thought to persist life-long (clinically latent infection *and/or* virologically latent infection) Comment: Current diagnostic techniques *cannot* rule out on-going low-level or transient replication (clinically latent) *versus* true virologically latent infection i.e., transcriptionally silent episomal BKPyV genomes inside replication-competent host cell nuclei
BKPyV replication	Evidence for ongoing BKPyV multiplication - Infectious units by cell culture; PyV particles by electron microscopy; PyV structural virion proteins Vp1, Vp2/3 by immunohistochemistry; - messenger RNA expression / transcripts of PyV late genes (e.g.*VP1, VP2/3*); - increasing PyV DNA loads per reference unit; PyV DNA in non-latency sites (e.g., in plasma); cytological (e.g. decoy cells) or histological evidence of PyV replication Comment: specific markers or adjunct techniques necessary to identify BKPyV as compared to other PyVs together with evidence of viral DNA replication within host cell nuclei (e.g., specific intranuclear inclusions)
BKPyV pathology	Any histopathological or ultrastructural evidence of PyV-attributable tissue involvement including viral replicative, inflammatory, degenerative, or neoplastic changes - Requires specific markers or adjunct techniques to identify damage and the specific presence/role of BKPyV
BKPyV-DNAuria	BKPyV genome detectable in native urine (by nucleic acid testing [NAT [1]])
BKPyV viruria	BKPyV virions detectable in urine (by electron microscopy [2], cytology such as “decoy cells” [2,3], virus isolation by cell culture, by NAT incl. protected genomes in urine after DNase digestion)
Urine BKPyV load	BKPyV-DNA load per urine volume by quantitative NAT (QNAT) [1] in copies/mL or IU/mL
BKPyV-DNAemia	BKPyV-DNA genome detectable in blood by quantitative NAT (QNAT) [1] (preferentially in plasma e.g., EDTA- or Citrate-anticoagulated; whole blood and serum also possible but less/no data on comparison with plasma and/or on respective clinical validation)
BKPyV viremia	BKPyV virions or infectious units detectable in blood (by electron microscopy, by cell culture, protected after DNase digestion)
BKPyV-DNA load	BKPyV-DNA quantified by quantitative NAT (QNAT) [1]
Whole-blood BKPyV load	BKPyV-DNA load per mL of EDTA- or Citrate-anticoagulated whole blood (less/no data on comparison with plasma and/or on clinical validation)
Tissue BKPyV load	BKPyV-DNA load per normalized DNA reference (e.g., diploid gene QNAT [1], ug, or cell count)
Biopsy-proven PyV nephropathy	Detection of compatible cytopathic effect *plus* immunohistochemistry using the cross-reacting monoclonal antibody (PAb416) that was made against SV40 large T-antigen [4] or using other e.g., PyV Vp1-specific antibodies [5] or other techniques to identify intranuclear PyV particles and/or PyV genomes (e.g., electron microscopy, *in situ* hybridization) [2]

Biopsy-proven BKPyV-nephropathy	Proven polyomavirus nephropathy *plus* marker specific for BKPyV (immunohistochemistry, *in situ* hybridization, tissue normalized QNAT, detection of BKPyV-DNAemia in time-matched plasma) [5]
Presumptive BKPyV-nephropathy	BKPyV-DNAemia >10,000 copies/mL plasma (or equivalent) [6]
Probable BKPyV-nephropathy	BKPyV-DNAemia >1,000 - <10,000 copies/mL plasma persisting for longer than 2 weeks [6]
Possible BKPyV-nephropathy	BKPyV-DNAuria > 10 million copies/mL urine and undetectable BKPyV-DNAemia [6]
Resolving BKPyV nephropathy	Disappearance of histological evidence of PyV-replication (PyV-attributable tissue involvement) in patients with BKPyV-DNAemia loads declining >10-fold (>1 $\log_{10}$ copies/mL (or *equivalent*)
Transient BKPyV-DNAemia	Clearance of sustained BKPyV-DNAemia without specific intervention such as changing or reducing immunosuppression
Blip BKPyV-DNAemia	Single detection (positive) of BKPyV-DNA by QNAT[1] in plasma preceded and followed by undetectable (negative) BKPyV-DNA by QNAT during patient screening and monitoring using the same assay in the same laboratory (analogous to definitions in HIV medicine [7])
Biopsy-proven JCPyV- nephropathy	Detection of PyV nephropathy plus marker specific for JCPyV [8] and demonstration that BKPyV is not detectable

[1] Detection of viral genome, mostly by nucleic acid testing (NAT) techniques such PCR or other techniques such as ligase or signal amplification

[2] May require specific markers and/or adjunct techniques to prove specific involvement of BKPyV

[3] Enlarged nuclei, intranuclear inclusion, in renal tubular epithelial cells and/or transitional cells

[4] Immunohistochemistry using PAb416 raised is not specific BKPyV, but recognizes also JC polyomavirus (JCPyV) in JCPyVAN; support in clinical routine through plasma BKPyV-DNAemia by QNAT

[5] BKPyV-specific immunohistochemistry using non-cross-reactive antibodies e.g., anti-Vp1

[6] S-creatinine elevation from baseline is NOT needed since focal PyV-nephropathy stages occur without crude functional impairment and impaired kidney allograft function may be due to other etiologies (e.g., rejection, immune reconstitution)

[7] https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/virologic-failure-adult-adolescent-arv.pdf

[8] JCPyV-DNA load is often low/undetectable in plasma, despite high-level urine JCPyV-loads of >10 million copies/mL and requires detection by JCPyV-specific assays such as *in situ* hybridization, immunohistochemistry or tissue JCPyV-DNA load and undetectable BKPyV

Supplement Table S2: LABORATORY METHODS - VIROLOGY

Virological Assays	Target (Method)	Matrix, compartment	Advantages	Limitations	Additional comments	References
BKPyV-DNA load	viral DNA (QNAT)	-Plasma, urine -Plasma is preferred (see recommendations) -Whole blood gives higher variability and should not be used	-High sensitivity/ specificity -High NPV/PPV -BKPyV-DNAemia loads define clinical definitions -Probable BKPyV-nephropathy >3 log_{10} c/mL for >2 weeks, - Presumptive BKPyV-nephropathy >4 log_{10} c/mL	- BKPyV-DNAemia loads in plasma correspond largely to non-encapsidated genome fragments being sensitive to degradation - keep processing times short - readily separate plasma from rest of blood - keep cool until extraction avoid prolonged shipment - avoid multiple freezing and thawing	-Standard of care -Most frequent QNAT targets (*sTag/LTag, VP1, VP2, VP3*) - avoid highly variable non-coding control region -Similar efficacy but higher reproducibility with automated *vs* manual DNA extraction methods -If only urine is tested and urine BKPyV-DNA loads are >7 log_{10} c/mL, consider to switch to plasma BKPyV-DNA loads	[1-7]
	viral DNA (ddNAT)	-Urine	-High sensitivity/ specificity -High reproducibility -Absolute quantification	-Requires equipment not routinely available in diagnostic laboratories	-Needs adaption for plasma samples	[8]
	viral DNA (PI-dNAT)	-Urine	-No DNA extraction needed -Short analysis time of 2 hours	-Requires equipment not routinely available in most diagnostic laboratories	-Potentially useful for point-of-care setting -Needs adaption for plasma samples	[9]
Cytology	decoy cells (urine cytology; cytospin)	-Urine	-High NPV >99% -Simple workflow -Cost-effective	-Low PPV -High NPV Intermediate specificity	-Used in routine screening when BKPyV-DNA loads are not available -Papanicolaou-, Wright-Giemsa-, Sternheimer-Malbin or hematoxylin/eosin staining techniques or phase contrast -Manuel or automated intelligent microscopy used -Decoy cells should not be confused with high-grade urothelial carcinoma -Specificity can be increased by preparation by immunohistochemistry staining for LTag and/or Vp1	[10-21]
	PyV-virions / aggregates (“hauffen”) Electron microscopy	-Urine	-proposed marker for biopsy-proven BKPyV-nephropathy -High PPV for biopsy-proven BKPyV-nephropathy	-Requires processing and routine access to EM technical services - Identifies more advanced disease at risk of limited response to interventions	-Mainly used by one dedicated center - missing comparison of treatment response rates with current standard of care using plasma BKPyV-DNA loads	[22,23]

Virological Assays	Target (Method)	Matrix, compartment	Advantages	Limitations	Additional comments	References
BKPyV-transcripts	viral RNA *VP1* (RT-QNAT)	-Urine -Urinary cell sediment	-Assessment of active BKPyV replication	-mRNAs is degradation-sensitive -Pre-analytic processing and cell enrichments, stabilization reagents, prompt -Labor-intensive	-Further clinical studies are required to evaluate the PPV and NPV diagnosis and managements -Comparison with BKPyV-DNA loads lacking	[24-26]
	Viral micro RNAs bkv-miR-B1-3p or bkv-miR-B1-5p (RT-QNAT)	-Urine, plasma, urine exosomes	-Higher sensitivity early, lower specificity -In extracellular environments, miRNAs are apparently more stable than *VP1* mRNAs	-Low PPV	-The first two weeks post-KT, urine BKPyV miRNA was detected more frequently than urine BKPyV-DNA -The 3p microRNA is conserved between JCPyV and BKPyV -Controlled studies are needed	[27-29]
Genotyping and subtyping	viral DNA (Multiplex NAT or multiplex QNAT)	-Plasma, urine, biopsy	-Rapid BKPyV-genotyping	-No subtyping of BKPyV-genotypes	-Assay uses one probe per genotype	[7,30]
	Genome sequence, majority and minority variants, mutants (NGS)	-Plasma, urine, biopsy	-Targeted or complete genome sequencing - BKPyV-genotyping and subtyping -Assessment of NCCR sequence -Assessment of BKPyV integration into the human genome	-Requires access to NGS equipment, technical and bioinformatics resources -Expensive -Slow and not available as point-of-care testing	-Long range and amplicon-based protocols available	[7,31-33]
	Sanger sequencing/ viral DNA or NAT products	-Plasma, urine, biopsy	-Targeted genome sequencing -BKPyV-genotyping/subtyping -Assessment of NCCR rearrangements	-Limited to sequencing of 1000bp regions -Minority variants with frequencies <15% are not detected	-Mainly applied for sequencing of specific genome regions such as the NCCR and VP1-typing regions	[33-37]

Supplement Table S3: LABORATORY METHODS - IMMUNOLOGY

Immunological Assays	Target (Method)	Matrix, compartment	Advantages	Limitations	Additional comments	References
BKPyV-specific antibody	BKPyV IgG or IgM or IgA or IgG/IgM (ELISA[1])	- Serum, plasma	-Rapid -High-throughput -Broad range -Highly reproducible -qualitative -quantitative	-Currently only one commercial assay available -Laboratory-developed assays require antigen production, purification and validation -Recombinant GST-Vp1 fusion proteins (monomeric or pentameric), VLPs -Purification from insect cells, yeast or E.coli -Background reactivity may be variable and need monitoring -Validation is laboratory dependent -No EQA available	- Usually based on VLPs mimicking native virions of the predominant serotype I and sometimes also IV - May be based on GST-Vp1 fusion proteins or mimotopes, *i.e.*, synthetic peptides - Antibodies binding GST-Vp1 fusion protein or mimotopes may differ from antibodies binding VLPs - VLP based ELISAs seem to have the highest specificity	7,38-45
	BKPyV IgG (bead-based assay, Luminex)	-Serum, plasma	- Can be multiplexed to measure antibodies to different serotypes or to different polyomaviruses -Semi-quantitative by titration or by normalization to reference serum standards	-Based on Vp1 fusion proteins with purification tagging (GST, 6xHis, biotinylated -Manual preparation, -Costly equipment needed	-Available to few research-oriented centers	7,46-49
	Neutralization assay/ Neutralizing antibodies	-Serum, plasma	- Measurement of functional activity preventing BKPyV -Semi-quantitative by titration entry and gene expression		-Requires cell culturing -Requires preparation of infectious virus or pseudovirions or reporter virus - Available to few research-oriented centers	7,50-55
	Hemagglutination Inhibition Assay	-Serum, plasma	-Fast and easy processing -Semi-quantitative by titration	-Less sensitive than ELISA	-Requires virions, VLPs or pseudovirions -Requires specific blood-type erythrocytes -Serum may contain nonspecific inhibitors	12,19,39,50,56
BKPyV-specific cell-mediated immunity (CMI)	Cytokine secretion (ELISPOT)	-PBMCs	-Functional response to 15mer peptide/epitope stimulation -No prior knowledge on HLA needed -(semi-)quantitative -More sensitive than other CMI assays - simple instrumentation	-Turn-around times of 24h -Technical skills required -No access to polyfunctional T-cells	-Positive responses associated with controlling BKPyV replication -Consensus on cut-off, T-cell activation procedure and cytokine not	57-65

			-Targetable to specific early and/or late viral proteins (LTag, sTag, Vp1, Vp2/3, agnoprotein) -applicable to CD8 T cells using immunodominant 9mer epitopes -targetable to genotype-specific CD8 T cell responses	--Mostly IFNγ secretion assessed -Moderately expensive	established across different studies and centers -Requires further logistic and technical work prior to role in routine clinical practice	
	Flow cytometry combined with intracellular cytokine secretion	-PBMCs	-Functional response to overlapping 15mer peptide epitope pool stimulation -No prior knowledge on HLA needed -(semi-)quantitative -Multiple parameters tested simultaneously -Targetable to specific early and/or late viral proteins (LTag, sTag, Vp1, Vp2/3, agnoprotein) -T cell subsets (CD4 *vs* CD8) -Naïve, TEMRA, effector *vs* central memory) -Polyfunctional cytokine secretion (IFN-γ, TNFα, IL-2, CD107a) -Applicable to CD8 T cells using immunodominant 9mer epitopes -Targetable to genotype-specific CD8 T cell responses	-Turn-around times 8h - 24h -Technical skills required -very expensive instrumentation -limited sensitivity -Limited sensitivity due to low number of circulating T cells -In vitro expansion needed	-Consensus on cut-off, T-cell activation procedure and cell gating not established across different studies and centers -Not easily applicable to routine clinical practice	[42,60-64,66-68]
	T-cell responses (MHC-restricted peptide multimers)	-PBMCs	-T-cell stimulation not always necessary -Detect MHC-specific T-cells - Targetable to specific early and/or late viral proteins (LTag, sTag, Vp1, Vp2/3, agnoprotein) -targetable to immunodominant CD8 T cell epitopes -targetable to genotype-specific T cell responses	-Technical abilities required -Prior HLA typing required -Very expensive	-Not easily applicable to routine clinical practice -observed cross-reactivities with JCPyV-specific HLA-peptide complexes	[60,66,69-71]
	T lymphocytes activity (ATP levels)	- Whole blood sorted CD4+ T-cells		-Long operating times (>48h) -High constraints on handling/shipping samples, -Technical abilities required -Off-site titration -Expensive	-One FDA-cleared assay -Not easily applicable to routine clinical practice	[72]

Supplement Table S4: LABORATORY METHODS – OTHER ASSAYS

Other Assays	Target (Method)	Matrix, compartment	Advantages	Limitations	Additional comments	References
Chemokines	Chemokine levels (bead-based multiplex assays)	-Plasma, urine	- Higher predictive value for BKPyV-nephropathy than serum creatinine reported in a single study	-Not discriminating BKPyV replication *vs* chronic rejection, such as TCMR	-CXCL-10 concentrations increase in plasma and in urine with increasing burden of BKPyV replication (viral loads) - CXCL-10/creatinine ratio in urine had no predictive value for BKPyV-nephropathy	[73-78]
Other immune cells	Killer cell-inhibitory receptors (KIR) of Donor and Recipient (Exon sequencing)	-PBMCs	-*KIR3DS1*/HLA-F interaction -AA telomeric motifs possibly protective against progression to BKPyV-nephropathy	-Technical abilities required - Time-consuming -Multiplexed PCR possible but expensive	-Not easily applicable to routine clinical practice -Additional clinical studies are required to evaluate its use for risk stratification in KTRs	[79-81]; for review see [82]
HLA-polymorphism	HLA-typing and polymorphism of Donor and Recipient (Chromosomal DNA, exon sequencing, amplicon NGS sequencing)	-PBMCs	-Donor *HLA-C*07, MICA A5.1* and recipient *HLA-B51* have been suggested to protect against BKPyV-DNAemia	-Technical abilities required -Time consuming -Not easily applicable to routine clinical practice -Expensive -PPV for BKPyV-DNAemia undefined	-Multiplexed NAT available -Additional clinical studies are required to evaluate its use for risk stratification in KTRs	[46,80,83-86]
	Torque teno virus (TTV) DNA load (QNAT)	-Plasma, serum, urine	-Surrogate marker for post-transplant immunosuppression -High TTV-DNA load in plasma may be predictive marker for infection (3 and more months post-transplant)	-PPV of TTV load of 5 log10/mL for plasma BKPyV-DNAemia	- Studies using high TTV-DNA loads in plasma of KT recipients are controversial as predictive marker for BKPyV-DNAemia/nephropathy	[87-94]
	Donor-derived (dd)-cell-free DNA AlloSure; minor allele SNP detection library and 150 bp Illumina X-ten)	-Urine -Plasma	-Surrogate marker for kidney injury -Plasma dd-cfDNA-load positively correlates with plasma BKPyV-DNA-loads -No differential between TCMR and biopsy-proven BKPyV-nephropathy	-Broader utility when using commercial assays and instrumentation -NGS equipment, technical and bioinformatics resources -Expensive	-Small sample size and study sites -Selected patients -Unspecific marker of donor tissue injury -Additional clinical studies are required to evaluate the PPV for biopsy-proven BKPyV-nephropathy -Expensive -Labor-intensive -Resource-demanding	[95,96]

Supplement Table S5: STUDIES INVESTIGATING REDUCTION OF IMMUNOSUPPRESSION (MYCOPHENOLATE REDUCTION FIRST)

Reference	Study Design	Participants (N)	Treatment	Outcome (*Follow-up / observation time*)
Brennan et al., 2005 [97]	Single-center open-label, prospective, randomized (2 TAC:1 CsA) trial.	*de novo* KT recipients Induction with 6 mg/kg of anti-thymocyte globulin. FK506 (n = 134) 69 (52%) received AZA and 65 (49%) received MMF. CyA (n = 66) 43 (65%) received AZA and 23 (35%) received MMF. BKPyV-DNAemia and BKPyV-DNAuria were collected weekly for 16 weeks and at months 5, 6, 9 and 12.	Identification of BKPyV-DNAemia (qualitative PCR measurement; quantitative PCR was performed retrospectively) triggered discontinuation of AZA or MMF. If viremia failed to clear within 4 weeks, the calcineurin inhibitor dose was tapered to trough CyA levels of 100–200 ng/mL or trough FK506 levels of 3–5 ng/mL.	70 patients (35%) developed viruria and 23 (11.5%) BKPyV-DNAemia. No BK nephropathy was observed. Reduction of immunosuppression per this protocol was associated with clearance of BKPyV-DNAemia in 22 of 23 patients (95%) by 1 year after transplant. In 7 patients, BKPyV-DNAemia cleared after cessation of the adjuvant agent alone, in 2 patients a decrease in the calcineurin dose alone was made. 6 patients required cessation of the adjuvant agent and a decrease in the calcineurin dose. Ten cases of acute rejection (5%), 6 (4%) occurred in the TAC group and 4 (6%) in the CsA group. Only one rejection episode was directly related to protocol-directed immunosuppression reduction. Patient survival was 99% in the FK506 group and 100% in the CsA group. Death censored graft survival was 95% in the FK506 group and 100% in the CsA group.
Seifert ME et al., 2017 [98]	Retrospective 10-year analysis	Ten-year follow-up. N=193	Discontinuation of AZA or MMF during the first year after kidney transplantation due to BKPyV-DNAemia	10-year outcomes of subjects undergoing immunosuppression reduction for BKPyV-DNAemia compared to patients without BKPyV-DNAemia, respectively. Acute rejection: 14% vs. 15% (p=0.96) Death with a functioning graft: 33% vs. 17% (p=0.02) Death-censored graft loss: 8% vs. 15% (p=0.25) eGFR: 63±22 vs. 60±22 ml/min/1.73 m2 (p=0.46)

Kharel A et al., 2021 [99]	Single-center retrospective study (n=224) BKPyV-DNAemia measured every 2 weeks for the first 3 months, monthly from months 3-12, and at the time of a kidney allograft biopsy.	224 with BKPyV-DNAemia > 1000 copies/mL. Induction: Basiliximab (49%) Anti-thymocyte globulin (35%) Alemtuzumab (16%) maintenance immunosuppressive regimen: CNI (mostly tacrolimus), and a mycophenolic acid, with or without prednisone	BKPyV-DNAemia 1000-10 000 copies/mL: the antimetabolite is decreased by 25%. BKPyV-DNAemia >10 000: the antimetabolite is decreased by 50% followed by decreases in calcineurin inhibitor (CNI) targets, with adjustments occurring no sooner than 2 weeks from prior regimen manipulation.	118 (53%) resolved or had persistent low BKPyV-DNAemia 64 (28%) had severe BKPyV-nephropathy 42 (19%) developed dnDSA (n=33) or AR (n=9).
Steubl D et al., 2012 [100]	Retrospecitve multicenter	Patients with sustained BKPyV-DNAemia > 500 copies/mL on at least two consecutive measurements. CNI, mycophenolate, prednisolone Immunosuppression of the patients had to be reduced in order to treat the BKPyV-DNAemia.	Group MMF ex (n = 14): discontinuation of MMF and reduction of the remaining immunosuppression after BKPyV-DNAemia was detected for the first time. Group IMMUN red (n=32): dosage of immunosuppressive therapy was reduced, but MMF was not discontinued at the time of first BKPyV-DNAemia detection.	Patients with sustained freedom from BKPyV-DNAemia Group MMF ex (n=13, 93%) Group IMMUN red (n=19, 60%) Patients in whom MMF was stopped had a higher chance of clearance of BKPyV-DNAemia (p = 0.022), which was achieved more rapidly (p = 0.048).
Devresse A et al., 2019 [101]	Single center, retrospective study (n = 111)	57 patients who underwent gradual tapering of IS vs 54 patients who underwent rapid tapering for sustained BKPyV-DNAemia (defined as two consecutive positive tests for BKPyV-DNAemia). 71 patients received rATG induction, 37 received basiliximab. Maintenance IS with tacrolimus, MPA and steroids.	Gradual group: stepwise reduction every month until BKPyV-DNAemia decreased in two consecutive steps of 50% MPA dose reduction before complete withdrawal and then tacrolimus reduction to reach troughs levels of 3-5 ng/ml. Rapid group: IS reduced as outlined above but changes were made every 2 weeks. No patients received specific anti-viral treatment.	The rapid minimization strategy shortened BKPyV-DNAemia ($P < 0.001$) and resulted in a better protection of graft function in patients with confirmed BKPyV-nephropathy ($P = 0.033$) without impacting 5-year graft survival. Survival without rejection was similar ($P = 0.571$), but the rapid group had increased *de novo* donor-specific antibodies (dnDSAs; $P < 0.001$).

Supplement Table S6: STUDIES INVESTIGATING REDUCTION OF IMMUNOSUPPRESSION (CALCINEURIN INHIBITOR REDUCTION FIRST)

Reference	Study Design	Participants (N)	Treatment	Outcome (*Follow-up / observation time*)
Bischof et al., 2019 [102]	Retrospective single-center cohort with pre-defined standard operating procedure for screening and treatment	KT recipients (N=644): -'no decoy cells' N=432 (66%) -'decoy cells/no BKPyV-DNAemia' N=105 (17%) - BKPyV-DNAemia (≥300 cp/mL) N=105,17%) =probable N=24, 4%; =presumptive N=48; 8%; = biopsy-proven N=33, 5%	Immunosuppression reduction, no other interventions Patients with BKPyV-DNAemia: -Step 1: Tac trough levels were set one step lower than intended by the protocol and targeted as predefined for the next time-period -Step 2: If BKPyV-DNAemia did not decrease within 4 weeks, Tac trough levels were further reduced by one step as predefined for the next time-period -Step 3: If BKPyV-DNAemia did not decrease within 4 weeks, the dosing of MPA was reduced in steps of 50% or discontinued	- 96% viremic patients cleared BKPyV-DNAemia. -Clearance after tacrolimus reduction alone for 39% of all patients, but response differed according to diagnosis -At 6-years post-transplant, no differences among the three groups regarding graft survival and clinical rejection -Patients (N=24) with probable BKPyV-nephropathy (i.e. 1000<x<10,000 c/mL) cleared BKPyV-DNAemia in 63% by Tac reduction alone; another 25% required MPA reduction -Patients (N=48) with presumptive BKPyV-nephropathy (>10,000 c/mL, biopsy not done or neg) cleared BKPyV-DNAemia by Tac-reduction alone in 51%; another 48% required MPA reduction -Patients (N=33) with biopsy-proven BKPyV-nephropathy cleared BKPyV-DNAemia by Tac-reductione alone in 21%; another 61% required MPA reduction *-Follow-up median 6.6 years post-transplant (min 1.3 yrs)*
Schaub et al., 2010 [21]	Retrospective single-center cohort with pre-defined standard operating procedure for treatment	KT recipients with BKPyV-DNAemia/Nephropathy (N=38) (biopsy-proven, N=13; presumptive, N=17; probable, N=8)	Patients with sustained BKPyV-DNAemia >1000 c/mL: Step 1: Tac trough levels were set one step lower as intended by the protocol and targeted as predefined for the next time-period Step 2: If BKPyV-DNAemia did not constantly decrease, Tac trough levels were further reduced by one step as predefined for the next time-period Step 3: If BKPyV-DNAemia did not constantly decrease, the dosing of MMF was reduced by 50% and then discontinued (step 4).	-35/38 (92%) patients cleared BKPyV-DNAemia after tacrolimus reduction alone -Patients (N=8) with probable BKPyV-nephropathy (i.e. 1000<x<10,000 c/mL) cleared BKPyV-DNAemia in 100%; requiring only Tac-reduction (100%) -Patients (N=17) with presumptive BKPyV-nephropathy (>10,000 c/mL, biopsy not done or neg) cleared BKPyV-DNAemia by Tac-reduction alone in 47%; another 41% required MPA reduction; 11% did not clear Patients (N=13) with biopsy-proven BKPyV-nephropathy cleared BKPyV-DNAemia by Tac-reduction alone in 17%; another 50% required MPA reduction; MPA discontinuation in 33%; 1 (8%) did not clear -Follow-up showed clinical rejection in 3 (8%); subclinical rejection in 7 (18%) -No graft loss *-Median follow-up time of 34 months (range 18–60*)

Ginevri et al., 2007 [64]	Prospective, single-center, observational, pediatric kidney transplantation cohort	KT recipients (N=62) BKPyV-DNAemia N=13 (21%)	Patients with stable baseline renal function, -Step 1: reduction following the predefined standard operating procedure without further intervention -Step 2: if BKPyV-DNAemia increased over the 4 next weeks, reduction of calcineurin inhibitor by 15-20% -Step 3: if BKPyV-DNAemia persisted MMF reduction by 50% -Step 4: If BKPyV-DNAemia persisted, MMF discontinuation Patients with presumptive BKPyV-nephropathy and decreasing renal function: -Step 1: reduction of calcineurin inhibitor by 15-20% -Step 2: if BKPyV-DNAemia increased over the 4 next weeks, MMF reduction by 50% -Step 3: If BKPyV-DNAemia persisted, MMF discontinuation	BKPyV-DNAemia clearance: - protocol reduction+/- calcineurin inhibitor reduction in 10/13 patients - 100% after a median of 2 months (range 1-8 months) -No biopsy-proven BKPyV-nephropathy diagnosed after a *-Median follow-up of 24 months*
Sood et al., 2012 [103]	Retrospective single-center cohort with pre-defined standard operating procedure for treatment	KT recipients (N=65) with BKPyV-DNAemia	- Step 1: 25% of simultaneous reduction in MMF and Tac dosing without any antiviral therapy. -Step 2: an additional 25% reduction in dosing of both MMF and Tac at 1 month if the decline in BKPyV-DNAemia level was less than 25% from peak levels -Tacrolimus target in the significant BKPyV-DNAemia group:4 to 6 ng/mL.	-The mean plasma BKPyV-DNA declined by 98% (range, 76%–100%) -Acute cellular rejection seen in four (14%) of 28 patients -No decline in estimated glomerular filtration rate *-Follow-up 1 year after peak BKPyV-DNAemia*

Note: All adult patients unless indicated otherwise

Supplement Table S7: STUDIES INVESTIGATING SWITCHING TO mTOR INHIBITOR FOR TREATMENT OF BKPYV-DNAEMIA/NEPHROPATHY

Reference	Study type	Study population	Treatment (Intervention *versus* Comparator)	Endpoint (*follow-up / observation time*)	Result	Acute Rejection after treatment (%)	Graft loss (%)
Wojciechowski et al., 2017 [104]	Prospective, randomized, open-label, Single-center pilot	KT recipients on Tac/MMF/pred (N=40) with BKPyV-DNAuria ≥6 log10 c/mL or BKPyV-DNAemia	Switch MMF to everolimus (N=20) *versus* MMF dose reduction by 50% (N=20) (*Note:* Tac trough levels were lowered in both groups from 8.4 ± 2.3 ng/mL at enrolment to 5.3 ± 2.1 ng/mL during follow-up)	BKPyV-DNAemia clearance or 50% reduction in BKPyV-DNAuria at 3 months (follow-up 12 months)	Primary endpoint 11 (55%) Vs. 8 (40%) *(P=0.53)* BKPyV-DNAemia clearance 8/15 (50%) vs. 5/15 (33%) *P=0.47* AE: Hypercholesterinemia at month 3 in everolimus group month 3 (212 % 56.8 mg/dL vs 170 % 29.8 mg/dL; *P=0.01*)	1/20 vs. 1/20 eGFR at 12 months 58.9± 21.5 vs. 65.1± 20.7)	0/20 vs. 0/20
Bussalino et al., 2021 [105]	Non-randomized, single-center, consecutive vs. historical controls	KT recipients on CNI/MMF/Pred (N=20) with consecutive diagnosis of biopsy-proven BKPyV-nephropathy (N=10) (CsA 4; Tac 6) compared with historical controls (N=10) (CsA 4; Tac 6)	Switch MMF to Everolimus + reduced CNI (N=10) *versus* reduced CNI + reduced MMF (N=10)	Graft function; BKPyV-DNAemia (follow-up 36 months)	eGFR 25 ml/min higher in cases (p=0.002); BKPyV-DNAemia loads decrease >2 log10 (p=0.001) in cases, 1.6 log10 lower than in controls (p=0.06)	1 /10 vs. 3 /10; also *de novo* DSA 1/10 vs. 1/10	0/10 vs. 5/10 P=0.03
Polanco et al., 2015 [106]	Case series	KT recipients (N=15) with biopsy-proven BKPyV-nephropathy	MMF stop and switch Tac to everolimus + pred (N=9) (Group 1) Group 2: continued (N=6)	BKPyV-DNAemia, eGFR, graft loss (follow-up min 36 months; mean 58m, range 39-73)	BKPyV-DNAemia -clearance in 6 (66%) -95% reduced in 3 (33%) -<1500 c/mL in 100%	At dx: AR in 4 (incl. 2 cases with biopsy-proven BKPyV-nephropathy (2 PyVAN-A; 2 PyVAN-B)	0/9 vs. 2/6

Belliere et al., 2016 [107]	Case series	ABOi KT recipients (N=7) on Tac/MPA with BKPyV-DNAemia including, 5 with plasma BKPyV load <10,000 c/mL and 2 with biopsy-proven BKPyV-nephropathy. at 1-18 m post-transplant	Switch Tac - MPA to reduced Tac - everolimus (N=7) versus reduced MPA (N=14): note: only 1/14 with BKPyV-DNAemia); (Note: Tac trough levels significantly lower in EVL group; median 4.9 ng/mL vs 6 ng/mL)	Observational, eGFR, BKPyV-DNAemia (follow-up mean 26m, range 13m – 29m)	No significant difference in eGFR (54.5, 0-128) vs. 40, 14-56) *P=0.07;* BKPyV-DNAemia decrease in 5/7 (71%) AE: dyslipidemia)	0 (note: C4d-staining in 5/7)	0/7 Vs 1/14 after ABMR;

Note: All adult patients unless indicated otherwise

Supplement Table S8: STUDIES INVESTIGATING USE OF INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Reference	Study design	Participants (N)	Dose of intervention	Graft function	Graft loss (%)	Viral clearance (%)	Rejection (%)
Sener et al., 2006 [108]	Case series	n = 8	2.0 g/kg over 2-5 days	Cr at: Diagnosis: 293±32 Last follow up:309±46	12	50	0
Anyaegbu et al., 2012 [109]	Case series	n = 4	2 mg/kg over 12-24 hours	eGFR at: Last follow up: 113	0	100	25
Vu et al., 2015 [110]	Case series	n = 30	1.0 g/kg	Median eGFR at: Diagnosis: 46 Last follow up: 63	3	90	-
Kable et al., 2017 [111]	Retrospective Cohort	n = 22 IVIG	100 mg/kg per dose (Total: 10 doses)	Cr at: Diagnosis: 164±52 At 3-mo follow up: 199±102	27	77	64
		n = 28 (no IVIG)	N/A	Cr at: Diagnosis: 184±54 At 3-mo follow up: 235±108	54	33	57

Supplement Table S9: STUDIES INVESTIGATING USE OF CIDOFOVIR

Reference	Study Design	Participants	Treatment	Outcome (follow-up) (Treatment vs. controls)
Kuypers et al., 2005 [112]	Retrospective cohort	KT recipients (N=21) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization + cidofovir (n=8) *versus* Immunosuppression minimization alone (n=13)	BKPyV-DNAemia clearance not different at 12 months (p=0.41) No graft loss in cidofovir group vs 69% graft loss in no cidofovir group (p=0.004) (*note: patients with worse renal function at time of diagnosis did not receive cidofovir*)
Scantlebury et al., 2002 [113]	Case series	KT recipients (N=16) with biopsy-proven BKPyV-nephropathy (15 adult/ 1 pediatric)	Immunosuppression minimization + cidofovir	BKPyV-DNAemia cleared in 14 (88%) patients after mean 3.5 months; graft loss in 4 (25%) patients.
Burgos et al., 2006 [114]	Case series	KT recipients (N=20) with biopsy-proven BKPyV-nephropathy n = 13 transplanted February 1998 to July 2003 (Group A) n = 7 transplanted July 2003 to February 2005 (Group B)	Immunosuppression minimization (n=20) + cidofovir (n = 13)	BKPyV-DNAemia cleared in 9 (69%) that received immunosuppression minimization plus cidofovir No difference in serum creatinine at 1 year of follow-up for those treated with cidofovir Graft loss occurred in 3 (23%) of Group A and 3 (43%) of Group B patients
Wadei et al., 2006 [115]	Case series	KT recipients (N=55) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization+ cidofovir (n=20) Immunosuppression minimization + IVIG (n=2) Immunosuppression minimization + cidofovir + IVIG (n=10) Immunosuppression minimization alone (n=23)	No association between cidofovir use and viral clearance or graft outcome, but serial measurement of BKPyV-DNAemia was not available on a sufficient number of patients. Relationship between prognostic factors and risk for any functional decline and failure of viral clearance on follow-up biopsy 3 to 6 months post diagnosis of BKPyV-nephropathy: Odds ratio of failure of viral clearance (n = 45): low dose cidofovir: 1.50 (0.44-5.23), p = 0.52 IVIG: 0.40 (0.08-1.72), p = 0.24 Conversion to cyclosporine: 1.99 (0.57-7.38), p = 0.29 Hazard ration for any functional decline (n = 55) Cidofovir: 1.24 (0.52-3.00) IVIG: 0.84 (0.24-2.26) Conversion to cyclosporine:1.03 (0.42-2.65) Post diagnosis: follow-up for the entire cohort was 19.7±11 months and 8 (15%) patients had graft loss
Kuten et al., 2014 [116]	Case series	KT recipients (N=75) with presumptive BKPyV-nephropathy (BKPyV-DNAemia >10,000 c/mL)	Immunosuppression minimization + cidofovir	BKPyV-DNAemia cleared in 53 (71%) patients -Failure to reduce BKPyV-DNAemia by 1 $\log_{10}$ c/mL after 1 month of cidofovir treatment increased risk for incomplete response to treatment. -Grade 3 or 4 bone marrow suppression was reported in the study. -Subgroup analysis of 18 patients treated with cidofovir compared to 15 patients treated with reduced immunosuppression alone failed to show a difference in clearance of BKPyV-DNAemia Graft loss attributable to BKPyV-nephropathy occurred in 2 (3%) patients and graft loss overall occurred in 12 (16%) patients including 2 (3%) deaths

Note: All adult patients unless indicated otherwise

Supplement Table S10: STUDIES INVESTIGATING USE OF LEFLUNOMIDE

Reference	Study Design	Participants (N)	Treatment	Outcome (follow-up) (Treatment vs. controls)
Josephson et al., 2006 [117]	Prospective, multicenter, case series	KT recipients (N=18) KPT recipients (N=7) and heart-KPT (N=1) (total N=26) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization + Leflunomide (n=17) or Leflunomide + Cidofovir (n=9)	BKPyV-DNAemia cleared in 22 (85%) patients; graft loss in 4 of 26 (15%). Patients with improving renal function had leflunomide dosed to obtain a targeted blood level of active metabolite, A771726, of 50 µg/ml to 100 µg/ml 1 (4%) patient had increasing alkaline phosphatase to 5 times above baseline, requiring dose reduction.
Faguer et al., 2007 [118]	Prospective,single center, case series	KT recipients (N=12) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization+ MMF switched to Leflunomide	BKPyV-DNAemia cleared in 5 (42%), serum creatinine concentration stabilized or improved in 8 (66%), dosed to targeted blood level of active metabolite A771726 of 40-80 µg/mL, dose limiting anemia adverse effects seen in 2 (17%). Graft loss occurred in 2 (17%) patients.
Leca et al., 2008 [119]	Retrospective, single center, cohort,	KT recipients (N=21) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization+ MMF switched to Leflunomide, patients stratified according to Leflunomide concentration (low level <40 µg/ml (n = 12) vs high-level >40 µg/ml) (n =9)	No difference in BKPyV-DNAemia clearance between both strata; 6 (50%) low-level group vs 5 (56%) high level group], hemolysis and thrombotic microangiopathy possibly associated with higher drug levels 3 (25%) graft losses in low-level (<40 µg/ml leflunomide concentration) and 1 (11%) in high-level group (>40 µg/ml leflunomide concentration) (no adverse events directly related to BK patients)
Teschner et al., 2009 [120]	Prospective, multicenter, case series, with pre-defined standard operating procedure for treatment	KT recipients (N=13) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization+ MMF switched to Leflunomide	BKPyV-DNAemia cleared in 12 (92%) patients; with stabilization of serum creatinine. Drug levels monitored in 8 (62%), dosed to targeted blood level of active metabolite A77126 of 40 µg /mL, but no correlation with treatment response; 1 (8%) experienced adverse effects (pain and paresthesia) 1 (8%) patient had graft loss.
Krisl et al., 2012 [121]	Retrospective, single center,cohort, with pre-defined standard operating procedure for treatment	KT recipients (N=76) with BKPyV-DNAemia or biopsy-proven BKPyV-nephropathy	Immunosuppression minimization (not uniform) Leflunomide use (n = 52), 32 (62%) also had BKPyV nephropathy No leflunomide use (n = 24),1(4%) also had BKPyV nephropathy	BKPyV-DNAemia cleared in 14 (29%) of those who had A771726 monitoring (n = 48 of 52 receiving leflunomide) BKPyV-DNAemia clearance associated with MMF discontinuation. Mean A771726 concentrations were 45±27 mg/ml and 47±19 mg/ml (P=0.75) in patients who did and did not achieve BKPyV-DNAemia clearance. There were similar rates of BKPyV-DNAemia clearance in patients with A771726 concentrations of > 40 mg/ml vs < 40 mg/ml 12 (23%) had at least one pre-specified adverse event, with thrombocytopenia being the most common, occurring in 15% patients experiencing adverse events. Graft loss occurred in 15% of patients in the leflunomide group and 7% of patients in the group who did not receive it. When evaluating patients with BKPyV-DNAemia but not biopsy-proven BKPyV-nephropathy, death or graft loss occurred in 15 of 20 (75%) of patients treated with leflunomide compared to 9 of 23 (39%) patients who were not treated with it, (p = 0.65)
Cuellar-Rodriguez et al., 2013 [122]	Retrospective, single center case series, with pre-	KT and KPT recipients (N=22) with BKPyV-DNAemia	Immunosuppression minimization + Leflunomide ± other antiviral	BKPyV-DNAemia cleared in 17 (77%) on leflunomide while 4 (18%) never cleared, and 1 (5%) early discontinued leflunomide

	defined standard operating procedure for treatment	(number of KT vs KPT was not defined)	therapies (n = 11 cidofovir, n = 7 IVIG)	and cleared on cidofovir, viral loads decline steadily (“smooth”) or fluctuating (“zigzag”) patterns Leflunomide adjusted per levels of teriflunomide metabolite, with a goal of 50, 000–80, 000 ng/mL Adverse reactions possibly associated with leflunomide occurred in 15 (68%) patients, with cytopenia being most common 10 (67%) Graft loss occurred in 10(45%) of patients, but of those graft losses, only 2 of 10 (20%) occurred during the era of BKPyV-DNAemia screening.
Nesselhauf et al., 2016 [123]	Retrospective, single center case series, with pre-defined standard operating procedure for treatment	KT recipients (N=26) and KPT recipients (N=2) with BKPyV-DNAemia or biopsy-proven BKPyV-nephropathy: BKPyV-DNAemia and concomitant biopsy biopsy-proven acute rejection 14 (50%), BKPyV-nephropathy 5 (18%), BKPyV-DNAemia and donor specific antibodies 2 (7%), and persistent BKPyV-DNAemia (25%).	Immunosuppression reduction of MMF 50% dose + Leflunomide	BKPyV-DNAemia cleared in 20 (71%) patients, only 15 (54%) patients achieved therapeutic drug levels; in those who achieved therapeutic levels (50-100 mcg/mL) 9 (60%) required high Leflunomide doses (≥60mg/day) 11 (39%) patients experienced possible adverse events related to leflunomide, with leukopenia being most commonly reported 10 (91%) Graft loss occurred in 6 (21%) patients and death occurred in 2 (7%) patients
Keller et al., 2019 [124]	Retrospective, observational, multicenter study	KT recipients (N=55) with biopsy-proven BKPyV-nephropathy	Immunosuppression minimization as per center protocol + Leflunomide	BKPyV-DNAemia cleared in 42 (76%), rejection in 18 (33%), graft loss in 11 (20%). Only 11 (20%) patients (20%) underwent leflunomide drug monitoring. No significant associations were observed between adverse events and trough levels Adverse events occurred in 10 (18%) patients with hematologic toxicity being most commonly reported in 6 cases.

- KT, kidney transplant; KPT, kidney pancreas transplant
- BKPyV, BK polyomavirus
- CsA, cyclosporine A
- JCPyV, JC polyomavirus
- MMF, mycophenolate mofetil
- MPA, mycophenolic acid
- PyVAN-A, -B, -C, polyomavirus-associated nephropathy stage-A, -B, -C,
- TAC, tacrolimus
- Note: All adult patients unless indicated otherwise

Supplement Table S11: STUDIES INVESTIGATING USE OF FLUOROQUINOLONES

Reference	Study Design	Participants	Treatment	Outcome (follow-up) (Treatment vs. controls)
Gabardi et al., 2010 [125]	Retrospective, single center, cohort study	KT (n =185) who had at least one BKV blood QNAT sample performed	Ciprofloxacin 250 mg (twice daily) or Levofloxacin (250 mg (daily) (n = 25) Control group (n = 160)	BKPyV-DNAemia at 12 months: 1 (4%) vs. 36 (22.5)% (p<0.03) Of patients with diagnosed BKPyV-DNAemia: Continued BKPyV-DNAemia after therapeutic interventions occurred in: 0 of 1 (0%) vs 20 of 40 (50%) patients (p = ns) Overall biopsy-proven BKPyV-nephropathy: 1 of 1 (100%) vs 14 of 40 (35%) (p = < 0.0001) Graft loss secondary to biopsy-proven BKPyV-nephropathy occurred in 0 of 1 (0%) compared to 4 of 40 (10%), (p= ns)
Wojciechowski et al., 2012 [126]	Retrospective, single center, historical control cohort study	130 vs. 106	Ciprofloxacin 250 mg (twice daily) prophylaxis immediately after transplant (n = 130) or none (historical control) (n = 106)	BKPyV-DNAemia (3 months) 6,5% vs. 16,1% (p<0.01) BKPyV-DNAemia at 12 months: 22% vs 25% (p=0.4058); biopsy-proven BKPyV-nephropathy at 12 months: 1 (0.,8%) vs.5 (4.7%), (p=0.057). Graft loss outcomes: not reported
Knoll et al., 2014 [127]	Prospective, multicenter, randomized double-blind placebo-controlled trial	76 vs. 78	Levofloxacin 500 mg (daily) prophylaxis within 5 days of transplant (n = 76) vs placebo (n =78)	BKPyV-DNAuria (within 12 m) 22 (29.0%) vs. 26 (33.3%) (RR 0.87; 95% CI 0.54-1.39) BKPyV-DNAemia (within 12 months) 6 (7.9%) vs. 9 (11.5%) (RR 0.68;95% CI 0.26-1.76) BKPyV-nephropathy: none Graft loss: 0 (0%) vs 1 (1.3%)
Patel et al., 2019 [128]	Prospective, single center, randomized, double-blind placebo-controlled trial	133 vs. 67	Ciprofloxacin 500 mg (daily) (n = 133) prophylaxis vs. placebo (n = 67)	BKPyV-DNAemia (6 months) 25 (18.8%) vs. 5 (7.5%) (p=0.03) BKPyV-DNAemia (12 months) 31 (23.3%) vs.8 (11.9%; p=0.06) biopsy-proven BKPyV-nephropathy (12 months) 7 (5.8) vs.1 (1.5%) (p=0.26) 13 patients with BKPyV-DNAemia excluded in whom biopsy was not performed. Graft loss at 12 months: 2 (1.5%) vs 2 (3.0%; p=0.48)

Supplement Table S12: STUDIES INVESTIGATING USE OF STATINS

Reference	Study Design	Participants	Treatment	Outcome (follow-up) (Treatment vs. controls)
Gabardi et al., 2015 [129]	Retrospective, two-center	32 vs. 36	Statin vs none before BKPyV-DNAemia diagnosis (>500 c/mL on 2 consecutive tests within 1 year of transplant) vs no statin exposure before or after BKPyV-DNAemia diagnosis	Biopsy-proven BKPyV-nephropathy incidence (12 months) 28.1% vs. 41.7% (p = 0.312). Mean follow-up time was 1428.0 ± 727.4 days in statin group and 1411.0 ± 680.7 days in no statin group (p = 0.921).

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