

# Pipiviridae



## Virus in Urine

In patients with acute viral infections the virus is often present in the blood, throat, faeces, or occasionally the cerebrospinal fluid. It may also be in the urine. Viruses can be found in the urine in three ways: firstly, by detection of inclusion bodies in the cells of the urinary sediment; secondly, by specific immuno-fluorescence of the cells; and, thirdly, by isolation of the virus in tissue culture or some other way.

Inclusion bodies<sup>1</sup> have been recognized as evidence of viral infection for more than 60 years. Before the development of modern virological techniques they provided an important means of confirming the diagnosis of infection. Among the best-known examples are the Guarneri bodies of smallpox and the Negri bodies of rabies. Inclusion bodies are acidophilic or basophilic-staining masses seen in the nucleus or cytoplasm of infected cells. Some are composed of virus particles which may be partially masked by ground substance. Others appear to be homogeneous and may be a sequela of cell damage rather than due to the presence of the virus itself. Cells containing inclusion bodies have been observed in the urine in various infections—for example, cytomegalovirus infection,<sup>2</sup> varicella-zoster,<sup>3</sup> rubella, measles, mumps, and herpangina,<sup>4</sup> and also in children after immunization with live poliovirus vaccine.<sup>5</sup> However, inclusion bodies are sometimes seen in cells in the urine of healthy children and adults and of patients with non-viral disease.<sup>6-7</sup> This has suggested they are due to degenerative changes in cells and are not associated with a specific disease.<sup>7</sup> Electron-micrographs of inclusion-bearing cells in the urine of patients with measles have failed to show virus particles within the inclusions, and at the same time attempts to find viral antigen in the inclusions were also unsuccessful.<sup>8</sup>

But though viral antigen is apparently not in the inclusion bodies themselves it has been detected by immuno-fluorescence in urinary cells in cases of viral infection. With this technique Coxsackie virus type B5 has been found in the urine,<sup>9</sup> and more recently B. L. Jones, R. D. Jones and G. L. Jones<sup>10</sup> have observed

and cannot be regarded as specific, since it would almost certainly have contained antibody to other viruses. However, all the cases of measles were confirmed by conventional virological techniques, and it is probable that the fluorescent cells in the urine did indeed contain measles virus antigen. There can be no doubt that measles virus was present in the urine of several of these patients, because the virus was isolated in tissue culture from specimens from 11 of the 42 patients.

Viruria in fact seems to be not uncommon in cases of viral infections when a search is made for it. In addition to measles,<sup>10</sup> it has been reported in infections with cytomegaloviruses,<sup>11</sup> Coxsackie viruses,<sup>12-13</sup> vaccinia,<sup>14</sup> rubella virus,<sup>15-16</sup> adenoviruses,<sup>14-17</sup> and mumps virus.<sup>18</sup> Viruria appears to be especially common in mumps, being found in all 21 patients in one study<sup>18</sup> and in 15 of 20 patients in another.<sup>19</sup> In the second study mumps was found to have impaired the renal function of all 20 patients, for tests of it gave abnormal results at some time in the course of the disease. The disturbance was mild and transient and did not appear to be due to fever. However, it suggests that viruria is due to direct infection of the kidney cells rather than to a filtering of the virus into the urine during viraemia.

Certainly the kidneys are attacked in congenital infection with cytomegaloviruses<sup>20</sup> and rubella virus,<sup>21</sup> and impaired renal function has been described in one case of infection with Coxsackie virus type B3 in which viruria was noted.<sup>13</sup> Examination of the kidneys of five children who died of measles showed some hyperplastic and degenerative changes in Bowman's capsule, and in the case of one child inclusions were seen in the cells of the capsule.<sup>6</sup> These changes were of a minor nature, but nevertheless suggest that the virus infects the kidney in measles also. Experiments have shown that in mice infected with herpes simplex virus viruria was not associated with viraemia but appeared to be due to seeding of the urine with virus from infected cells in the renal tract as a result of disseminated infection.<sup>22</sup> The pathogenesis of viruria in man may be similar, so that viruses may fairly commonly infect the renal tract in the course of acute systemic

# **The human urine virome in association with urinary tract infections**

TM. Santiago-Rodriguez, M Ly, N Bonilla and DT Pride

While once believed to represent a sterile environment, the human urinary tract harbors a unique cellular microbiota. We sought to determine whether the human urinary tract also is home to viral communities whose membership might reflect urinary tract health status. We recruited and sampled urine from 20 subjects, 10 subjects with urinary tract infections (UTIs) and 10 without UTIs, and found viral communities in the urine of each subject group. Most of the identifiable viruses were bacteriophage, but eukaryotic viruses also were identified in all subjects. We found reads from human papillomaviruses (HPVs) in 95% of the subjects studied, but none were found to be high-risk genotypes that are associated with cervical and rectal cancers. We verified the presence of some HPV genotypes by quantitative PCR. Some of the HPV genotypes identified were homologous to relatively novel and uncharacterized viruses that previously have been detected on skin in association with cancerous lesions, while others may be associated with anal and genital warts. On a community level, there was no association between the membership or diversity of viral communities based on urinary tract health status. While more data are still needed, detection of HPVs as members of the human urinary virome using viral metagenomics represents a non-invasive technique that could augment current screening techniques to detect low-risk HPVs in the genitourinary tracts of humans.

# The human urine virome in association with urinary tract infections

TM. Santiago-Rodriguez, M Ly, N Bonilla and DT Pride

Subjects	Sex	Age	Symptoms	Immuno compromised <sup>a</sup>	Organism	Catheter <sup>b</sup>
<b>NEGATIVE URINE CULTURES</b>						
URN1	Male	94	None	No	None	No
URN2	Male	57	Sepsis <sup>c</sup>	Yes	None	Yes
URN6	Male	51	Pain in prostate area	No	None	Yes
URN9	Male	47	Pain with urination	No	None	No
URN10	Female	27	Vaginal bleeding	No	None	No
URN11	Female	31	Pain with urination	No	None	No
URN12	Female	25	Abdominal pain	No	None	No
URN13	Female	51	Urine odor	Yes	None	No
URN15	Female	54	Sepsis <sup>c</sup>	No	None	Yes
URN16	Male	72	None	No	None	No
<b>POSITIVE URINE CULTURES</b>						
URP1	Male	62	Urinary retention	No	<i>E. coli</i>	No
URP2	Female	34	Sepsis <sup>c</sup>	Yes	<i>E. coli</i>	Yes
URP3	Female	50	Stroke	No	<i>E. coli</i>	No
URP4	Male	65	None	No	<i>E. coli</i>	Yes
URP6	Female	18	Dysuria	No	<i>E. coli</i>	No
URP7	Female	22	Autonomic instability	No	<i>E. faecium</i>	Yes
URP9	Male	52	Sepsis <sup>c</sup>	Yes	<i>E. coli</i>	No
URP10	Male	58	Sepsis <sup>c</sup>	Yes	<i>Acinetobacter</i>	Yes
URP12	Male	78	Sepsis <sup>c</sup>	Yes	<i>E. coli</i>	Yes
URP14	Female	69	Dysuria	Yes	<i>E. coli</i>	No

<sup>a</sup>Includes subjects with cancer and organ transplants, and those taking immunosuppressive medications such as steroids.

<sup>b</sup>Includes subjects with catheters in their bladders and a single subject with a nephrostomy.

<sup>c</sup>Potentially life threatening complication of infection resulting in severe inflammation and blood pressure drops.



# Epifluorescence Microscopy



Epifluorescence Microscopy

Urine:  **$1 \times 10^7$**  VLP/ml



## Epifluorescence Microscopy

Urine:  **$1 \times 10^7$**  VLP/ml

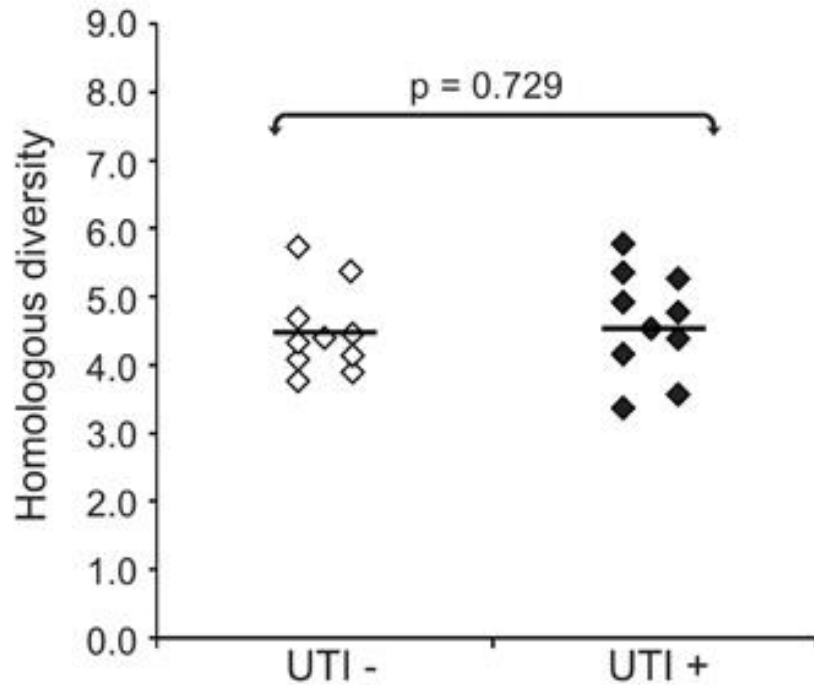
Saliva:  **$1 \times 10^8$**  VLP/ml

Feces:  **$5 \times 10^8$**  VLP/ml

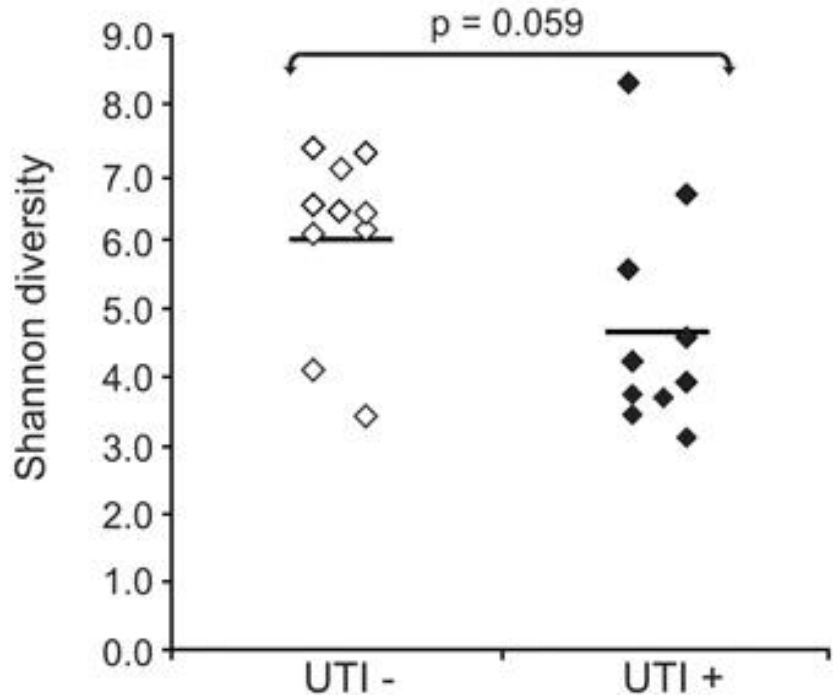
# The human urine virome in association with urinary tract infections

TM. Santiago-Rodriguez, M Ly, N Bonilla and DT Pride

**A** viromes



**B** 16S rRNA





hantavirus  
bof  
HIV  
JC  
coxsackievirus  
adenovirus  
HPV  
BK  
bacteriofagen  
rubella  
ebola  
CMV  
HSV-2  
mazelen  
HSV-1  
HBV

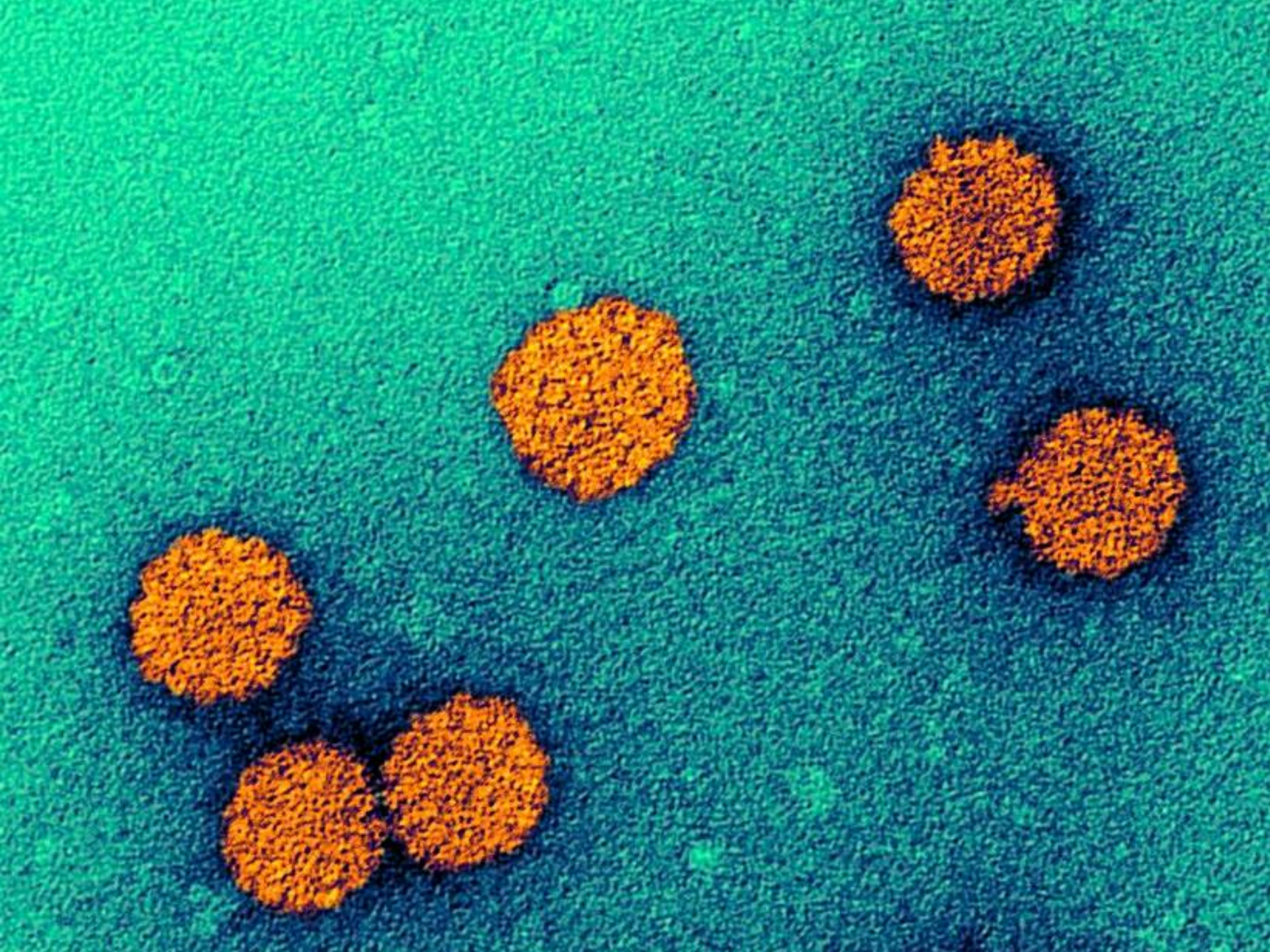




# **HPV**

## **Human papillomavirus**







HPV-702









bovine enzootic hematuria





**Pteridium aquilinum**  
**Bracken fern**  
**Adelaarsvaren**





## **Human papillomaviruses in urological malignancies: A critical assessment**

Yanis Tolstov, , Boris Hadaschik, Sascha Pahernik, Markus Hohenfellner, Stefan Duensing

A number of previous reports have implicated HPVs in urological malignancies including penile, prostate, and bladder cancer. Most reports, however, rely only on a limited number of detection methods and frequently use contamination-prone polymerase chain reaction based methods. To firmly establish a link between a viral infection and a human malignancy, it is paramount that an array of techniques is employed and that the virus is ultimately traced by either direct visualization or, in the case of viral genome that has integrated into the host genome, detection of viral genes and gene products as well as functional cellular perturbations. In any case, seroepidemiological studies are likewise crucial to support the evidence. Such evidence for a role of HPV in urological malignancies based on currently available techniques is only present for penile squamous cell carcinomas.

An increasing number of immunocompromised patients as well as novel developments in patient care may change the spectrum of HPV-associated neoplasms. This is exemplified by results demonstrating a role of HPVs in rare urothelial carcinomas with squamous differentiation in patients with neurogenic bladder. Hence, it is important to keep HPV infection in mind when confronted with unusual disease manifestations of the urogenital tract.

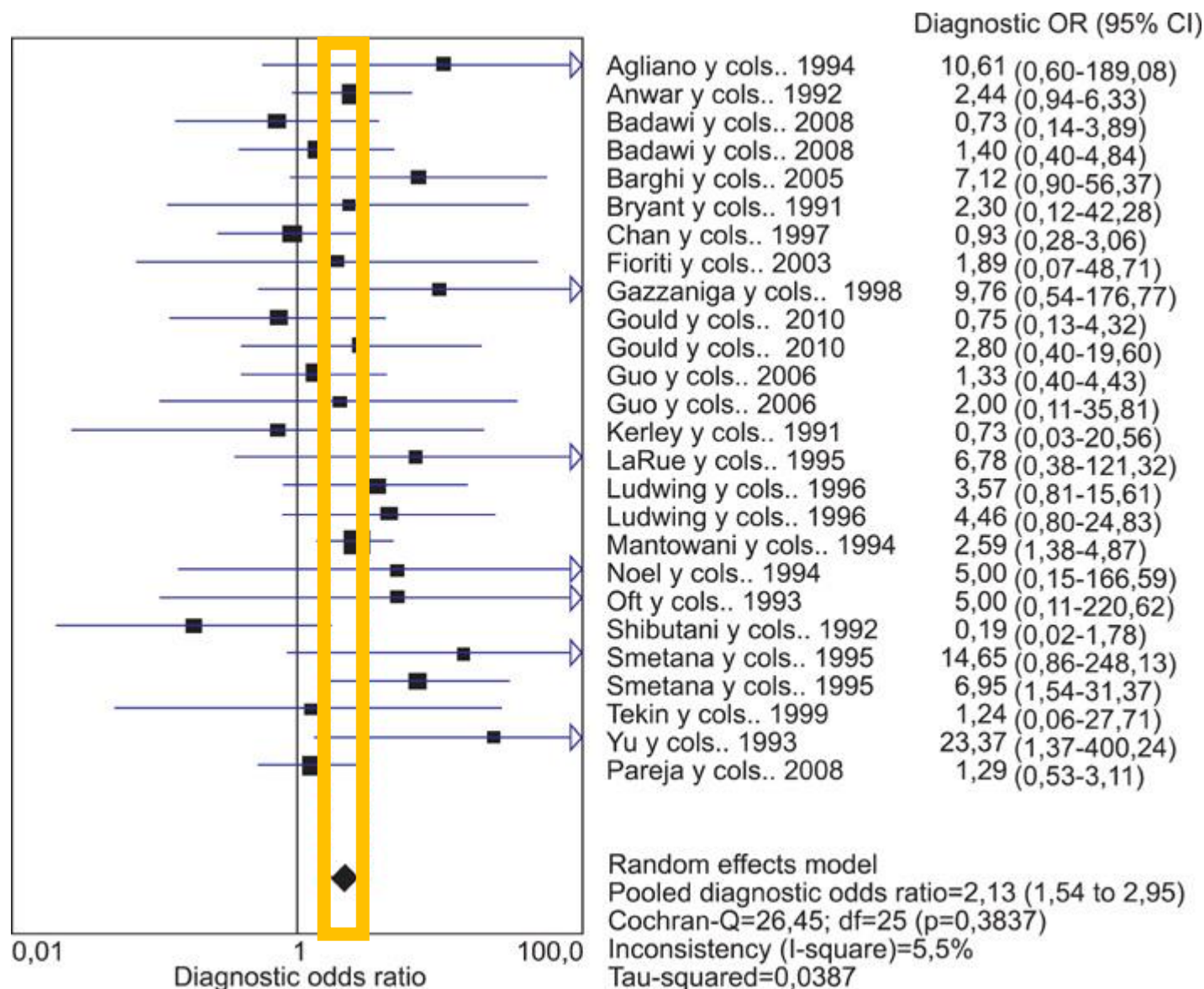


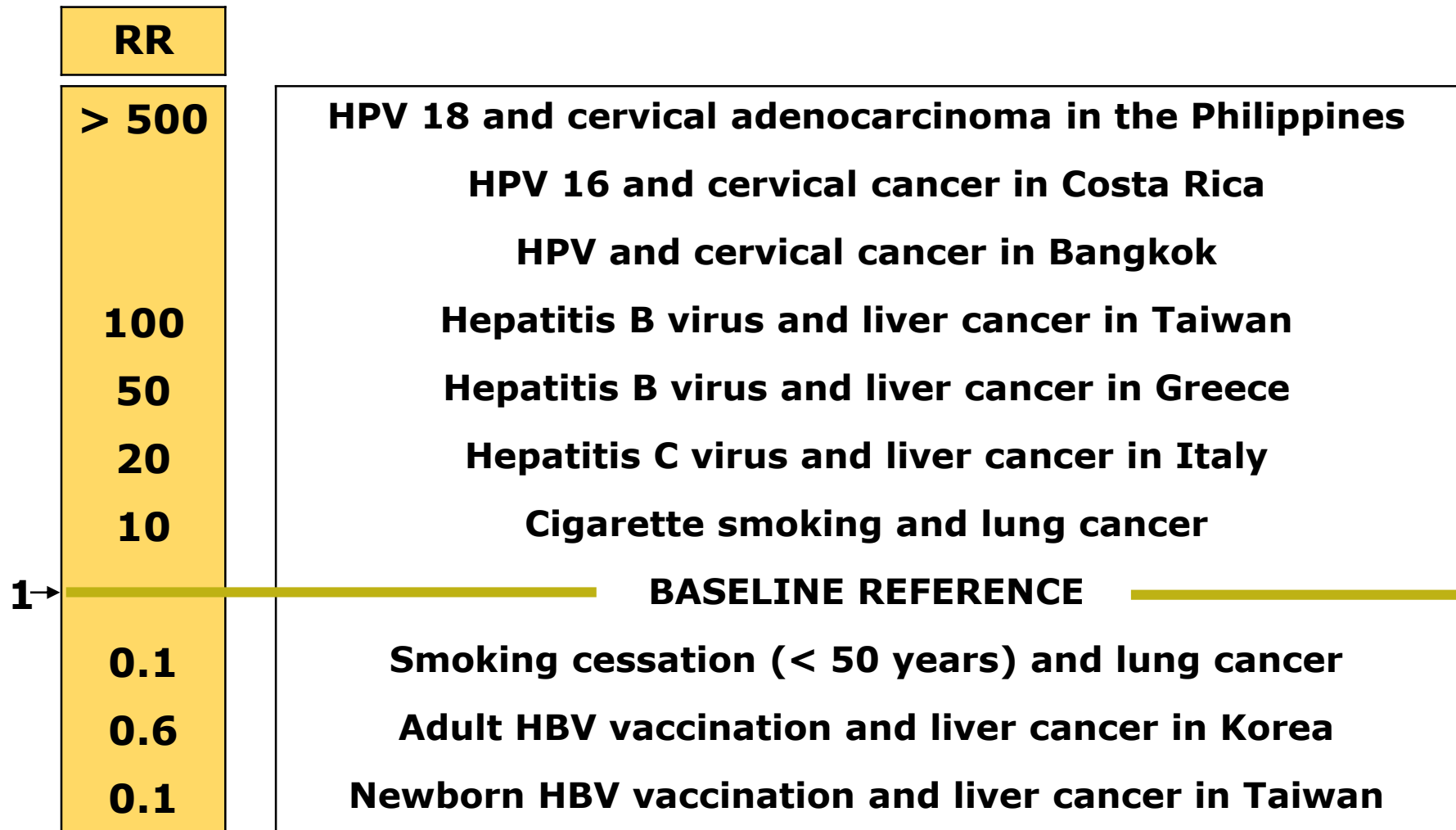
Taking into account the 21 studies that were included in the meta-analysis, we obtained a heterogeneity chi-squared value of  $Q_{exp}=26.45$  ( $p=0.383$ ). The pooled odds ratio (OR) was 2.13 (95% confidence interval [CI], 1.54 to 2.95), which points to a significant effect between HPV and bladder cancer. Twenty studies assessed the presence of DNA. The overall effect showed a significant relationship between virus presence and bladder cancer, with a pooled OR of 2.19 (95% CI, 1.40 to 3.43). Of the other six studies, four examined the virus's capsid antigen and two detected antibodies in serum by Western blot. The estimated pooled OR in this group was 2.11 (95% CI, 1.27 to 3.51), which confirmed the relationship between the presence of virus and cancer.

**Conclusions:** The pooled OR value showed a moderate relationship between viral infection and bladder tumors.

# Meta-Analysis of Studies Analyzing the Role of Human Papillomavirus in the Development of Bladder Carcinoma

Antonio Jimenez-Pacheco, Manuela Exposito-Ruiz, Miguel A Arrabal-Polo, and Alfonso J Lopez-Luque



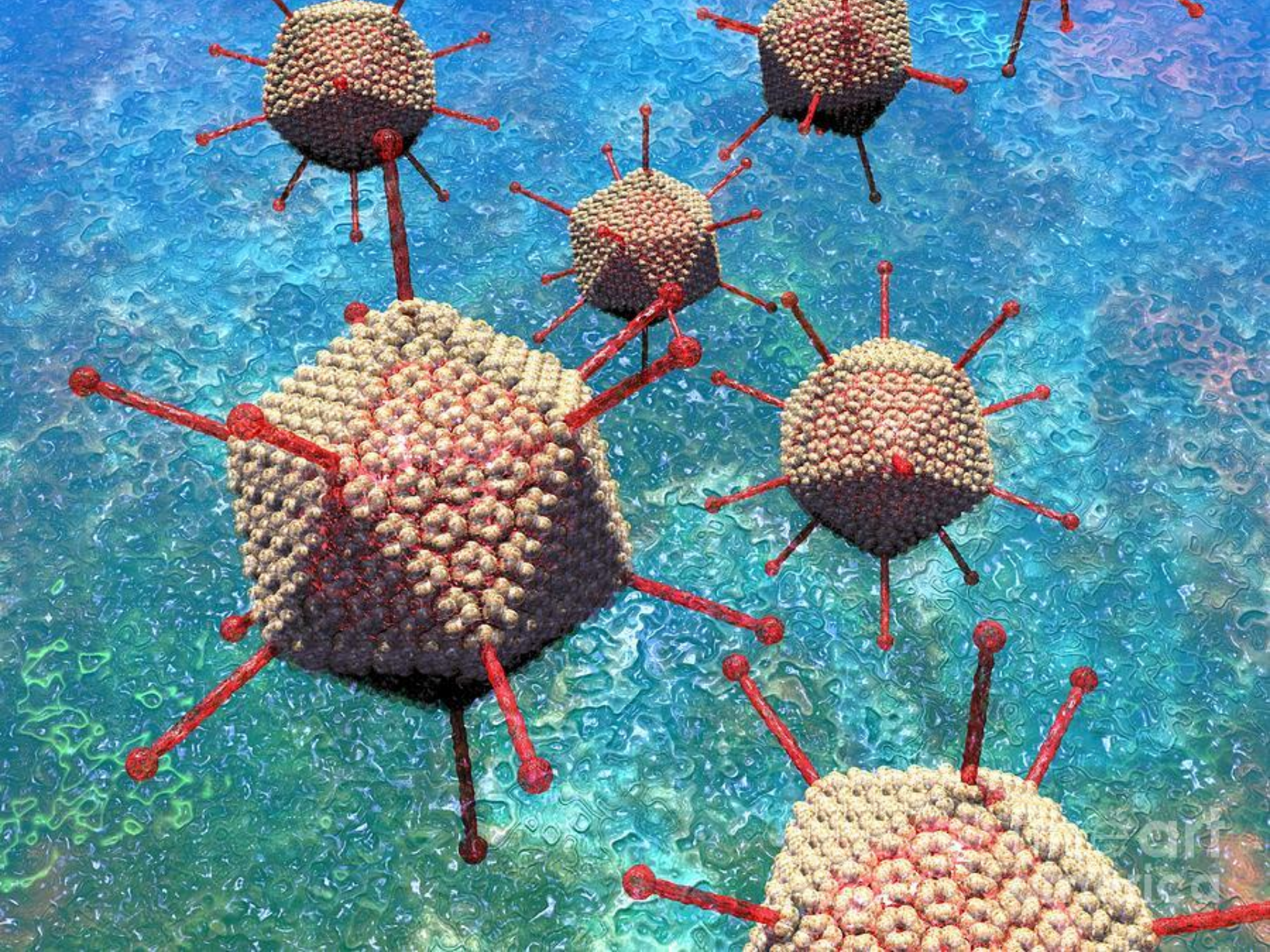




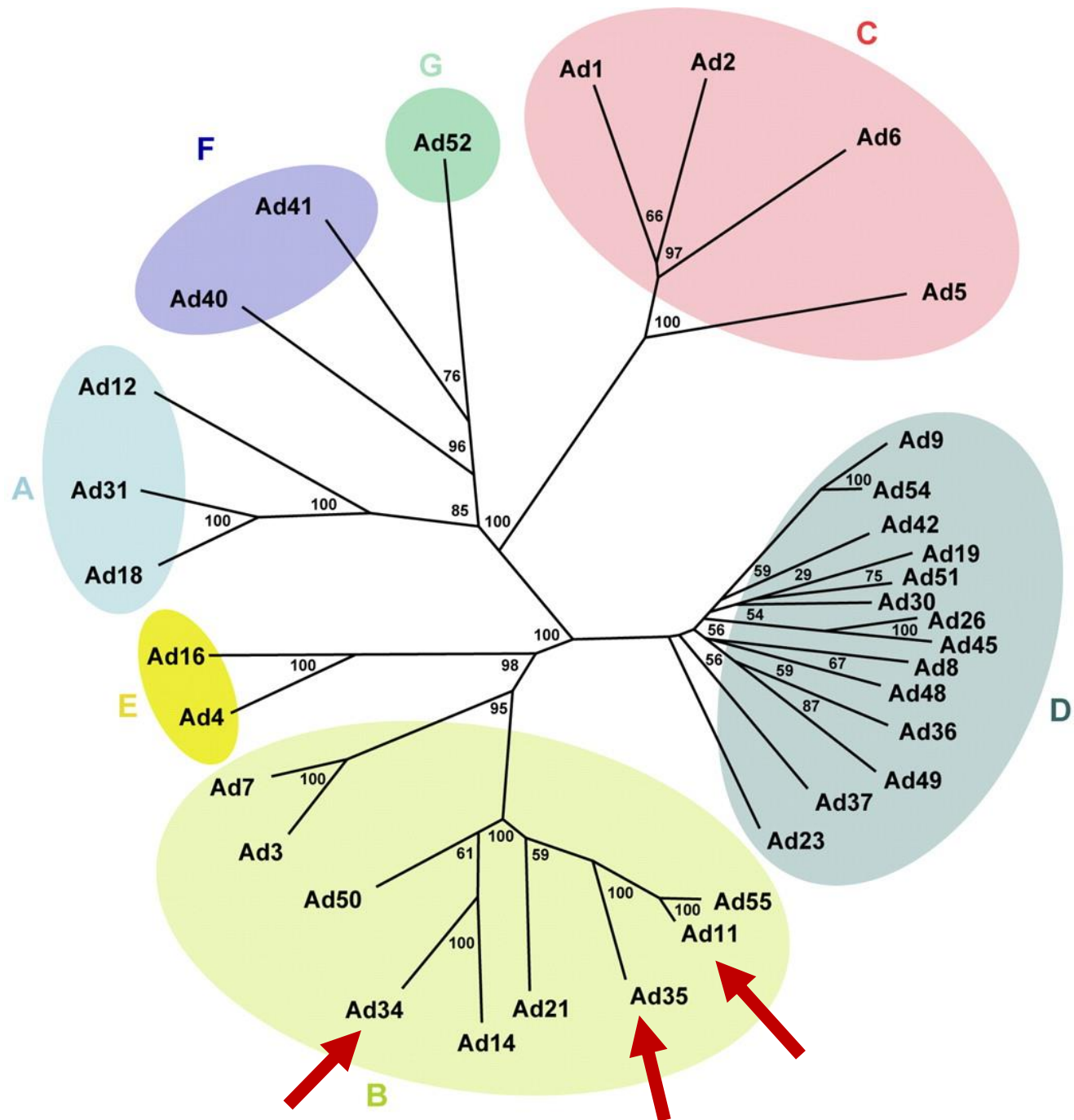


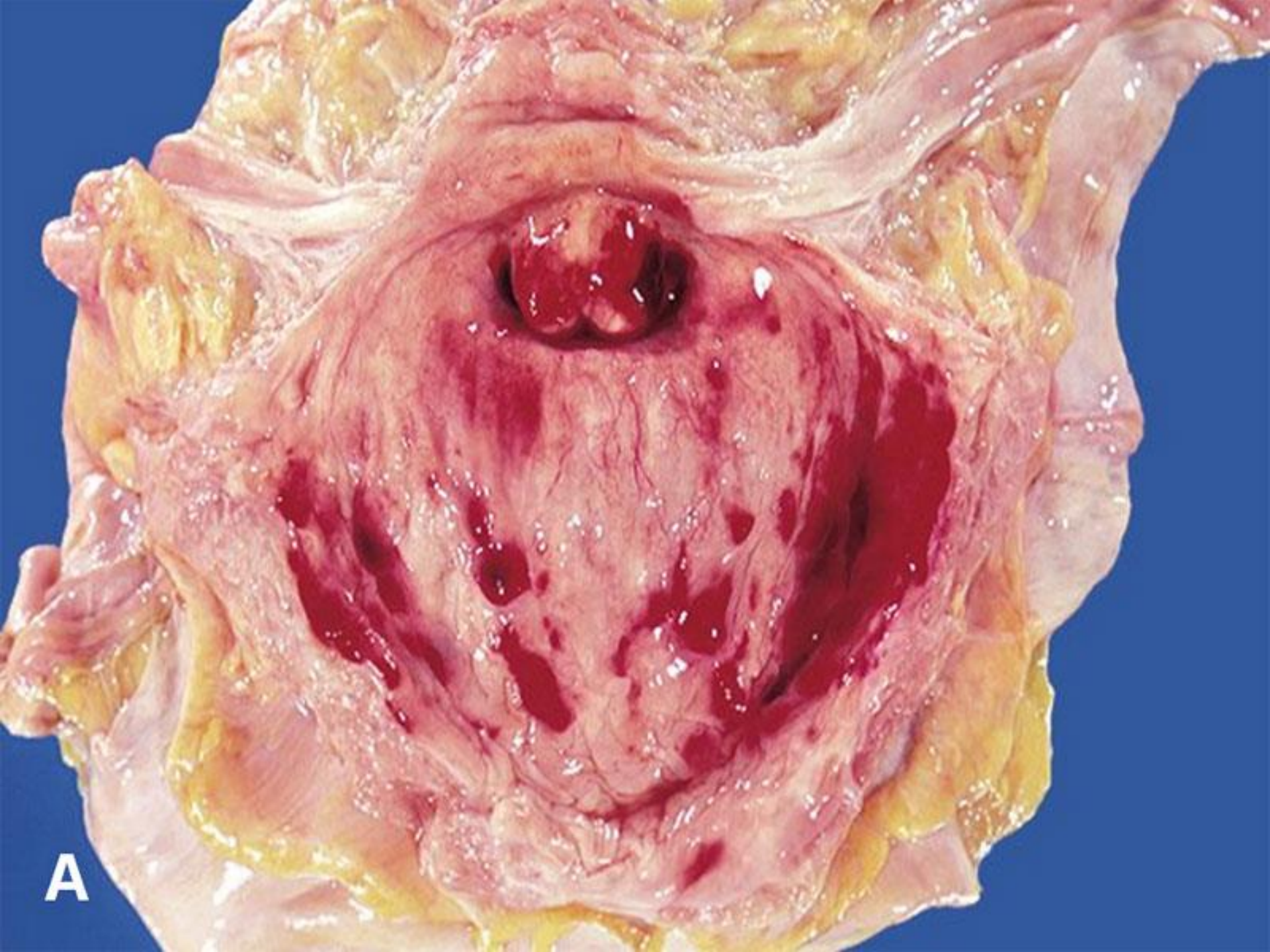
# Adenovirus











A





# Adenovirus Is a Key Pathogen in Hemorrhagic Cystitis Associated with Bone Marrow Transplantation

Hideki Akiyama, Tetsuya Kurosu, Chizuko Sakashita, Takashi Inoue, Shin-ichiro Mori, Kazuteru Ohashi, Shu Tanikawa, Hisashi Sakamaki, Yasusuke Onozawa, Qin Chen, Huaiying Zheng, and Tadaichi Kitamura

Late-onset hemorrhagic cystitis (HC) is a well-known complication of bone marrow transplantation (BMT) that is mainly attributed to infection with BK virus (BKV) and adenovirus (AdV). From 1986 through 1998, 282 patients underwent BMT, and 45 of them developed HC. Urine samples tested positive for AdV in 26 patients, of which 22 showed virus type 11. Among patients who underwent allogeneic BMT, logistic regression analysis revealed acute graft-versus-host disease (grade,  $\geq 2$ ) to be the most significant predictive factor for HC ( $P < .0001$ ). In addition, a total of 193 urine samples regularly obtained from 26 consecutive patients who underwent allogeneic BMT were examined for BKV, JC virus (JCV), and AdV by means of polymerase chain reaction. Of patients without HC, approximately 30% of the specimens tested positive for BKV (58 samples) and JCV (55 samples), whereas 5 (3%) tested positive for AdV. Of the 3 samples obtained from patients with HC, the numbers of positive results for BKV, JCV, and AdV were 3, 1, and 1, respectively; the numbers of positive results increased to 14 of 17, 9 of 17, and 10 of 17, respectively, when we added another 14 samples obtained from 14 patients with HC ( $P < .0001$ ,  $P = .026$ , and  $P < .0001$ , respectively). In conclusion, there was significant correlation between AdV and HC in the patients we studied.

In this study on 69 allogeneic hematopoietic SCT, we used a neutralizing antibody test to detect anti-AdV11 antibodies because this test is serotype-specific and can detect IgG antibodies for longer period after primary infection than can the complement fixation test. This prospective study revealed that the cumulative incidence of AdV-HC was 64% in the seropositive patients, but only 2% in the seronegative patients (log-rank test,  $P < 0.001$ ). Accordingly, recipient AdV11 serostatus is suggested to be the sole predictor of late-onset HC in Japanese allogeneic HSCT patients. Therefore, patients seropositive for AdV11 may be candidates for prophylactic anti-AdV treatment. It is likely that AdV-HC occurs in approximately 90% of allogeneic HSCT patients when the urine AdV load reached  $1.0 \times 10^5$  copies/mL or more. Taken together with the finding of the time-course study, preemptive treatment may be recommended to begin when the urine AdV load reaches  $1.0 \times 10^4$  copies/mL or higher.



## Recipient seropositivity for adenovirus type 11 (AdV11) is a highly predictive factor for the development of AdV11-induced hemorrhagic cystitis after allogeneic hematopoietic SCT

Y Nakazawa et al.

<i>Variable</i>	<i>Number of patients (n=69)</i>	<i>Number of patients with HC (AdV-HC)</i>	<i>P</i>
<i>Univariate analysis<sup>a</sup></i>			
<i>Age<sup>a</sup></i>			
≥16 years	27	9 (5)	0.061
<16 years	42	6 (2)	
<i>Sex</i>			
Male	45	12 (5)	0.174
Female	24	3 (2)	
<i>Disease status<sup>b</sup></i>			
Advanced (non-CR)	27	8 (4)	0.203
Stable (CR or non-malignant)	42	7 (3)	
<i>AdV11 serostatus of recipients<sup>c</sup></i>			
Positive	11	6 (6)	0.009
Negative	54	8 (1)	

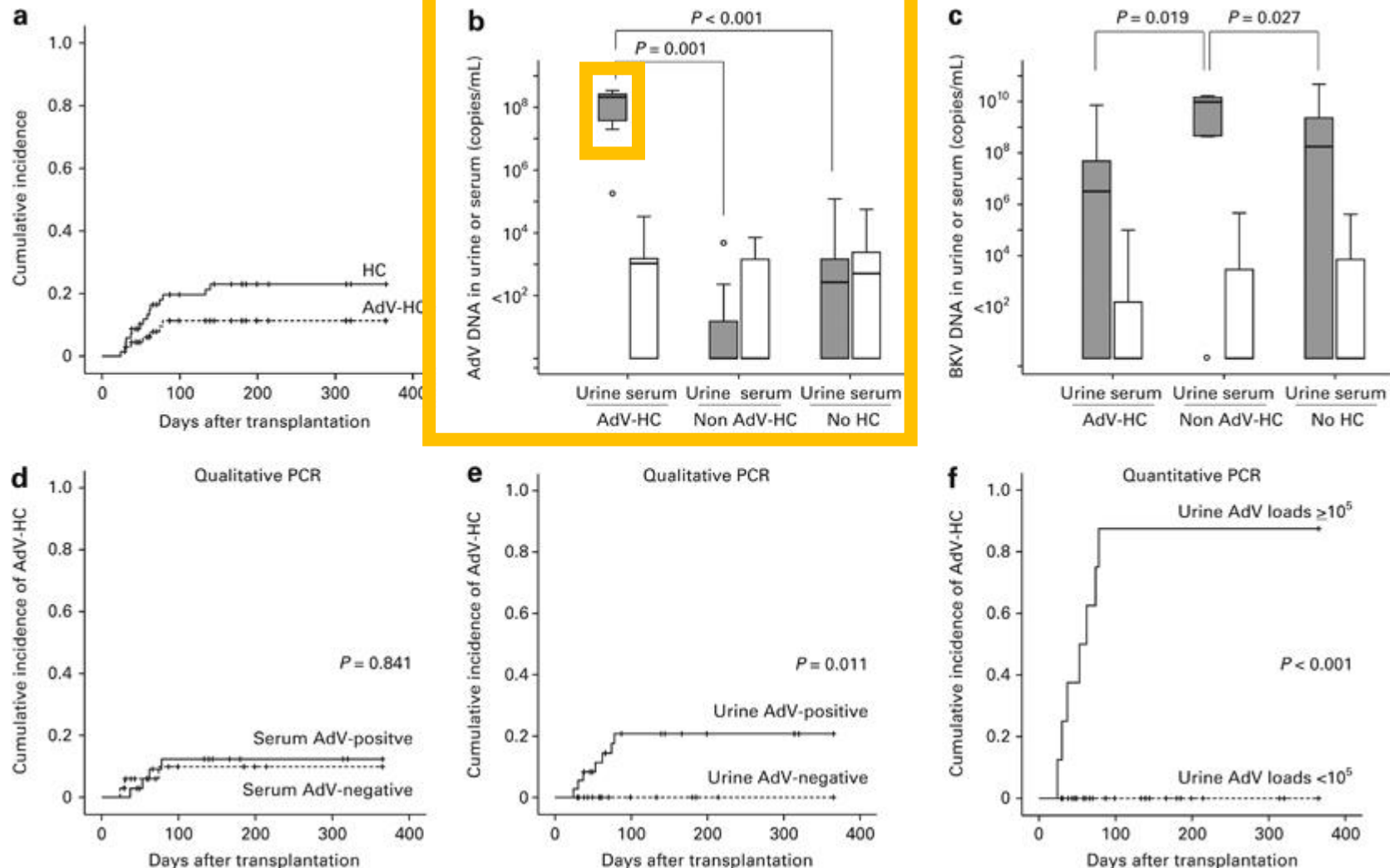
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# Bone Marrow Transplantation

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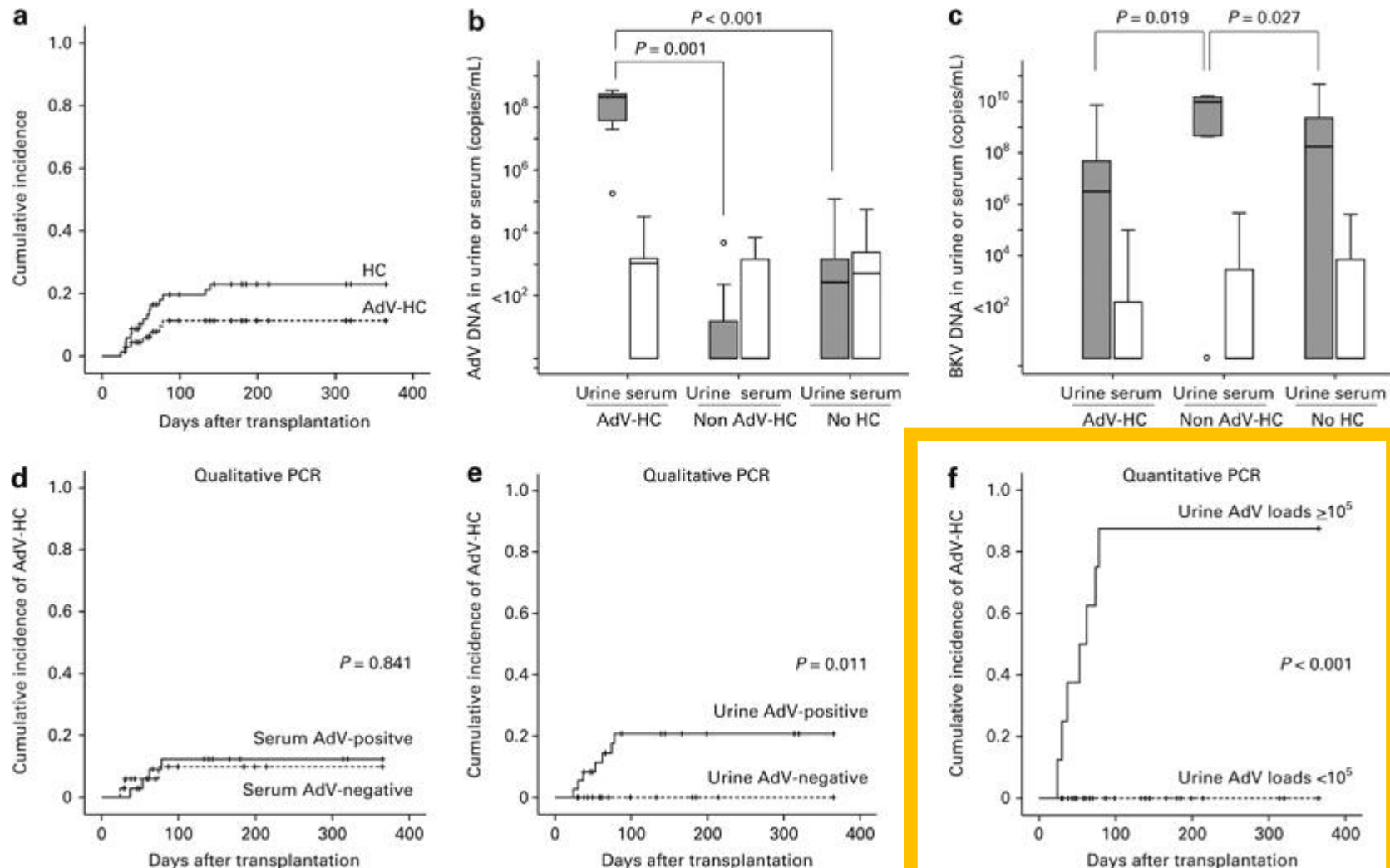
Y Nakazawa et al.



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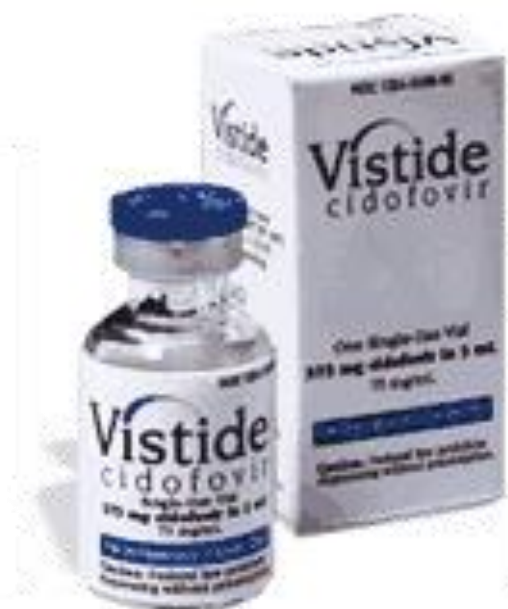
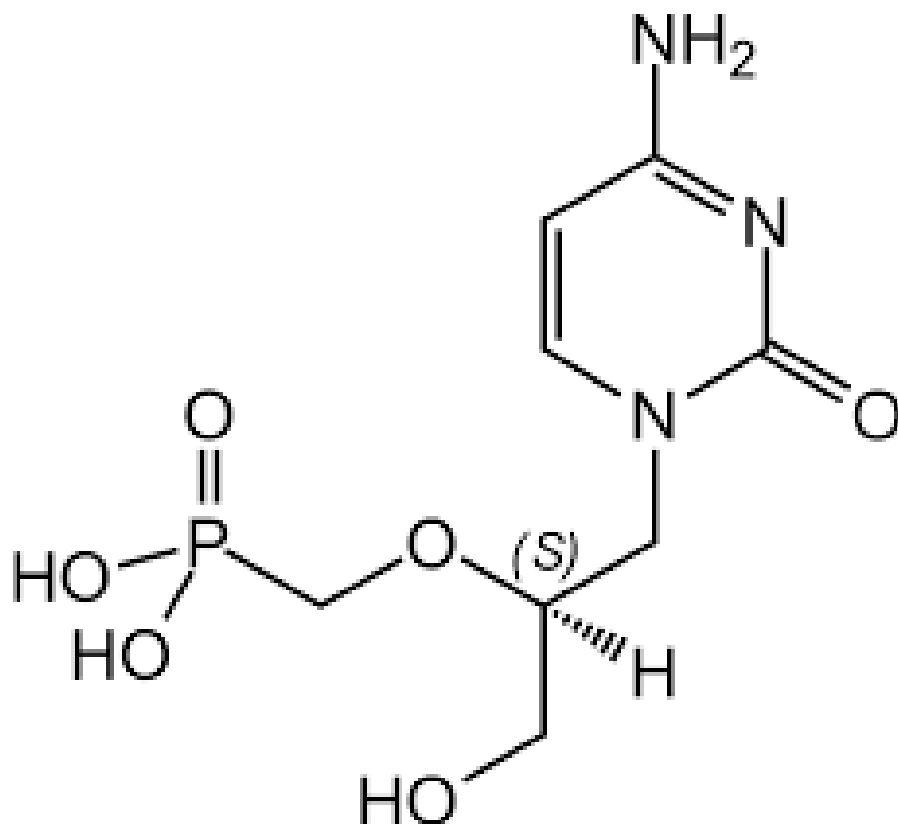






# Intravesical Instillation of Cidofovir in the Treatment of Hemorrhagic Cystitis Caused by Adenovirus Type 11 in a Bone Marrow Transplant Recipient

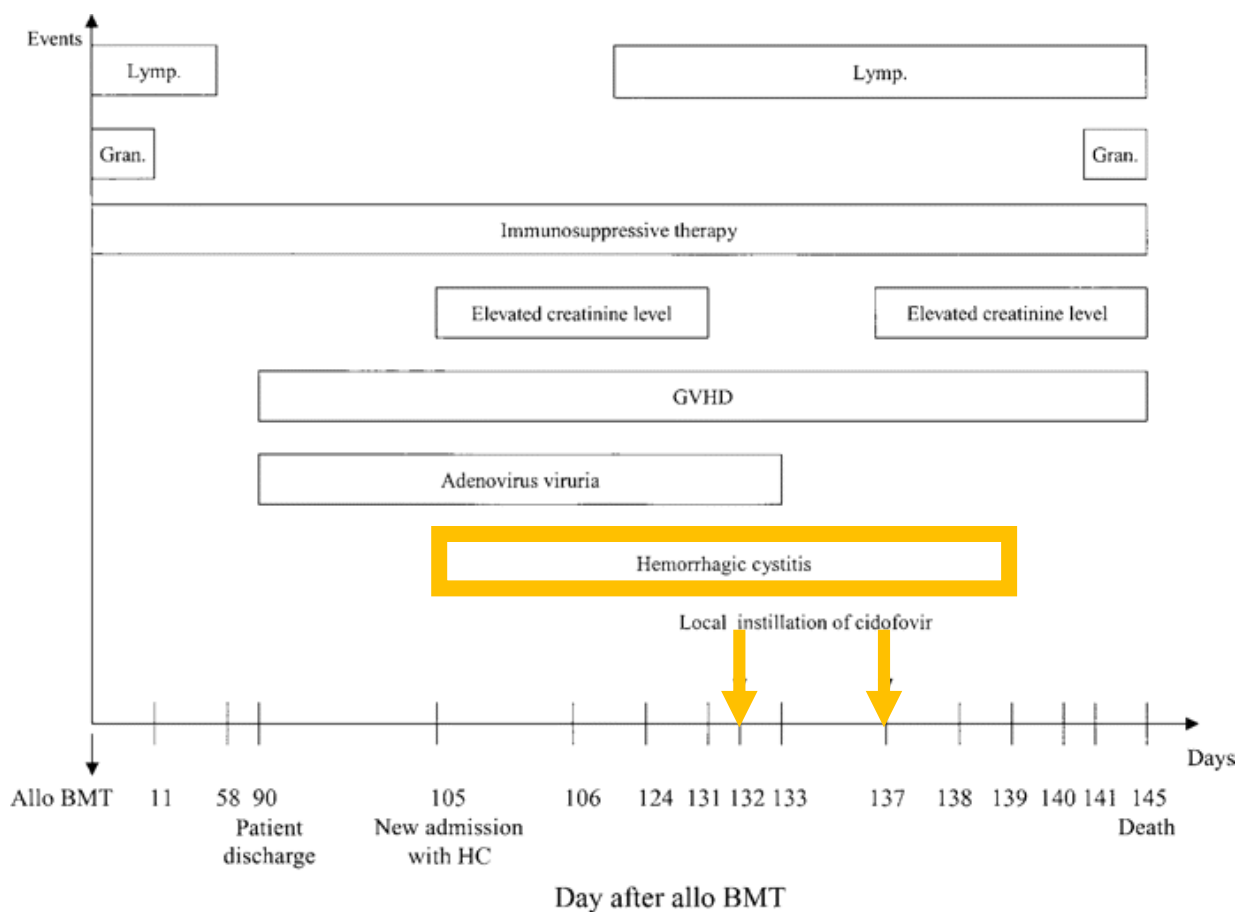
Panagiotis Fanourgiakis, Aspasia Georgala, Marc Vekemans, Agnes Triffet, Jean-Marc De Bruyn, Valerie Duchateau, Philippe Martiat, Erik De Clercq, Robert Snoeck, Elke Wollants, Annabel Rector, Marc Van Ranst, and Michael Aoun





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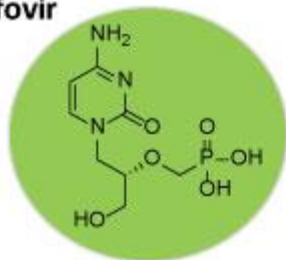




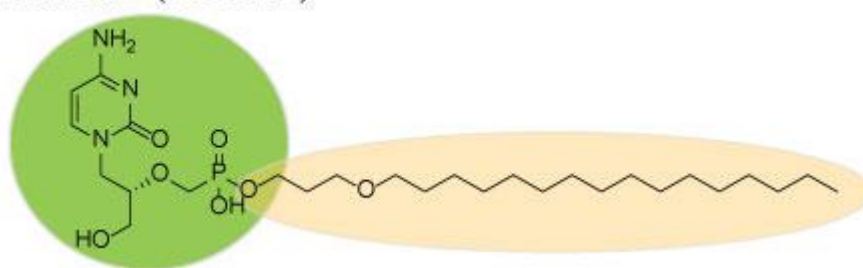
**Cidofovir** — Cidofovir appears more active against adenovirus in vitro than other antiviral drugs such as ganciclovir and also appears active in vivo as demonstrated by reductions in adenoviral load measured by real-time polymerase chain reaction (PCR). Published data on the efficacy of cidofovir for adenovirus infection in humans are limited to case reports and small nonrandomized studies. In hematopoietic stem cell and lung transplant recipients, cidofovir therapy has been associated with clinical improvement and a suggestion of increased survival. Prior to the use of cidofovir, the mortality in patients with invasive adenoviral disease following allogeneic hematopoietic cell transplantation (HCT) varied from 25 to 75 percent in different series, with the higher rates being described in patients with pneumonia and disseminated disease. In contrast, the mortality rate from adenoviral disease was only 19 percent in a review of 70 published cases of definite or probable adenovirus infection treated with two or more doses of cidofovir; most of these patients were severely immunocompromised (eg, graft-versus-host disease and/or T cell-depleted allografts). Nephrotoxicity is a major dose-limiting factor for cidofovir. As a result, doses of 1 mg/kg every other day or three times per week instead of the standard treatment dose of 5 mg/kg weekly have been used in an attempt to reduce this toxicity.

**Lipid-ester derivatives of cidofovir** — An experimental series of oral lipid-ester derivatives of cidofovir exhibit enhanced in vitro activity against adenoviruses and have lower potential for nephrotoxicity than cidofovir. In a report of therapy with an oral cidofovir prodrug, **brincidofovir** (CMX001), in 13 immunocompromised patients (including 11 allogeneic HCT recipients), 9 of 13 demonstrated a virologic response. Patients with a virologic response had longer survival than those without a virologic response (median 196 days versus 55 days). No serious adverse events were attributed to the drug. Brincidofovir is currently undergoing evaluation for the treatment of adenovirus infection in a phase III open-label study.

Cidofovir



Brincidofovir (CMX001)







# HSV

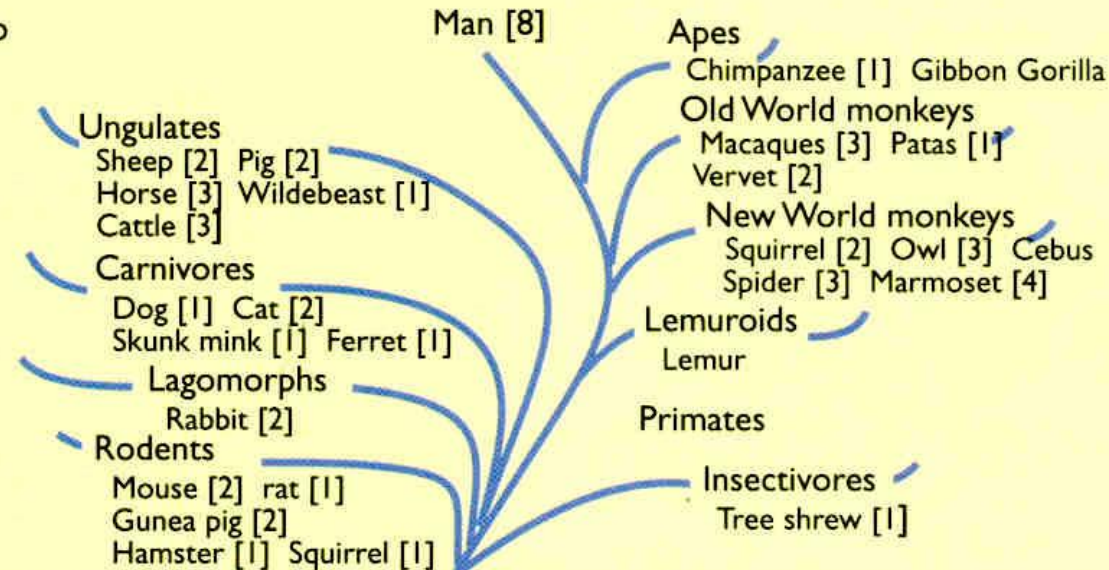
**Herpes simplex  
virus**







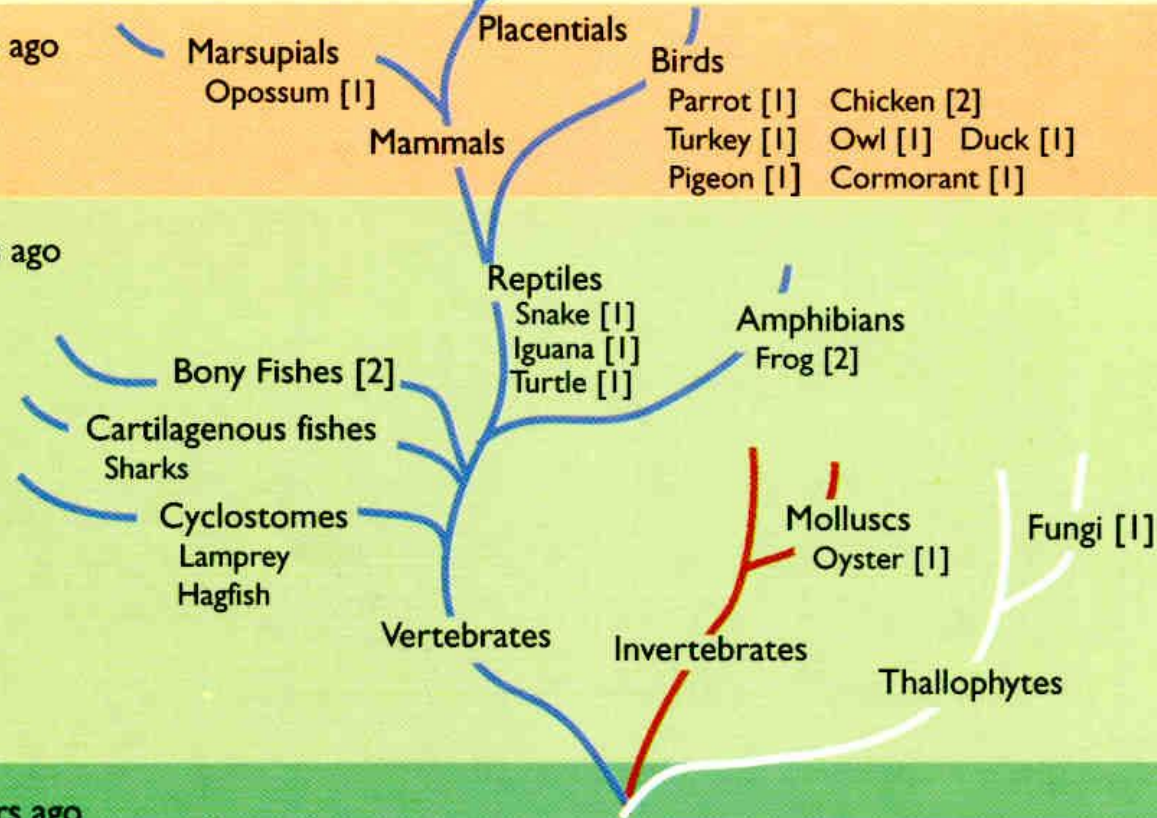
70 million years ago



200 million years ago

500 million years ago

>500 million years ago



A 45-year-old man presented with hemorrhagic cystitis and was found to have herpes simplex infection of the bladder by biopsy, immunohistochemistry and in situ hybridization. The patient had no clinical evidence of immunosuppression or disseminated infection. Although viral etiologies of hemorrhagic cystitis are recognized, to our knowledge only 4 cases of hemorrhagic cystitis due to herpes simplex virus have been reported.



# Herpes simplex virus type-2 in Egyptian patients with bladder cancer or cystitis

HALA BADAWI, HANEM AHMED, LAILA ABOUL FADL, AMIRA HELMI, NEVINE FAM, MANAL DIAB, AHMED ISMAIL, AFKAR BADAWI and MOHAMED SABER

The present study was designed to investigate the prevalence of herpes simplex virus type-2 (HSV-2) in Egyptian patients with bladder cancer or cystitis and to evaluate the performance of different diagnostic HSV-2 assays. The study included 50 patients: 27 with bladder cancer (group I), 23 with cystitis (group II) and 20 subjects as controls (group III). HSV-2 DNA was detected using polymerase chain reaction (PCR) on bladder tissue and buffy coat cells (BCC). Electron microscopic studies (EMS) on BCC and ELISAs for IgM, IgG and specific glycoprotein G-2 (gG-2) IgG were performed. HSV-2 DNA was detected by PCR on bladder tissue biopsies in 29.6% and 21.7% of group I and II respectively and it was also detected by PCR on BCC in 22.2% and 21.7% of group I and II respectively. EMS revealed HSV like particles in 16.6% of cases. IgG, specific gG-2 IgG and IgM were detected in 30%, 16% and 6% of cases respectively. The different assays were evaluated in relation to PCR on bladder tissue biopsies. The gG-2-based ELISA and EMS on BCC were found to be highly specific (97.3% and 100% respectively), with similar low sensitivity of approximately 54%. PCR on BCC was the most sensitive assay. The association of HSV-2 with bladder cancer is suggested especially in schistosomal patients.



# Herpes simplex virus type 2 modulates the susceptibility of human bladder cells to uropathogenic bacteria

Superti F, Longhi C, Di Biase AM, Tinari A, Marchetti M, Pisani S, Gallinelli C, Chiarini F, Seganti L

The present study analyses the susceptibility of human bladder-derived cells (HT-1376) to the infection by herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis*, as well as to the adhesiveness of uropathogenic bacteria. HT-1376 cells were efficiently infected by HSV-2 strain 333, as demonstrated by immunofluorescence staining of viral antigens, titration of cytopathic effect, and visualisation by transmission EM. This cell model was also prone to *C. trachomatis* (serovar E, Bour strain) replication and to the adherence of clinical uropathogenic isolates of *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Enterococcus faecalis*. The pre-infection of HT-1376 cells with HSV-2 caused a tenfold increased adherence of an *E. coli* strain (U1), isolated from a patient affected by severe haemorrhagic cystitis, whereas in HSV-2 pre-infected cells the number of *C. trachomatis* inclusion bodies was significantly reduced. Our findings indicate that these cells are a suitable in vitro model for studying infection and super-infection of the lower urinary tract by viruses and bacteria.

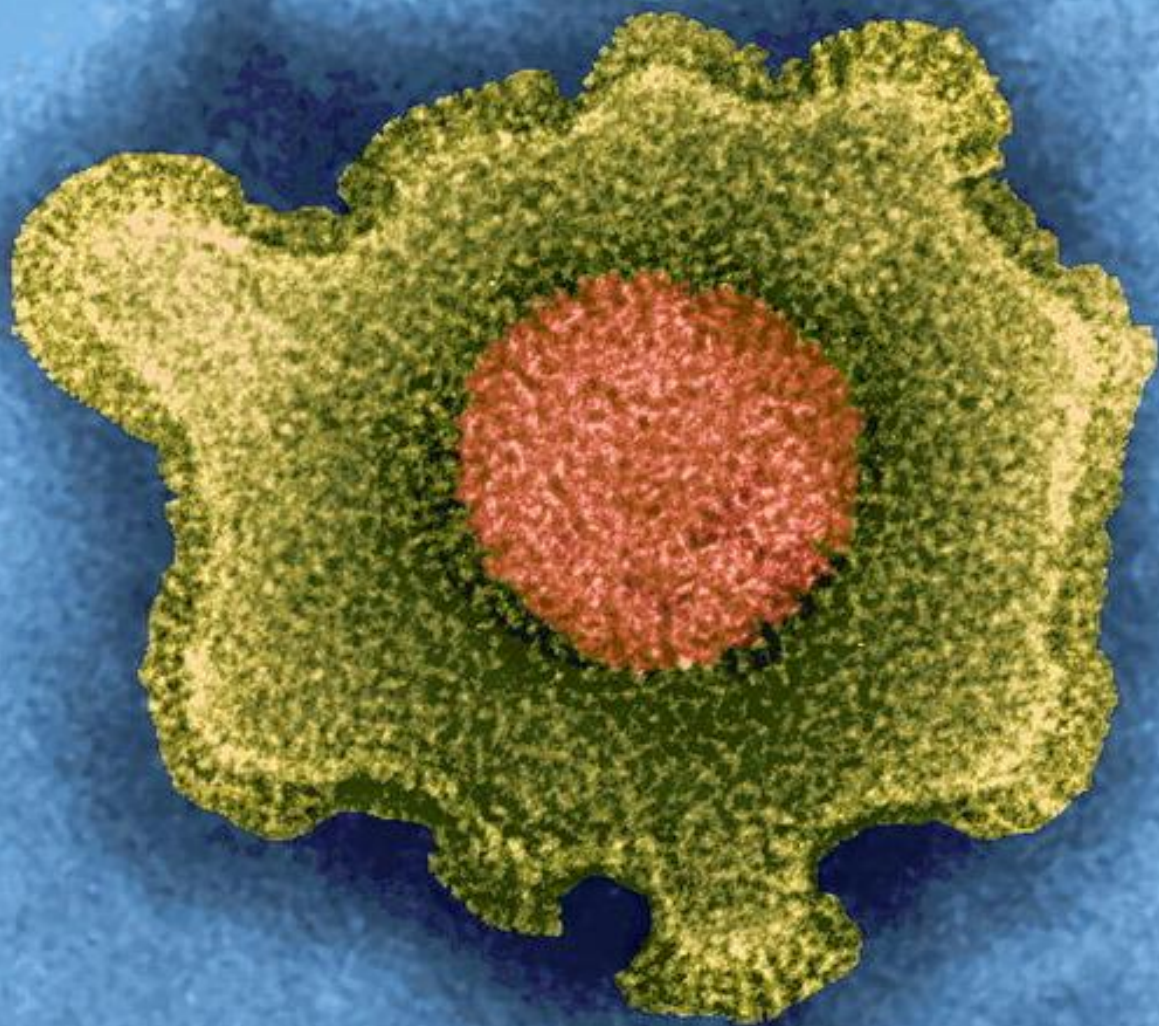




**CMV**

**Cytomegalovirus**









# Cytomegalovirus Viruria and DNAemia in Healthy Seropositive Women

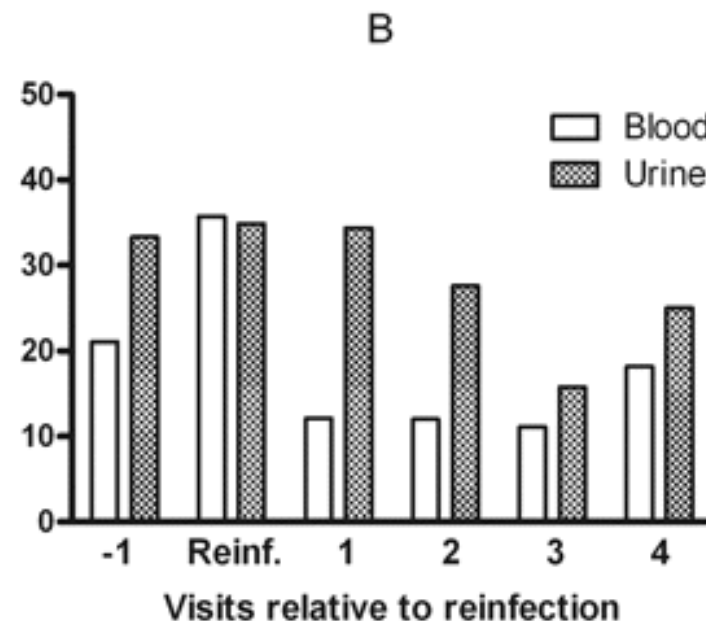
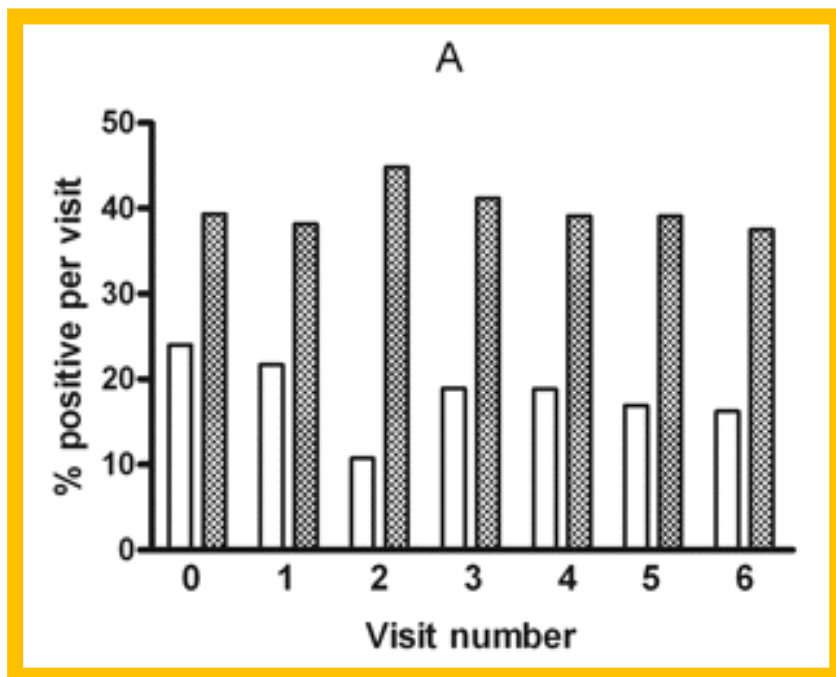
Nitin Arora, Zdenek Novak, Karen B. Fowler, Suresh B. Boppana and Shannon A. Ross

Viruria and DNAemia patterns were investigated in 205 seroimmune women enrolled in a prospective cytomegalovirus (CMV) reinfection study. CMV DNA was detected at least once in urine and blood specimens from 83% and 52% of patients, respectively. At baseline, 39% of patients had viruria, and 24% had DNAemia.

Intermittent viruria and viremia was observed throughout the study. There were no differences in baseline CMV positivity by polymerase chain reaction or in longitudinal DNAemia and viruria between the women with and without serological evidence of reinfection. In young seropositive women, CMV DNAemia and viruria are common, which suggests that naturally acquired immunity to CMV does not alter shedding patterns.

# Cytomegalovirus Viruria and DNAemia in Healthy Seropositive Women

Nitin Arora, Zdenek Novak, Karen B. Fowler, Suresh B. Boppana and Shannon A. Ross



A, Proportion of healthy, seropositive women ( $n = 205$ ) with cytomegalovirus (CMV)-positive blood and urine samples by polymerase chain reaction (PCR) over the study period ("0" corresponds to baseline visit). B, Proportion of participants reinfected with a new virus strain ( $n = 59$ ) with CMV-positive blood and urine samples by PCR relative to the visit of reinfection. "-1" corresponds to visit before serological determination of reinfection; "Reinf" corresponds to visit with serological evidence of reinfection.





## Impact of Cytomegalovirus on Long-Term Mortality and Cancer Risk After Organ Transplantation

Desai R, Collett D, Watson CJ, Johnson PJ, Moss P, Neuberger J.

**BACKGROUND:** There is conflicting evidence of the effect of cytomegalovirus (CMV) infection on survival and the risk of cancer after transplantation.

**METHODS:** All recipients of kidney, liver, heart, and lung transplants in the United Kingdom between 1987 and 2007 with known CMV immunoglobulin G status were identified from the U.K. Transplant Registry. Based on the donor-recipient CMV status, recipients were grouped into: donor (D) negative recipient (R) negative (D- R-), D-R+, D + R+ and D + R-. Cancer data were obtained from the Office for National Statistics. The impact of CMV infection on survival and cancer incidence was assessed.

**RESULTS:** The 10-year posttransplant survival in D-R- recipients (73.6% [95%CI, 72.3, 74.9]) was significantly higher ( $P < 0.0001$ ) than in other recipients (66.1% [65.3, 66.9]). Compared with the D- R- group, the risk-adjusted hazard of death within 10 years of transplantation for D+ R- group was 14% higher for kidney recipients ( $P = 0.0495$ ), 13% higher for liver recipients ( $P = 0.16$ ), 34% higher for heart recipients ( $P = 0.01$ ), and 35% higher for lung recipients ( $P = 0.006$ ). The proportion of recipients with a cardiovascular cause of death was higher ( $P = 0.03$ ) among the recipients exposed to CMV (18%) as compared to the D- R- recipients (16%). The CMV status was not associated with an increased risk of cancer.

**CONCLUSIONS:** The results from this large study demonstrate that CMV is associated with a significantly increased long-term mortality in kidney and cardiothoracic transplant recipients and an increased risk of cardiovascular death but not of posttransplant cancer.

## **Clinical outcome with low-dose valacyclovir in high-risk renal transplant recipients: a 10-year experience**

Fredrik Sund, Gunnar Tufveson, Bernd Döhler, Gerhard Opelz and Britt-Marie Eriksson

**Background** Cytomegalovirus (CMV) remains an important pathogen in transplant patients, and valacyclovir (VACV) prophylaxis 8 g/day has been used in high-risk CMV-seromismatched [D+/R–] renal transplant patients to decrease CMV disease.

Neurotoxic adverse effects have limited its use, and the aim of the present study was to retrospectively evaluate low-dose VACV prophylaxis, 3 g/day for 90 days after transplantation, in 102 D+/R– renal transplant patients.

**Methods** We compared patient and graft survival rates up to 5 years after transplantation with the data from the Collaborative Transplant Study Group (CTS) database. The incidence of CMV disease, rejection and neurotoxic adverse effects was analyzed up to 1 year after transplantation.

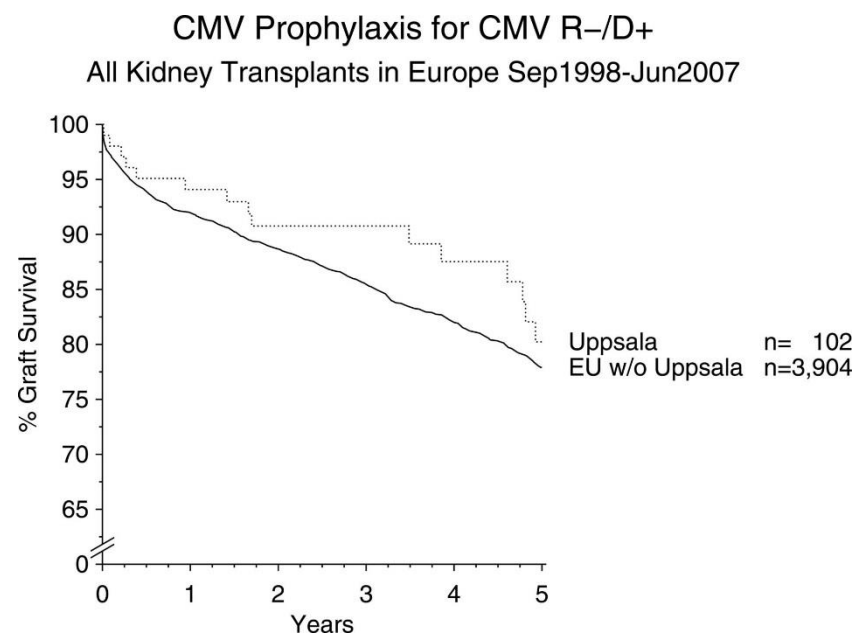
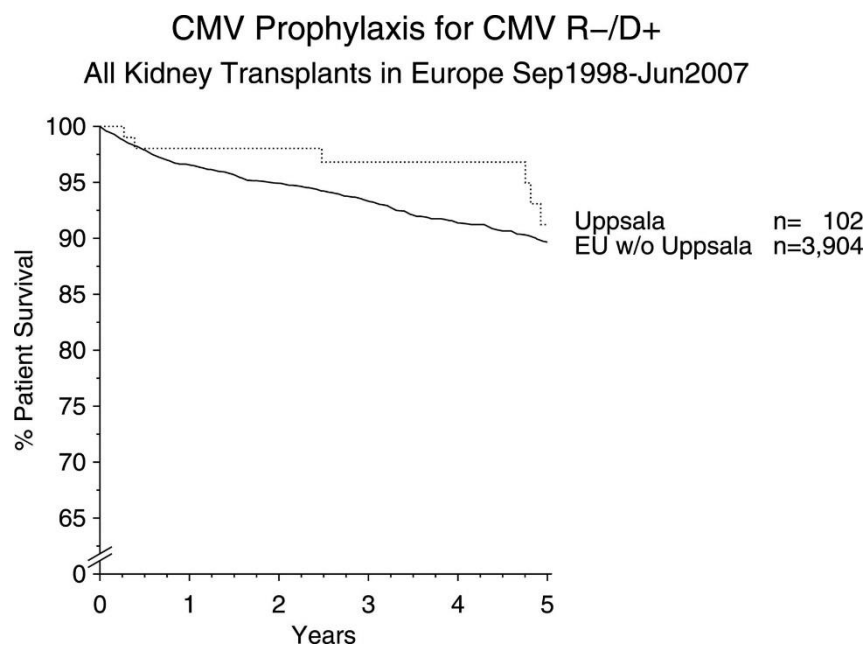
**Results** The patient and graft survival rates up to 5 years were comparable with those derived from the CTS. CMV disease was diagnosed in 25% of the patients and 2% developed tissue-invasive CMV disease. The rejection frequency was 22% and neurotoxic adverse effects were seen in 2% of the patients.

**Conclusions** Low-dose VACV prophylaxis (3 g/day) for 90 days post-transplantation results in high patient and graft survival rates and reduces the incidence of CMV disease. Neurotoxic adverse effects are minimal. We believe that low-dose VACV prophylaxis should be considered to form one of the arms in future prospective comparison studies for the prevention of CMV disease in the high-risk D+/R– population of renal transplant patients.



# Clinical outcome with low-dose valacyclovir in high-risk renal transplant recipients: a 10-year experience

Fredrik Sund, Gunnar Tufveson, Bernd Döhler, Gerhard Opelz and Britt-Marie Eriksson



## **Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients**

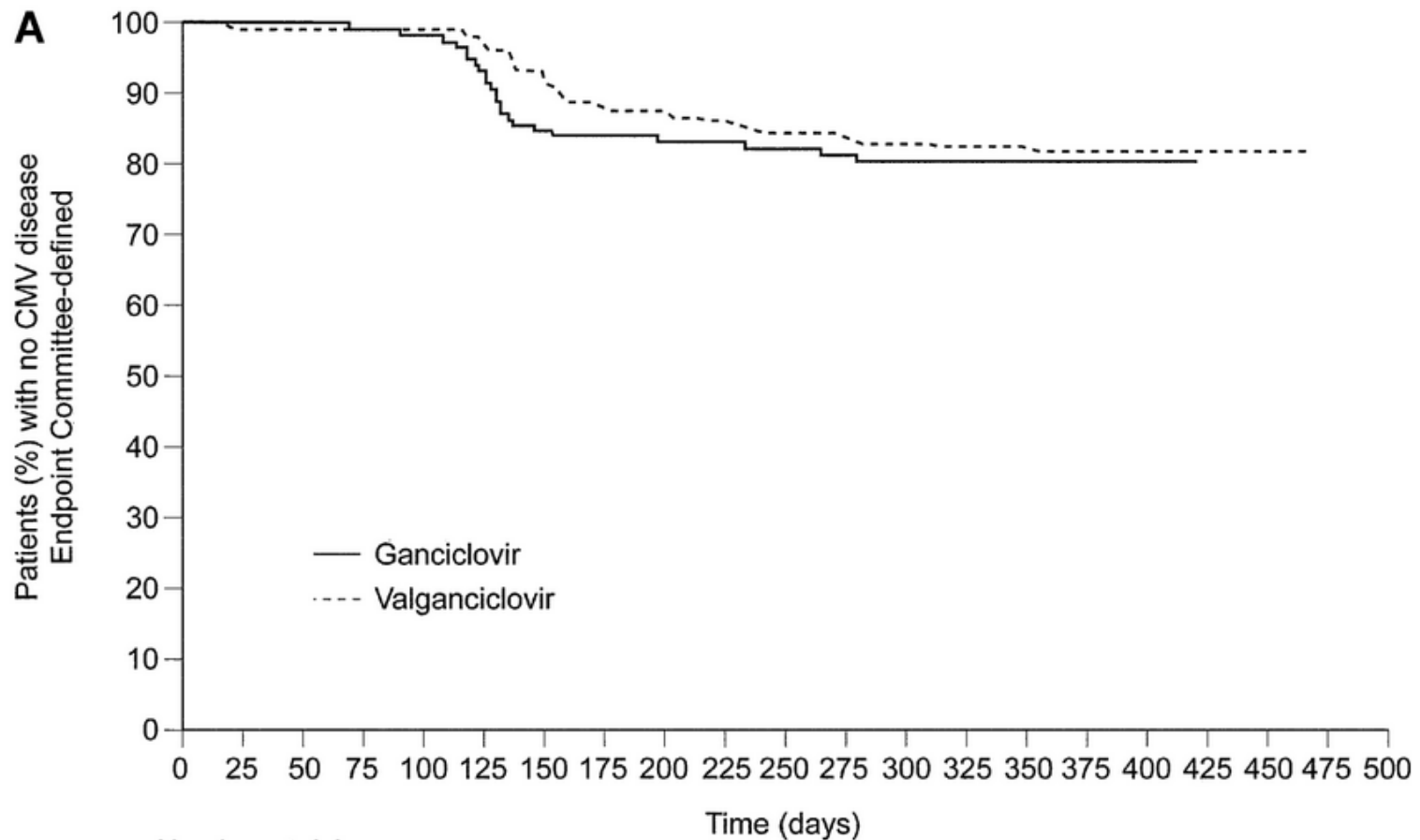
Carlos Paya, Atul Humar, Ed Dominguez, Kenneth Washburn, Emily Blumberg, Barbara Alexander, Richard Freeman, Nigel Heaton, Mark D. Pescovitz and Valganciclovir Solid Organ Transplant Study Group

**We compared the efficacy and safety of valganciclovir with those of oral ganciclovir in preventing cytomegalovirus (CMV) disease in high-risk seronegative solid organ transplant (SOT) recipients of organs from seropositive donors (D+/R-). In this randomised, prospective, double-blind, double-dummy study, 364 CMV D+/R- patients received valganciclovir 900 mg once daily or oral ganciclovir 1000 mg three times a day (tid) within 10 days of transplant and continued through 100 days. CMV disease, plasma viremia, acute graft rejection, graft loss and safety were analyzed up to 6 and 12 months post-transplant. Endpoint committee-defined CMV disease developed in 12.1% and 15.2% of valganciclovir and ganciclovir patients, respectively, by 6 months, though with a difference in the relative efficacy of valganciclovir and ganciclovir between organs (i.e. an organ type-treatment interaction). By 12 months, respective incidences were 17.2% and 18.4%, and the incidence of investigator-treated CMV disease events was comparable in the valganciclovir (30.5%) and ganciclovir (28.0%) arms. CMV viremia during prophylaxis was significantly lower with valganciclovir (2.9% vs. 10.4%;  $p = 0.001$ ), but was comparable by 12 months (48.5% valganciclovir vs 48.8% ganciclovir). Time-to-onset of CMV disease and to viremia were delayed with valganciclovir; rates of acute allograft rejection were generally lower with valganciclovir. Except for a higher incidence of neutropenia with valganciclovir (8.2%, vs 3.2% ganciclovir) the safety profile was similar for both drugs. Overall, once-daily oral valganciclovir was as clinically effective and well-tolerated as oral ganciclovir tid for CMV prevention in high-risk SOT recipients.**



## Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients

Carlos Paya, Atul Humar, Ed Dominguez, Kenneth Washburn, Emily Blumberg, Barbara Alexander, Richard Freeman, Nigel Heaton, Mark D. Pescovitz and Valganciclovir Solid Organ Transplant Study Group



## **Resolution of Mild Ganciclovir-Resistant Cytomegalovirus Disease with Reduced-Dose Cidofovir and CMV-Hyperimmune Globulin**

Samir J. Patel, Samantha A. Kuten, Richard J. Knight, Dana M. Hong, and A. Osama Gaber

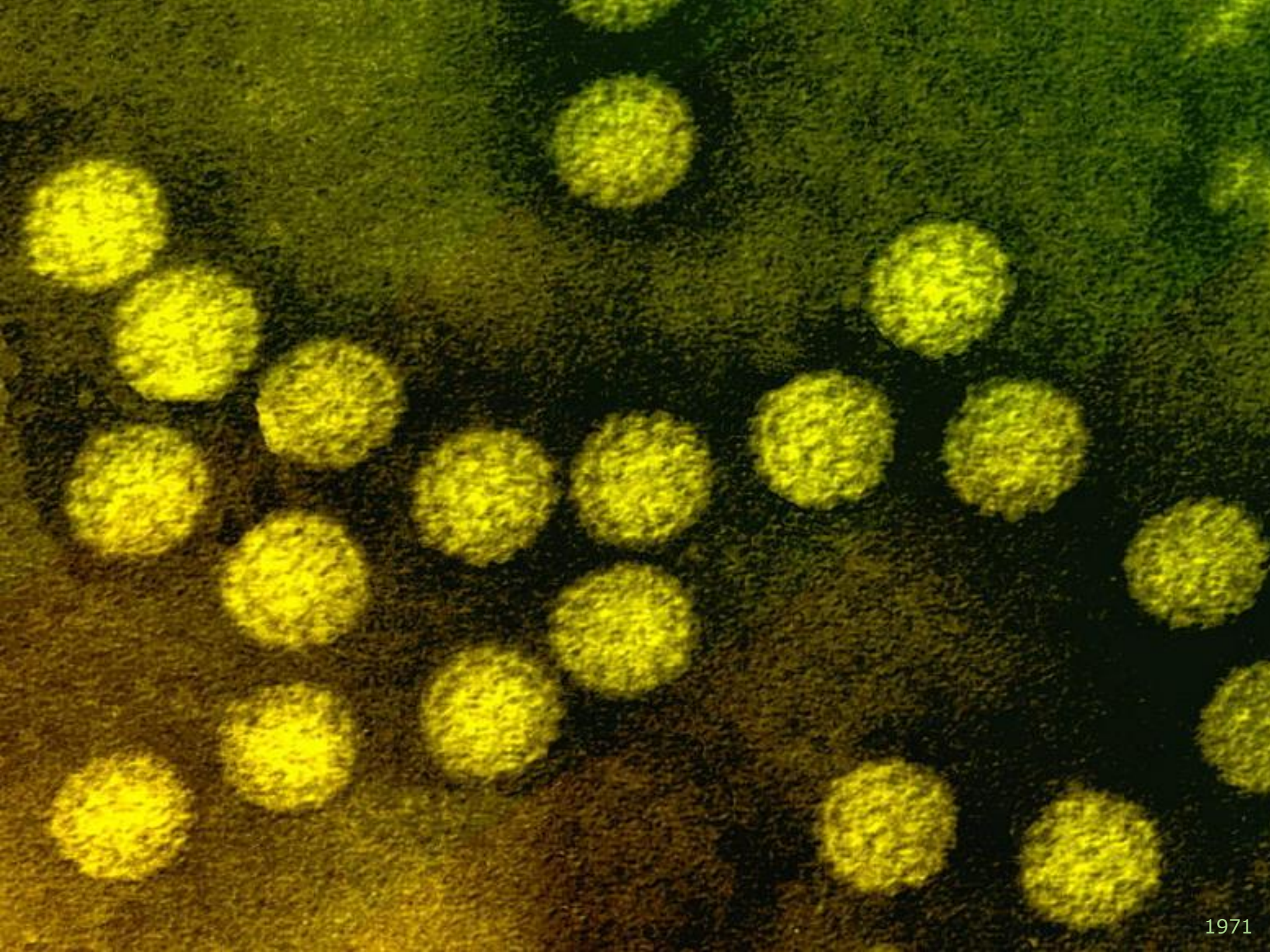
Ganciclovir-resistant cytomegalovirus (CMV) is associated with significant morbidity in solid organ transplant recipients. Management of ganciclovir-resistant CMV may be complicated by nephrotoxicity which is commonly observed with recommended therapies and/or rejection induced by “indirect” viral effects or reduction of immunosuppression. Herein, we report a series of four high serologic risk (donor CMV positive/recipient CMV negative) kidney transplant patients diagnosed with ganciclovir-resistant CMV disease. All patients initially developed “breakthrough” viremia while still receiving valganciclovir prophylaxis after transplant and were later confirmed to exhibit UL97 mutations after failing to eradicate virus on adequate dosages of valganciclovir. The patients were subsequently and successfully treated with reduced-dose (1-2 mg/kg) cidofovir and CMV-hyperimmune globulin, given in 2-week intervals. In addition, all patients exhibited stable renal function after completion of therapy, and none experienced acute rejection. The combination of reduced-dose cidofovir and CMV-hyperimmune globulin appeared to be a safe and effective regimen in patients with mild disease due to ganciclovir-resistant CMV



**BK**

**polyomavirus**

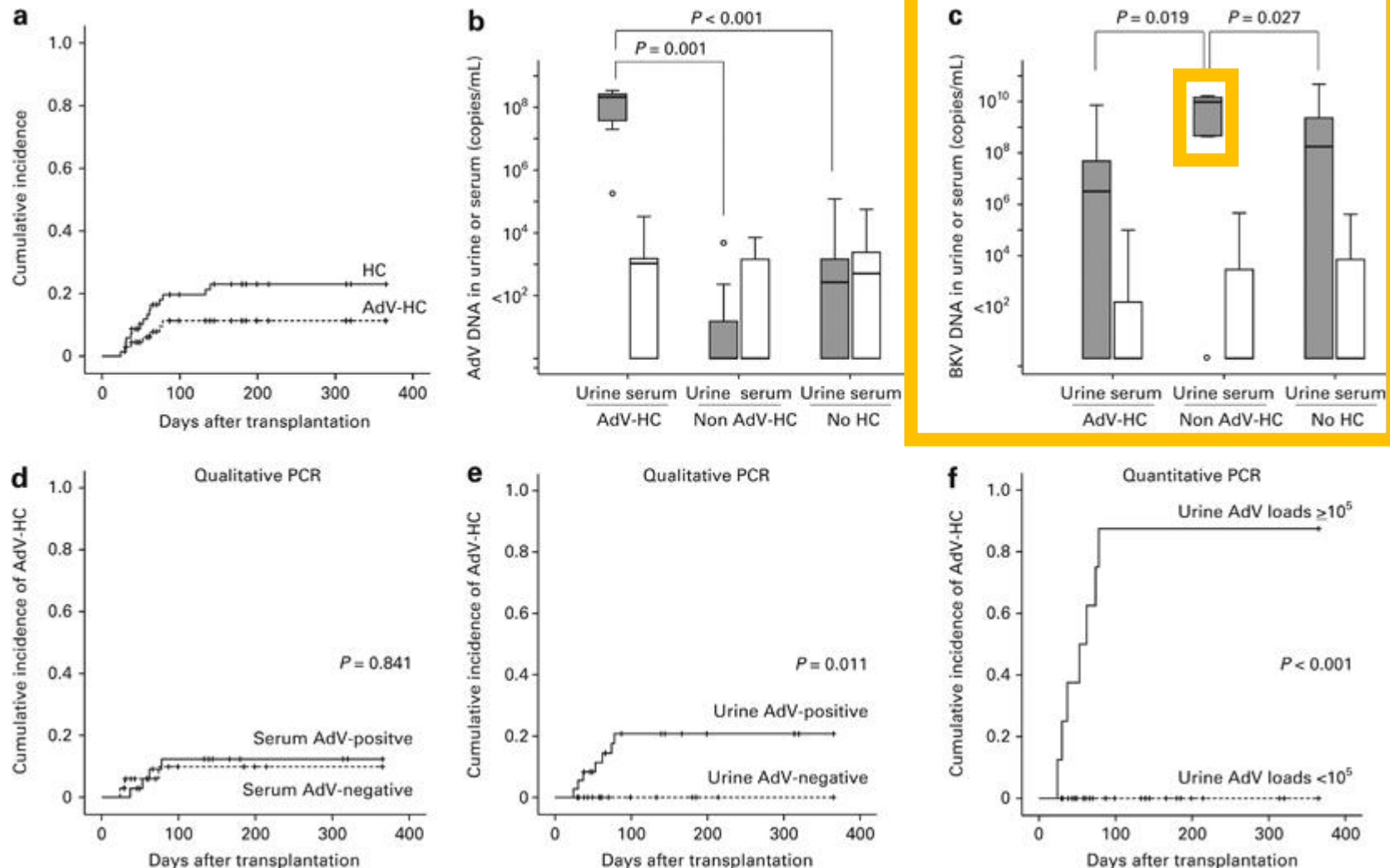




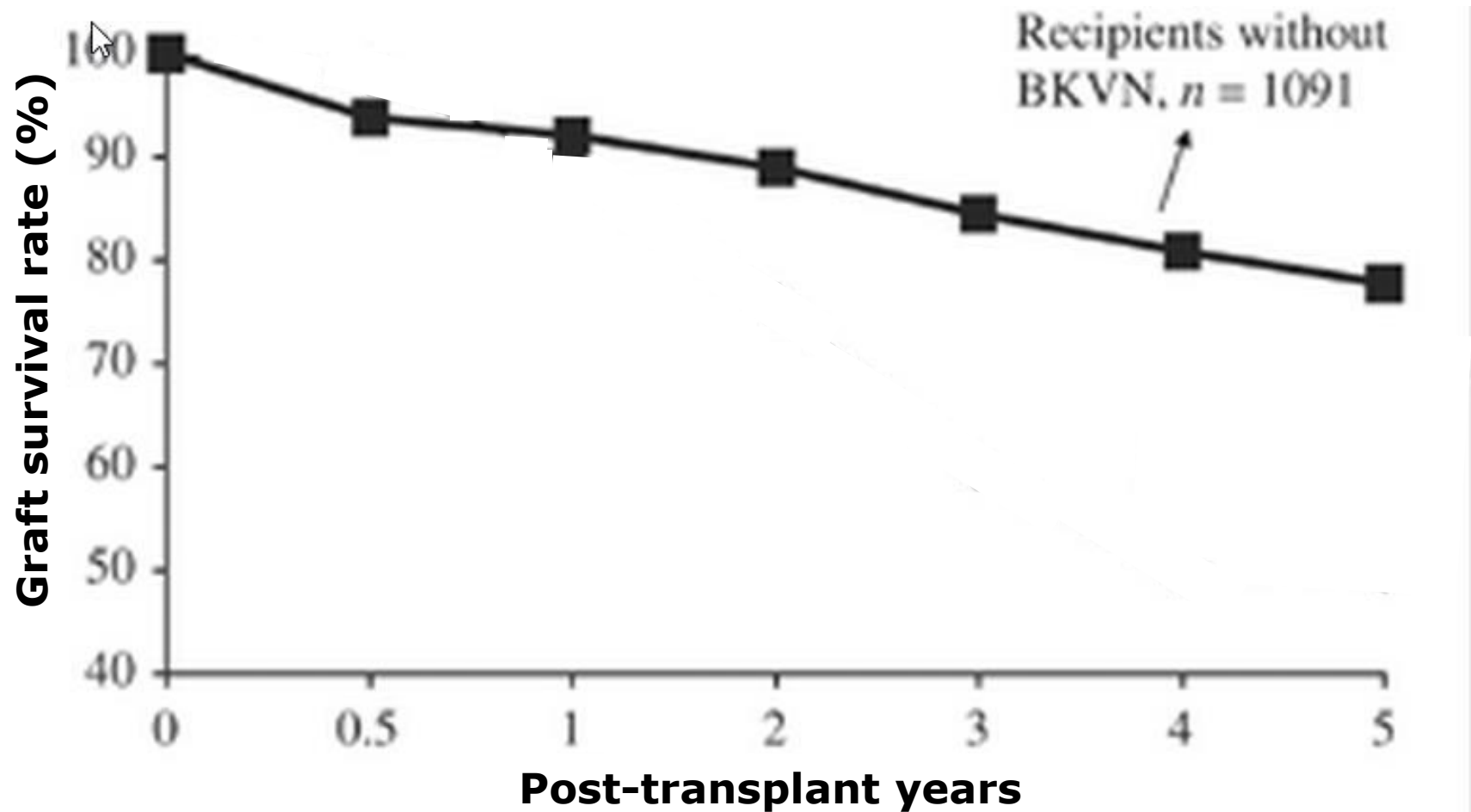
# Bone Marrow Transplantation

## Recipient seropositivity for adenovirus type 11 (AdV11) is a highly predictive factor for the development of AdV11-induced hemorrhagic cystitis after allogeneic hematopoietic SCT

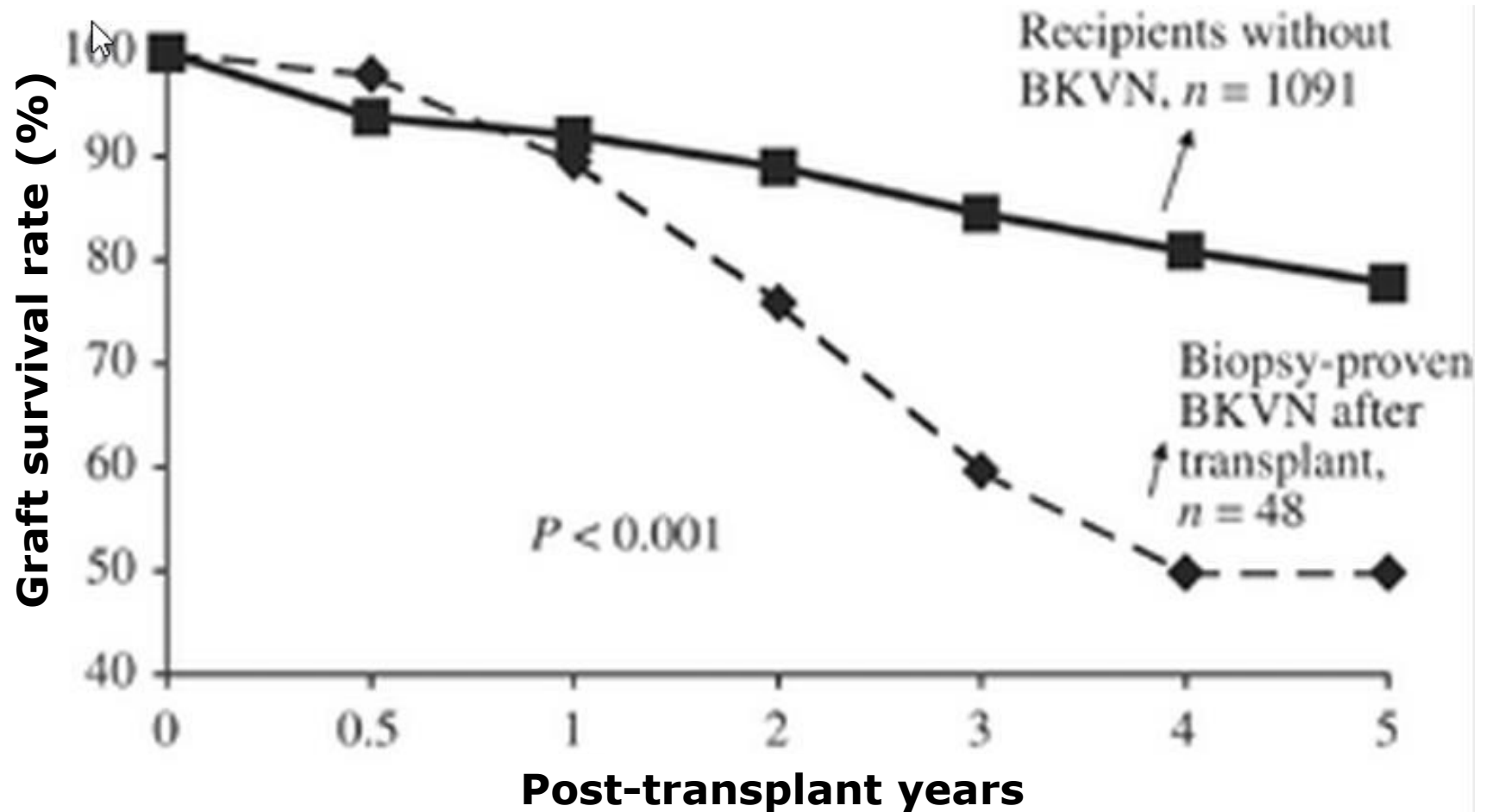
Y Nakazawa et al.





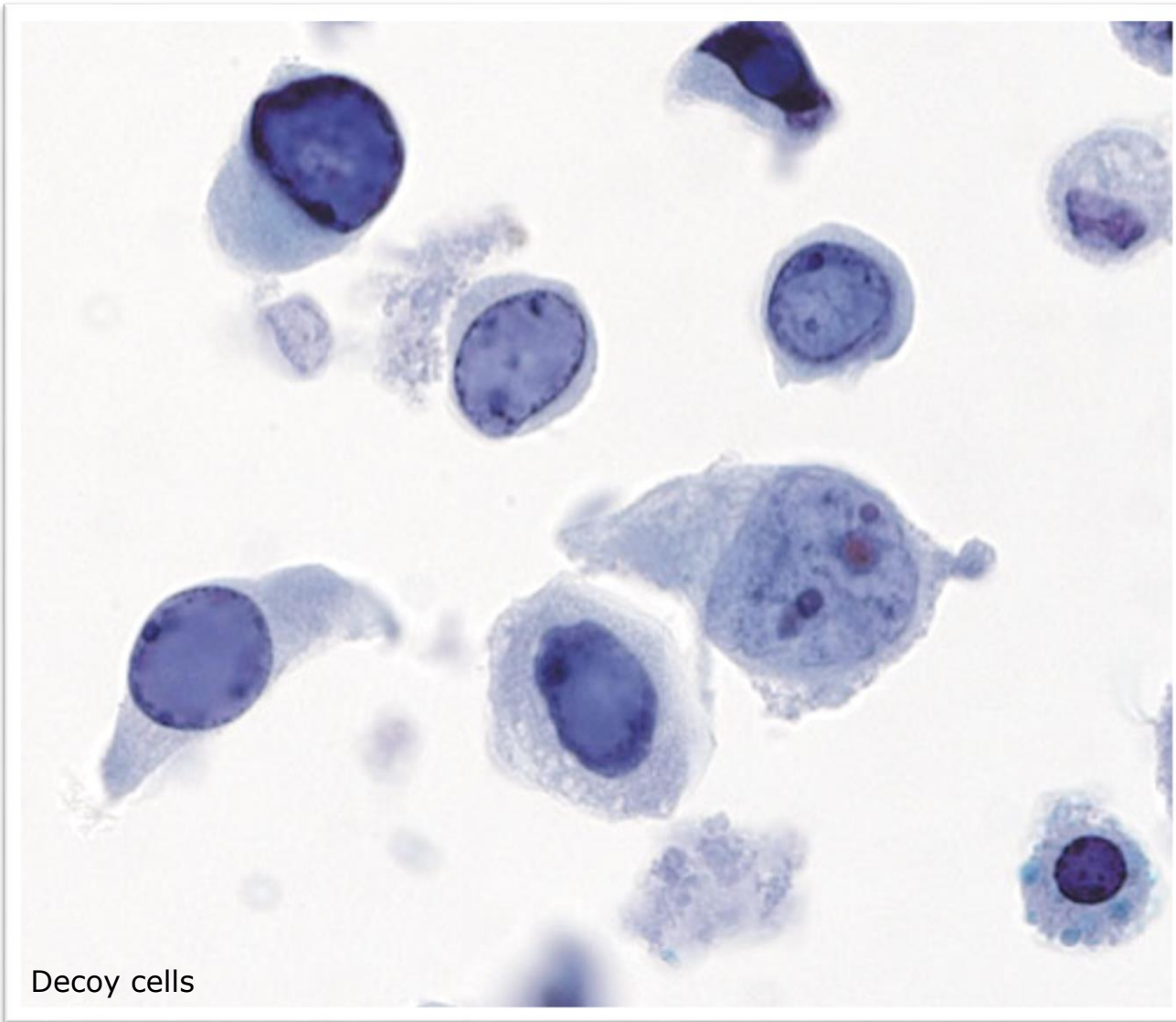




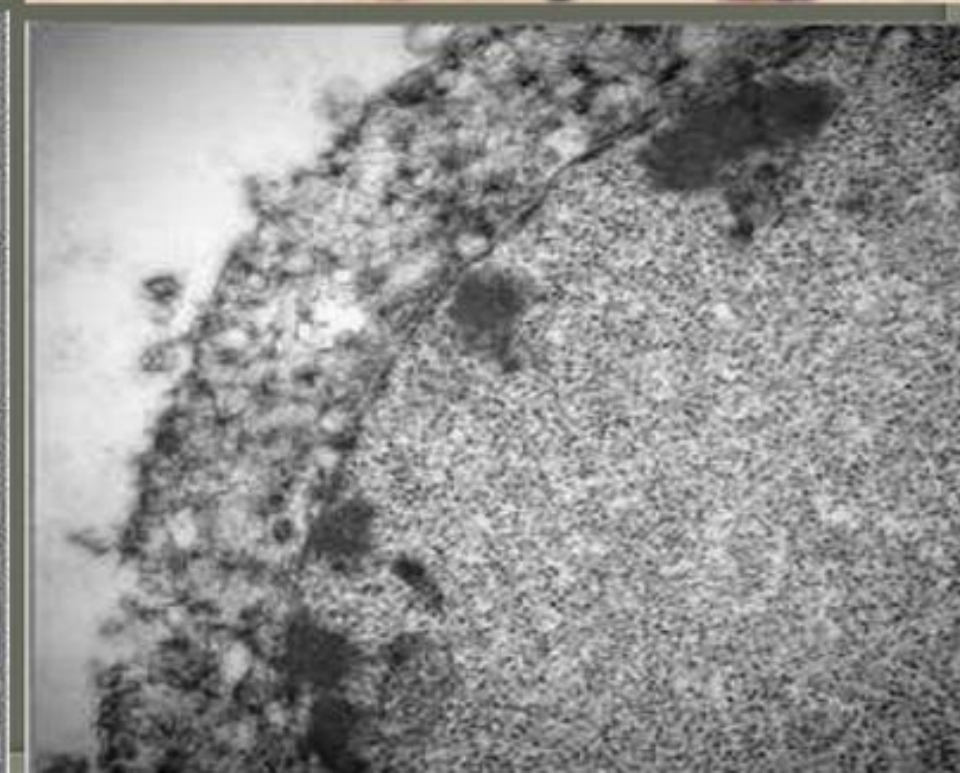
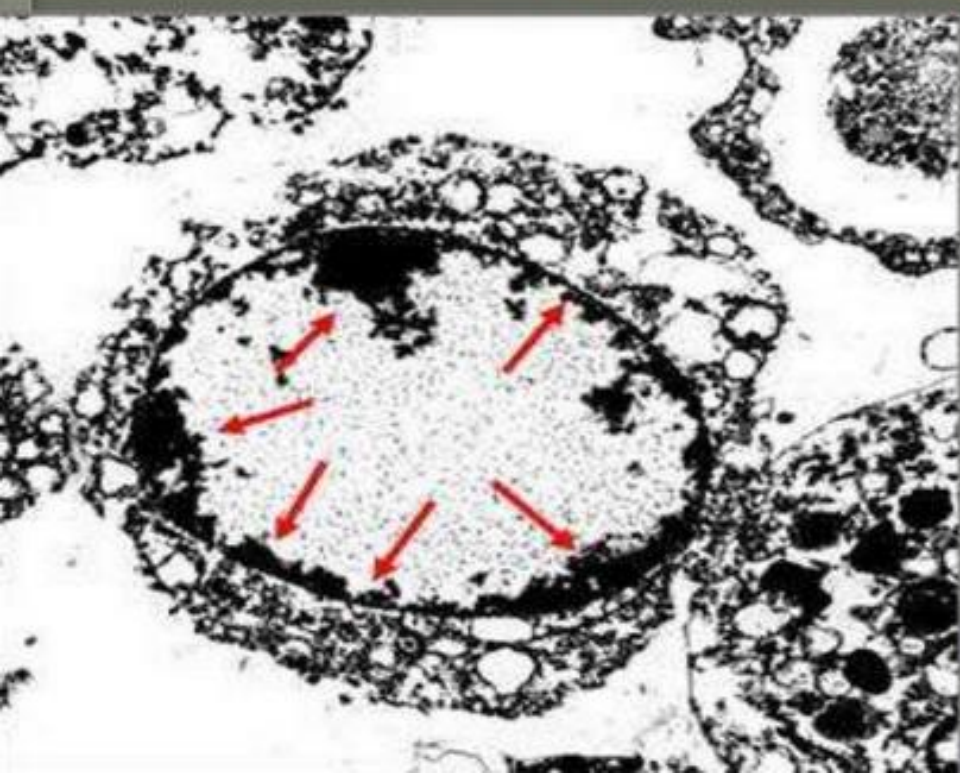
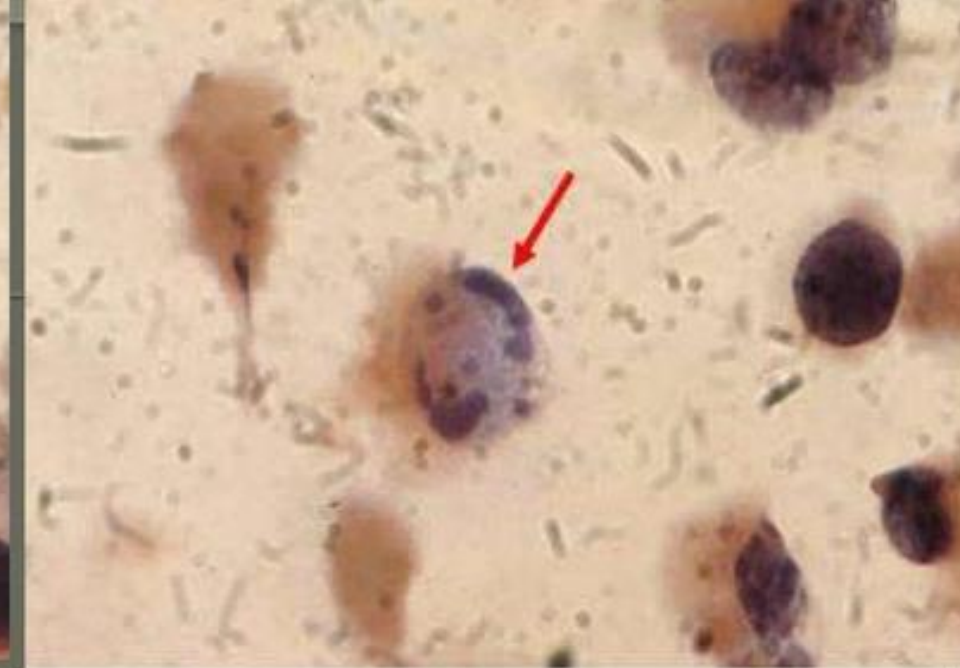
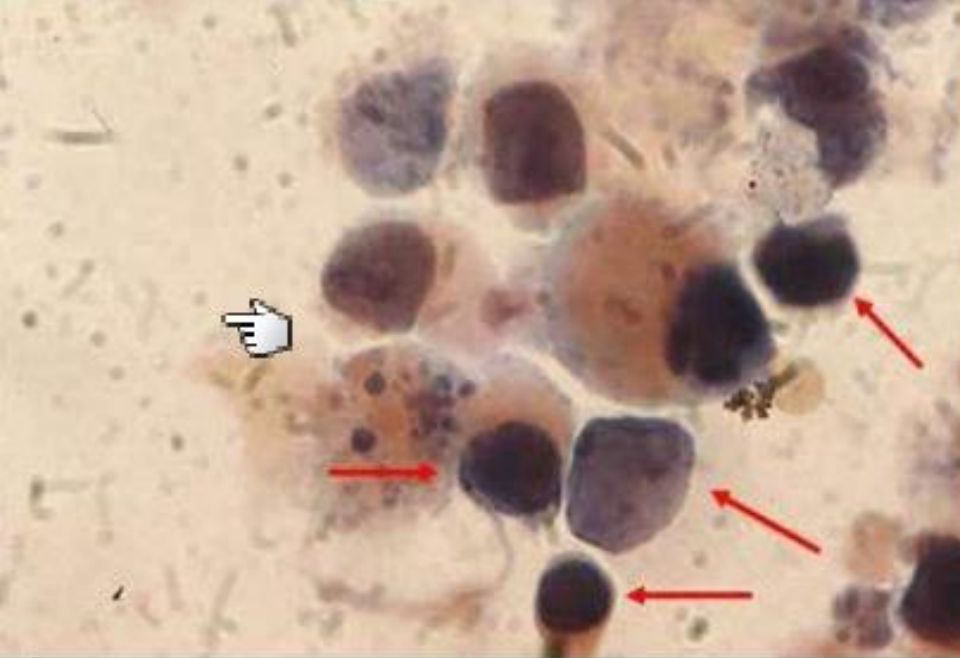


## Periodic Assessment of Urine and Serum by Cytology and Molecular Biology as a Diagnostic Tool for BK Virus Nephropathy in Renal Transplant Patients

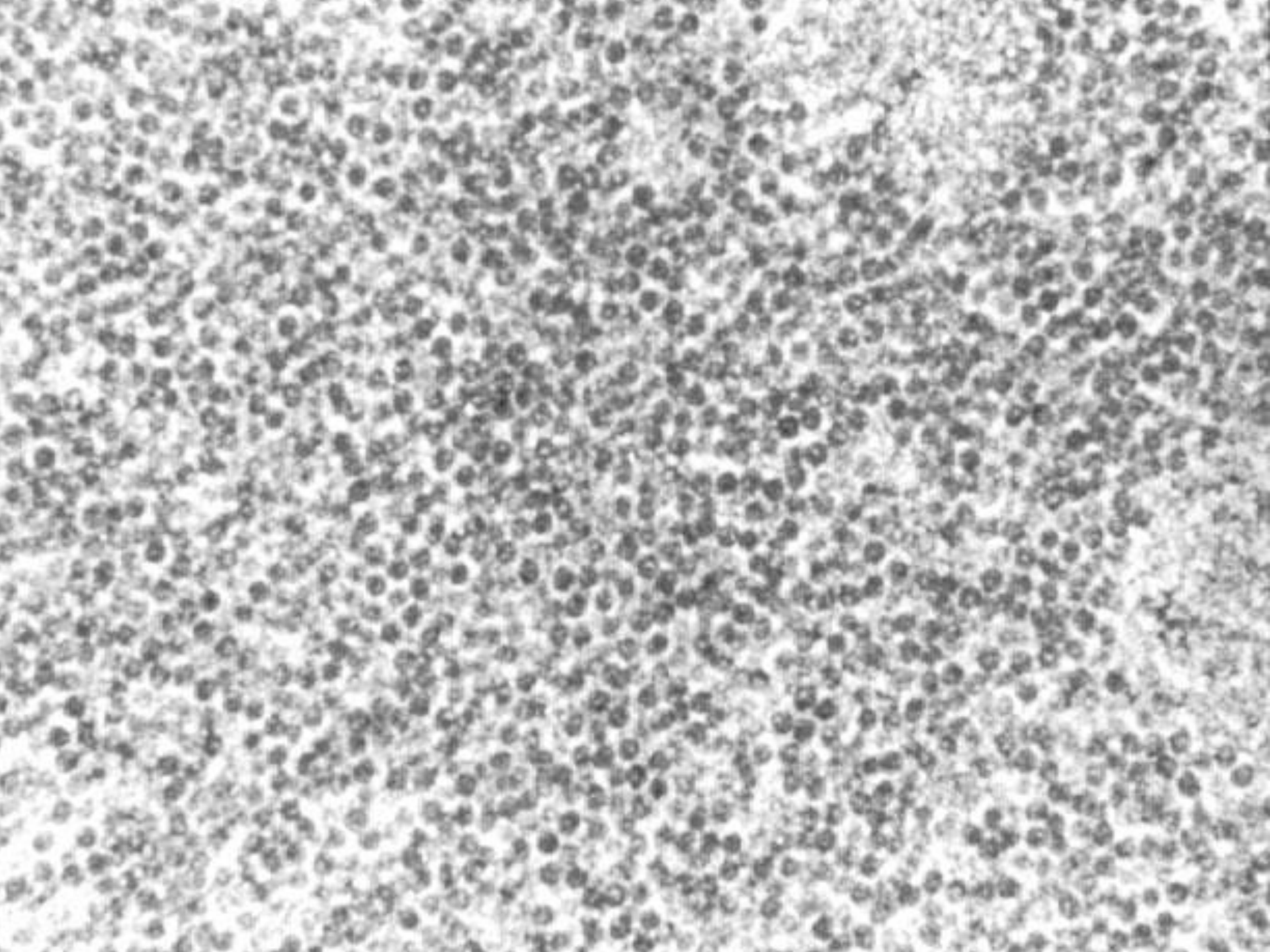
Renzo Boldorini, Maddalena Brustia, Claudia Veggiani, Diana Barco, Silvano Andorno, and Guido Monga



Decoy cells







**Table IV** *Comparison of PV Genotypes and Viruria*

Genotypes	Levels of viruria <sup>a</sup>			p
	Low	Intermediate	High	
JCV (n = 16)	9 (56%)	5 (31%)	2 (13%)	0.01
BKV (n = 24)	4 (16.6%)	7 (29%)	13 (54.4%)	0.003
JCV+BKV (n = 13)	5 (38.5%)	5 (38.5%)	3 (33%)	NS

<sup>a</sup>Decoy cells per 5 hpf.

$\chi^2$  For linear trend.

Percentages refer to rows.

N = 53.

## Risk factors for hemorrhagic cystitis in pediatric allogeneic hematopoietic stem cell transplant recipients

R.T. Hayden\*, Z. Gu, W. Liu, R. Lovins, K. Kasow, P. Woodard, K. Srivistava and W. Leung

**INTRODUCTION:** Hemorrhagic cystitis (HC) results in significant morbidity among hematopoietic stem cell transplant (HSCT) recipients. Several potential causes for HC have been postulated, including viral infection, but definitive evidence is lacking, particularly in pediatric HSCT patients.

**METHODS:** Ninety pediatric HSCT recipients were prospectively tested on a weekly basis for adenovirus (ADV) and BK virus (BKV) by quantitative real-time polymerase chain reaction in blood and urine samples. Results were correlated with the occurrence of grade II-IV HC. The odds ratio (OR) of HC (95% confidence interval) for BKV  $\geq 1 \times 10^9$  copies/mL of urine was 7.39 (1.52, 35.99), with a P-value of 0.013. Those with acute graft-versus-host disease (aGVHD) also had higher odds of developing HC, with an OR of 5.34. Given a 20% prevalence rate of HC, positive and negative predictive values of 29% and 95% were seen with a cutoff of  $10^9$  copies/mL.

**RESULTS:** BK viremia did not reach significance as a risk factor for development of HC ( $P = 0.06$ ). Only 8 patients showed ADV viruria and 7 showed ADV viremia; all had low viral loads and 4 had no evidence of HC.

**CONCLUSION:** HC in pediatric HSCT is correlated most strongly to elevated urinary viral load of BKV and to aGVHD, but less strongly to BK viremia.



## **Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis of an algorithmic approach**

N. Ganguly, L.A. Clough, L.K. DuBois, J.P. McGuirk, S. Abhyankar, O.S. Aljitawi, N. O'Neal, C.L. Divine and S. Ganguly

BK virus (BKV) reactivation occurs in 50% of allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. Standardized antiviral management of BKV infection has not been established. In order to develop a uniform guideline, a treatment algorithm for the management of symptomatic BKV replication was implemented for our allo-HSCT population. This is a retrospective analysis of patients treated according to the protocol between January 2008 and January 2009. Eighteen patients developed symptomatic BKV replication a median of 43 days after allo-HSCT. All patients had BK viruria and 12 patients had BK viremia in addition to viruria. Patients with isolated viruria were treated with intravenous (IV) low-dose cidofovir (0.5-1mg/kg IV weekly) until symptom resolution. In patients with BK viremia, therapy was continued until virological clearance was achieved in the blood. Four patients also received intravesical instillation of cidofovir per physician discretion. Thirteen of 18 (72%) patients with viruria and 8 of 12 (75%) patients with viremia responded to treatment. Three patients developed transient renal dysfunction. Low-dose cidofovir is safe and effective in allo-HSCT recipients.

## Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial

Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, Ramsay T, Chassé M, Pang X, Zaltzman J, Cockfield S, Cantarovich M, Karpinski M, Lebel L, Gill JS.

Quinolone antibiotics have antiviral properties against BK virus but efficacy at preventing this infection has not been shown in prospective controlled studies.

**DESIGN, SETTING, AND PARTICIPANTS:** Double-blind, placebo-controlled randomized trial involving 154 patients who received a living or deceased donor kidney-only transplant in 7 Canadian transplant centers between December 2011 and June 2013. **INTERVENTIONS:** Participants were randomly assigned to receive a 3-month course of levofloxacin (500 mg/d; n = 76) or placebo (n = 78) starting within 5 days after transplantation.

**RESULTS:** The mean follow-up time was 46.5 weeks in the levofloxacin group and 46.3 weeks in the placebo group (27 patients had follow-up terminated before the end of the planned follow-up period or development of viruria because the trial was stopped early owing to lack of funding). BK viruria occurred in 22 patients (29%) in the levofloxacin group and in 26 patients (33.3%) in the placebo group (hazard ratio, 0.91; 95% CI, 0.51-1.63; P = .58). There was no significant difference between the 2 groups in regard to any of the secondary end points. There was an increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group vs placebo (14/24 [58.3%] vs 15/45 [33.3%], respectively; risk ratio, 1.75; 95% CI, 1.01-2.98)

**CONCLUSIONS AND RELEVANCE:** Among kidney transplant recipients, a 3-month course of levofloxacin initiated early following transplantation did not prevent BK viruria. Levofloxacin was associated with an increased risk of adverse events such as bacterial resistance. These findings do not support the use of levofloxacin to prevent posttransplant BK virus infection.