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Origine de la réactivation virale chez les patients transplantés rénaux avec une néphropathie à BK virus

J Gras, ML Nere, L Bonnet-Madin, M Salmona, MN Peraldi, J Verine, E Brochot, A Amara, JM Molina and C Delaugerre

Service de Maladies Infectieuses, Hôpital APHP-Saint Louis, Paris
INSERM U944 « Cellular biology of viral infections », Institut de recherche Saint Louis, Paris

Déclaration d'intérêts de 2014 à 2020

- **Aucun**

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Gras Julien

Titre : Origine de la réactivation virale chez les patients transplantés rénaux avec une néphropathie à BK virus

- L'orateur ne souhaite pas répondre ☐

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Investigateur principal d'une recherche ou d'une étude clinique	☐ OUI	☑ NON

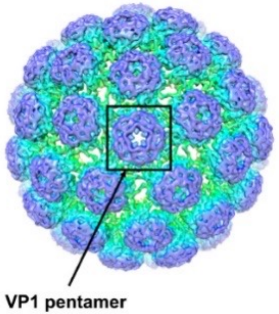
BK virus: an opportunistic pathogen

- A member of the ***Polyomaviridae*** **family**
  - **ds-DNA virus** (5.2kb genome)
  - **Icosahedral capsid** (40-45nm)

- **Natural acquisition in childhood**
  - **Persistent infection** (renourinary tract)
  - **Intermittent reactivation**

    (asymptomatic viruria → hemorragic cystitis / **interstitial nephropathy**)

- **BKV genetic diversity** > Sequence variation of **VP1-gene**
  - **4 main genotypes** (distinct serotypes)
  - **BKV-I** largely predominant **> BKV-IV** (>> BKV-II / BKV-III)
  - ***In vivo*** **coexistence of different genotypes**



BK virus associated nephropathy (BKVN)

- **A major complication** following **kidney transplantation (KT)**
  - 1 to 10% of KT recipients [KTR] : **poor renal prognosis** (30 to 65% of graft loss)
  - **No specific antiviral drug** available

- **Natural history of BKV infection in KTR**

- **Physiopathology of BKVN : several unanswered questions**
  - **Viral origin** of the BKV strain responsible for BKVN ?
  - Impact of ***in vivo BKV*** **genetic diversity** ?
  - Mechanisms of **BKV immune escape** ?

Objectives

Kidney transplant recipients with biopsy-proven **BKV associated nephropathy**

1. **Analyze the kinetics of BKV replication** following kidney transplantation in **plasma & kidney**

2. **Study BKV genetic diversity** in different biological compartments using **VP1 Sanger sequencing**

3. **Quantify the anti-VP1 humoral response** associated with BKV infection using **neutralizing antibody testing**

Retrospective study (01/2016 – 06/2020)

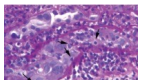
Kidney transplantation in APHP-Saint Louis

Biopsy-proven BKVN
- **N = 32 patients** (3.7%)
- Delay : **12.5 mo.** [8.6-17]

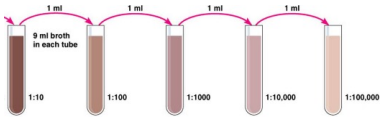
Sample collection

Plasma

Kidney biopsy



Serum (*10^{-2} to 10^{-7} dilution*)



DNA extraction
(NucliSENSTM easyMAG)

BK virus qPCR
(artus® BK Virus RG, Qiagen)

VP1-Sanger sequencing
(Genetic Analyzer 3500xL, Applied Biosystems)

BKV VP1 NAb Testing
(Genotype specific VLP with Luc reporter gene)

BKV DNA detection in plasma & kidney biopsy

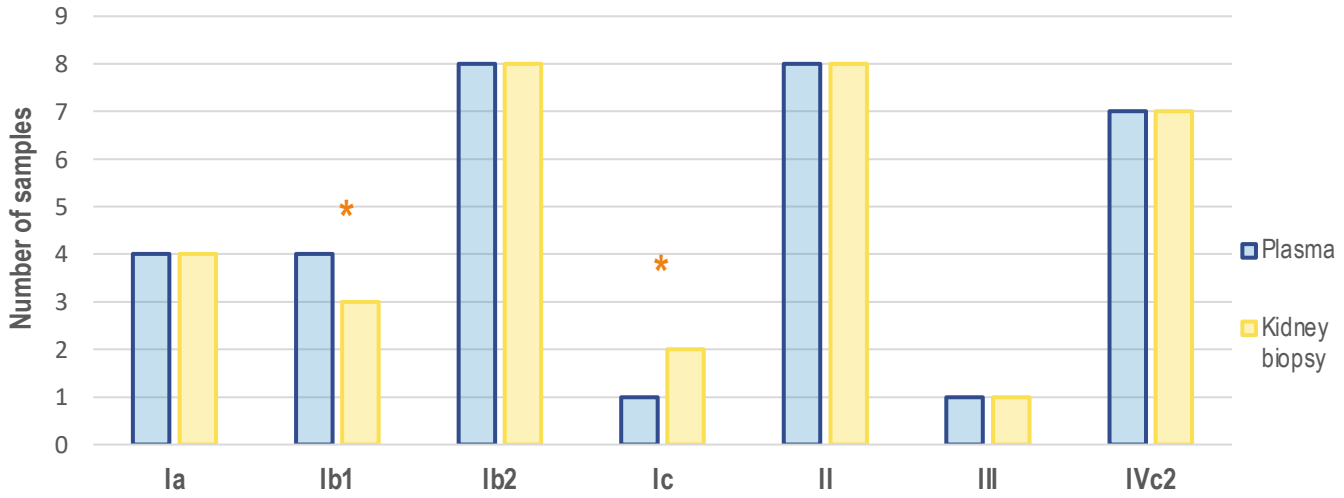
	Day 0 - KT (N=20)	M3 (N=23)	BKVN diagnosis (N=32)
BKV DNA in kidney biopsy			
BKV+ samples (N, %)	8 (40)	12 (52) *	32 (100)
Median VL [IQR] in BKV+ (logIU/10^6 cells)	3.7 [3.5-4.4]	5.7 [3.7-6.4]	8.2 [5.8-8.9]
BKV DNA in concomitant plasma			
BKV+ samples (%)	0 (0)	7 (30)	32 (100)
Median VL [IQR] in BKV+ (logIU/ml)	-	3.5 [3.7-6.4]	5.4 [4.3-6.0]

* 8/12 of KTR with BKV+ biopsy at month 3 had a negative concomitant plasma

➔ **BK virus DNA is detectable in kidney from KTR with BKVN** before the onset of viremia

In vivo BKV genetic diversity (1)

- BKV genotyping at **BKVN diagnosis**

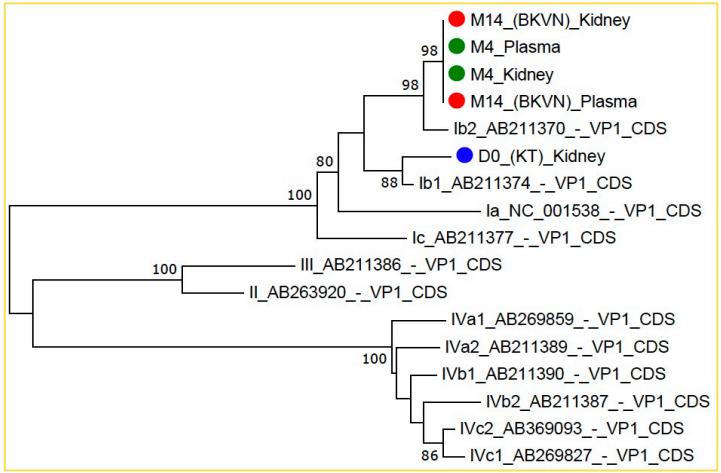


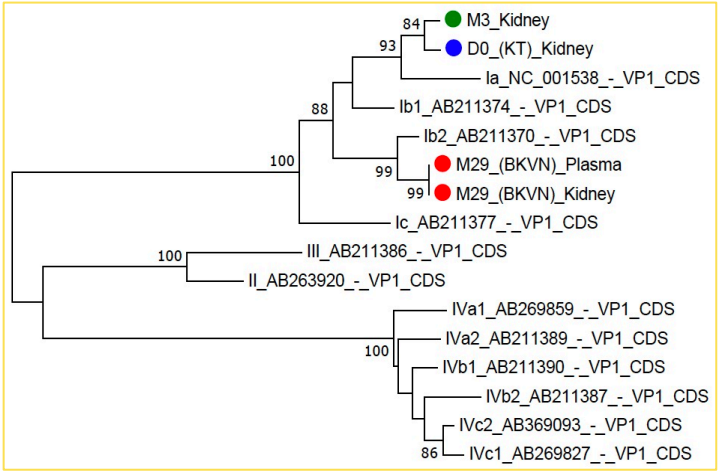
* In one patient, VP1 Sanger sequencing identified a different BKV-subtype at the time of BKVN diagnosis in kidney biopsy (BKV-Ic) and concomitant plasma (BKV-Ib1)

➔ **The BKV circulating strain** is the one **responsible of BKVN** at diagnosis

In vivo BKV genetic diversity (2)

- **Plasma: Identical BKV-subtype** at first viremia & BKVN (N=19/19, 100%)
- **Kidney biopsy: Different BKV subtype** isolated in KB at **day 0 ≠ BKVN** (N=5/6, 83%)

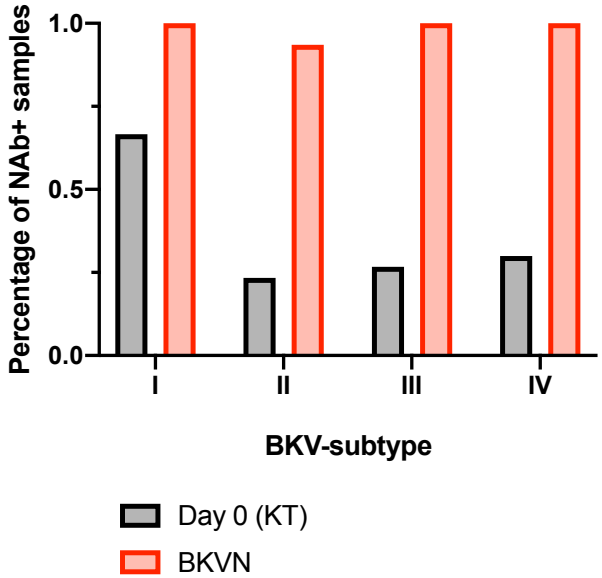


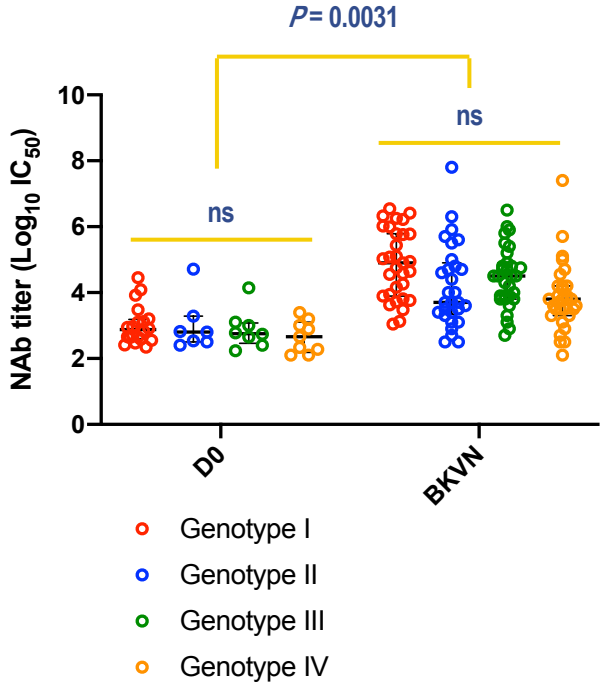


➔ BKVN results at least in part from the **reactivation of the recipient BKV subtype**

BKV-VP1 Nab response in KTR with BKVN (1)

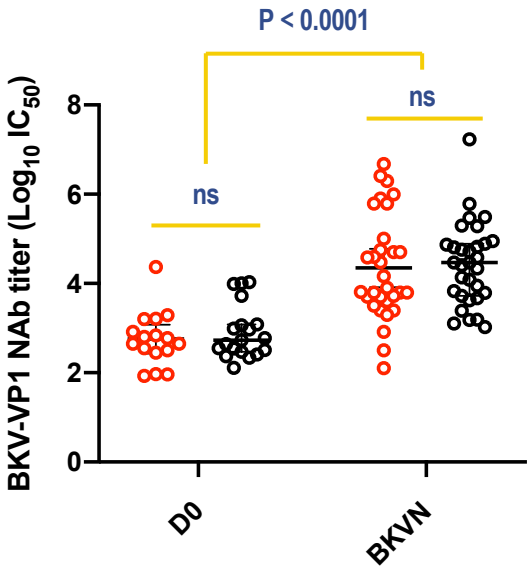
- **BKV VP1 NAb titers** are **significanty increased at BKVN diagnosis** compared to day 0

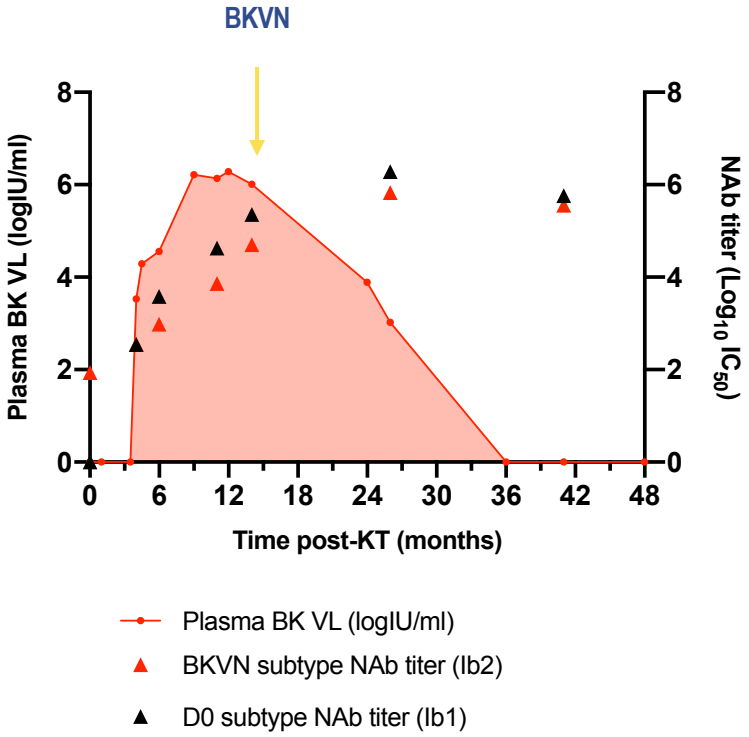




BKV-VP1 Nab response in KTR with BKVN (2)

- **BKV-VP1 NAb response** against BKVN strain does not differ from other subtypes





Conclusion and perspectives

1. **BK virus is detectable early in kidney of KTR with BKVN**
   - Early marker to better predict the risk of BKVN in KTR ?
   - Comparative analysis with KTR without BKV infection

2. **BKVN results at least in part from the reactivation of the recipient's strain**
   - Concomitant infection with the donor's virus ?
   - Whole genome sequencing ongoing

3. **BKV VP1 NAb response is non specific in KTR with BKVN diagnosis**
   - Humoral escape from specific VP1 variants ?
   - Role of impaired cellular immunity

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« Cellular biology of viral infections »

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