

# **Immunologia e infettivologia dei trapianti**

**Prof. Enzo Raise**

**Spec. in Malattie Infettive e Tropicali**

**Immunologia Clinica e Allergologia**

**Epatologia**

**Venezia-Mestre 17 maggio 2018**

# Biologic agents in rheumatology

- **Psoriatic arthritis**
  - TNF alpha inhibitors
  - IL 23 and IL12 (p40) inhibition (MoAb) **SC**
    - *Ustekinumab*
  - IL17 inhibition (MoAb) **SC**
    - *Sekukinumab*
- **Ankylosing Spondylitis/axial SpA** -TNF alpha inh, Sekukinumab
- **SLE** - BLYS inhibition (MoA) **IV**
  - *Belimumab*
- **Osteoporosis** - RANKL inhibition **SC**
  - *Denosumab* (MoAb)
- **ANCA associated Vasculitis** - Rituximab
- **Autoinflammatory syndromes / JCA / refractory gout**
  - IL 1 inhibition

# Safety of Anti-Tumor Necrosis Factor- $\alpha$ Therapy in Patients with Rheumatoid Arthritis and Chronic Hepatitis C Virus Infection

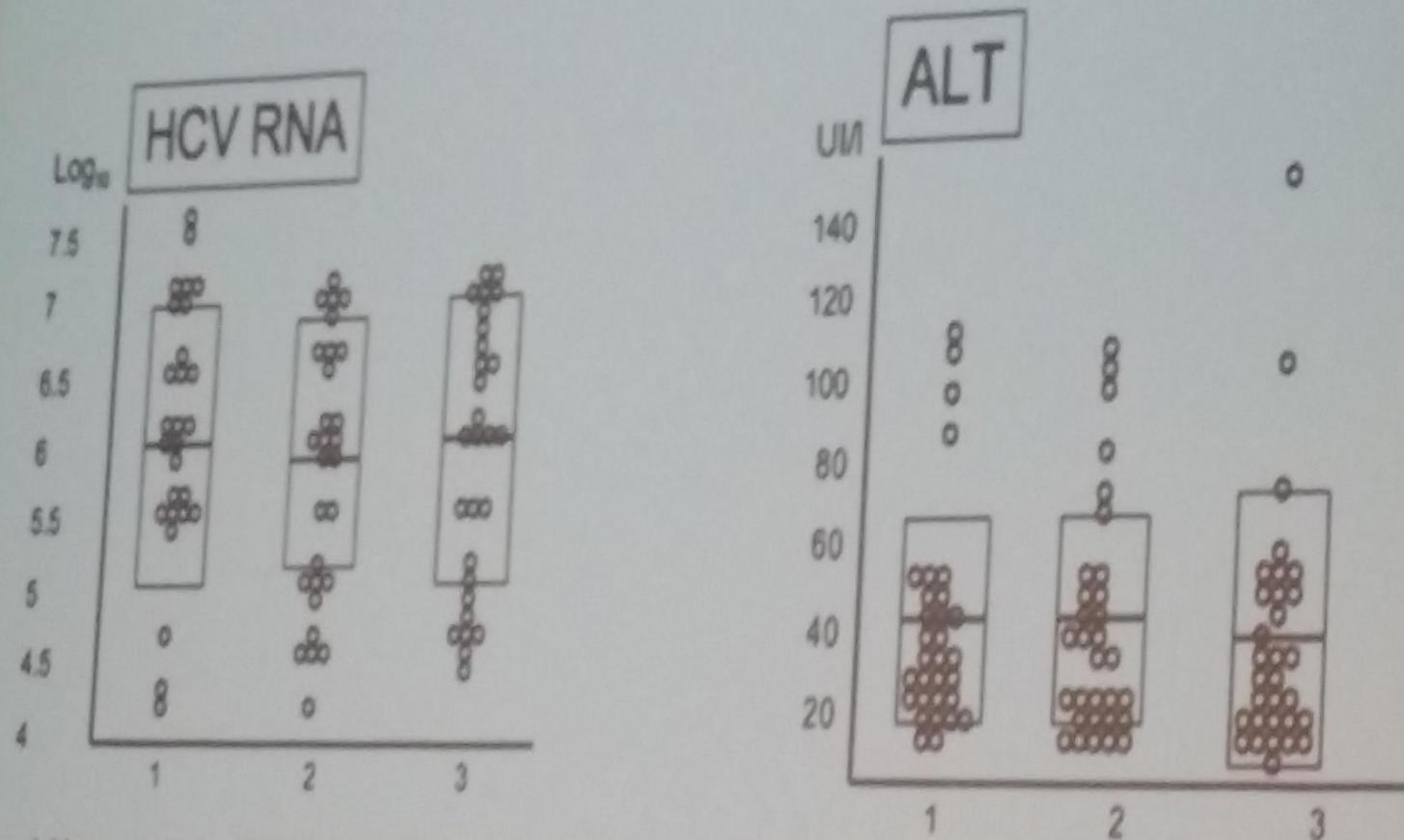


Figure 2. Mean serum levels of HCV RNA and ALT showed no statistically significant variations after the first 3 months of anti-TNF- $\alpha$  treatment (2), and at the last recorded visit (3), compared to baseline (1).

# Infezione da HCV con Rituximab

## Rituximab in HCV carriers

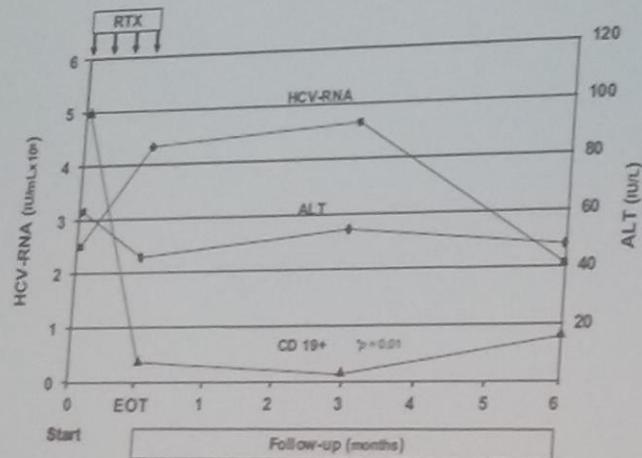


Figure 2. Pattern of HCV RNA, alanine aminotransferase, and CD19 mean values of the 19 patients with HCV-positive MC during the study. RTX indicates rituximab infusions; EOT, end of treatment; and ALT, alanine aminotransferase.

Petrarca A, Blood 2010

# HCV

- **La terapia è pangenotipica con SOF+VEL+VAX oppure SOF+VEL. Entrambe le associazioni determinano il 96% di eradicazione virale ma se vi è cirrosi epatica gen 3, la triplice terapia è più efficace nel 97% vs 95%**
- **SOF+GLEC+PIBR per 12 settimane si effettua nel 2% di coloro che hanno fallito**
  - **(rescue therapy)**
- **HCV acuta: trattare per 8-12 settimane con pangenotipico**

# TRAPIANTO EPATICO HCV

- **La percentuale sui trapianti era del 25% in epoca pre DAA, attualmente è al 5%. Sono aumentati i trapianti per NASH dal 3,6 all' 8,9%**
- **Si è ridotta la mortalità post trapianto per cirrosi da HCV nei pre-trattati con DAA e trattati poi con Tacrolimus /ciclosporina**
  - **Se trattati con DAA pre trapianto si ha eradicazione nel 96% di HCV, se post trapianto nell' 80%**
- **Si sono evidenziati 29 casi mondiali di riattivazione di HBV dopo 4-8 settimane dall' inizio della DAA ( SOF+LED)**

## Epatocarcinoma (HCC) da HCV

- **La media di comparsa di HCC nei trattati con IFN era dell' 1% vs il 5% nei trattati con DAA e la media di comparsa era di 11,2 mesi e recidiva media a 11,6 mesi**

**SVR HCC/100 paz/anno : 0,90**

**NO SVR HCC/100 paz/anno: 3,45**

**SVR no cirrosi HCC: 0,34**

**NO SVR no cirrosi HCC : 1,82**

# HBV trapiantati epatici

- **In Italia il 10% dei trapiantati è stato causato da HBV, se si considera anche l' HDV il totale è il 18%.**
- **L' integrazione ccc DNA nel genoma cellulare rende quasi impossibile eradicare HBV ( presente anche nella tiroide, rene, linfonodi, app. gastrointestinale), nel futuro la terapia genica dovrà scindere il legame e la terapia antivirale lo distruggerà**
- **Il TAF ha minori effetti collaterali del TDF con 0.1% di resistenze**
- **ETV ( Baraclude-Entecavir) ha allo stato attuale lo 0,2% di resistenze, in Cina, per il largo utilizzo 1,5%**

# Terapia di HBV

- **Farmaco di prima scelta :  
ENTECAVIR ( Baraclude)**
- **Farmaco , in caso di resistenza  
all' Entecavir:**
  - **Tenofovir alafenamide**

# Anti TNF in anticore +

## Surface Antigen (HBeAg) Positive (Anti-HBc) With Rheumatic Diseases

R. CAPORALI,<sup>1</sup> F. BOBBIO-PALLAVICINI,<sup>1</sup> F. ATTENU,<sup>2</sup> G. SAKELLARIDOU,<sup>1</sup> M. CAPRIOLA,<sup>1</sup> C. MONTECUCCHI,<sup>1</sup> and P. SARIS-PUTTINI<sup>1</sup>

**Objective:** To assess the safety of anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) therapy on the course of hepatitis B virus (HBV) infection in carriers of antibodies to hepatitis B core antigen (anti-HBc) affected by chronic inflammatory arthropathies.

**Methods:** From January 2001 to December 2006, HBV markers were determined before the first administration of anti-TNF- $\alpha$  agents in all 722 patients affected by inflammatory arthropathies treated with anti-TNF- $\alpha$  at 2 outpatient rheumatology clinics in Northern Italy. Anti-HBc-positive patients were prospectively evaluated and HBV markers and HBV DNA were assessed every 4 months, in case of immunosuppressive alteration, and at the end of the study.

**Results:** At the time of recruitment, 72 patients were anti-HBc carriers, 5 of whom were positive for hepatitis B surface antigen (HBsAg) and not included in the study. The ratio of men/women was 26/46 and the mean  $\pm$  SD follow-up was 42.32  $\pm$  25.33 months. Of the patients, 21 were treated with infliximab, 23 with etanercept, and 19 with adalimumab. Fifty-one patients were treated also with methotrexate, 32 with immunosuppressive anti-inflammatory drugs, and 43 with prednisone ( $\geq$  with a dosage  $>$ 7.5 mg/day). All anti-HBc patients were HBV DNA negative at the first observation. During follow-up, no patient presented HBV reactivation with viral load increase and no patient became HBsAg positive. **Conclusion:** Anti-HBc positivity in HBsAg-negative patients is a sign of previous HBV infection and does not indicate chronic hepatitis. In these patients, anti-TNF- $\alpha$  therapy appears to be quite safe, as no HBV reactivation was found in our study. Nevertheless, careful monitoring is necessary.

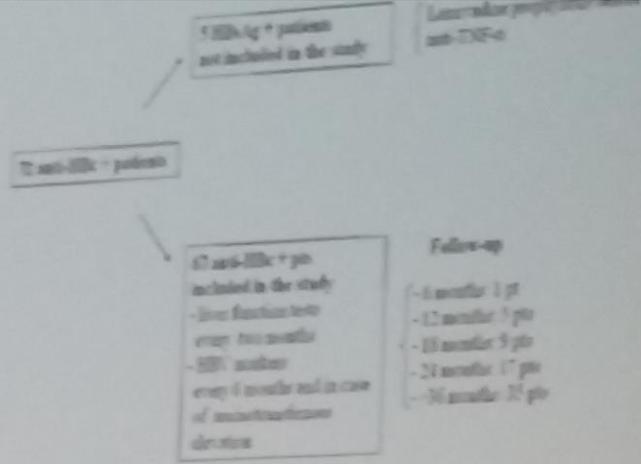


Table 2. Serologic hepatitis markers and liver tests at baseline and at the end of follow-up\*

Liver assessment	Baseline	End of follow-up†
HBsAg positive	0	0
HBcAg positive	0	0
Anti-HBc positive	67	65†
Anti-HBe positive	21	23
Anti-HBx positive	28	32
HBV DNA positive	0	0
Hepatitis C virus positive	2	2
AST, median (IQR) mU/ml§	21 (17–25.75)	19 (17–25)
ALT, median (IQR) mU/ml§	20 (12.25–28.75)	20 (15.75–24.25)

Anti-TNF appears to be safe in our cohort of HbcAb+ patients suffering from rheumatic diseases.

# Profilassi

- Se il paziente è anticore positivo, S negativo, anti DNA HBV negativo si può non fare la profilassi con lamivudina facendo uno stretto follow-up. E' mia opinione che sarebbe meglio fare la profilassi se non è possibile il follow-up stretto

# Tacilizumab e abatacept in HBV

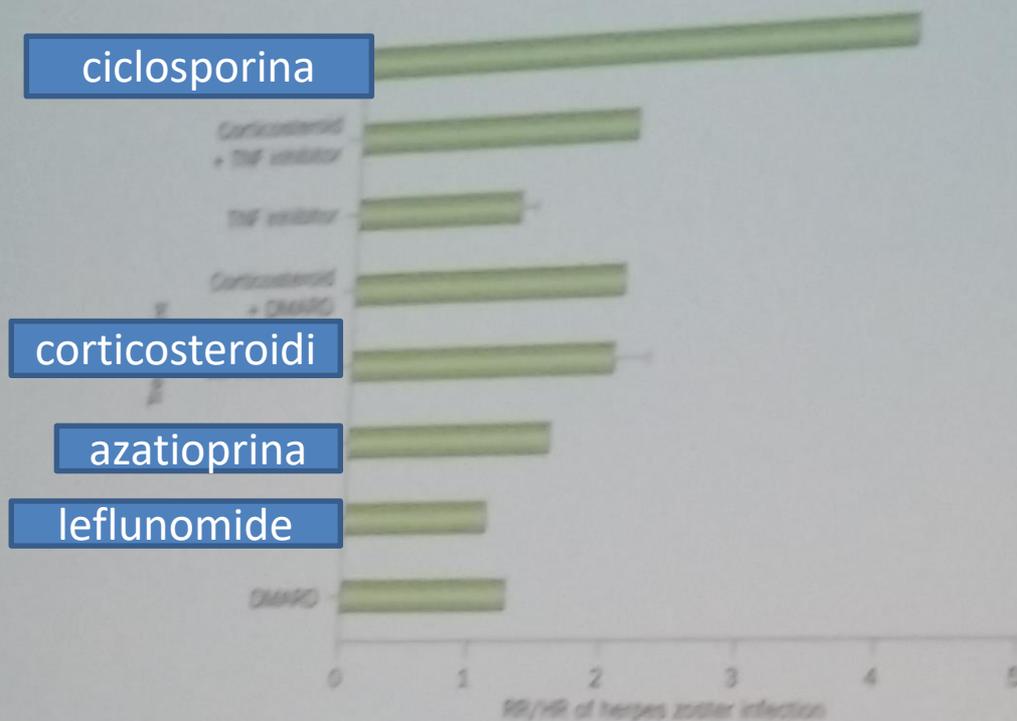
Tacilizumab: Possible transient HBV-DNA fluctuation during the first 3-6 mo of TCZ described.

Abatacept: Should usually be administered with pre-emptive profilaxys.

Monitor HbsAg and HBV-DNA every 3-6 months  
Consider vaccination in patients at risk

# Treatment-related of VZV in RA-numero episodi per tipo di farmaco per paziente

Figure 1 Treatment-related RR of herpes zoster in RA



# Varicella zoster in terapia con TNF

## Varicella Zoster

**Table 2** Incidence of hospitalisations due to shingles in population aged  $\geq 18$  years exposed to TNF antagonists

	Cases	Person-years	Incidence rate per 100 000 (95% CI)	SIR per 100 000 (95% CI)	SIR (95% CI)
BIOBADASER 2.0					
All rheumatic diseases exposed to TNF antagonist	5	15389	32 (14 to 78)	29 (9 to 67)	9 (3 to 20)
Rheumatoid arthritis exposed to TNF antagonist	4	9055	44 (17 to 118)	34 (9 to 87)	10 (3 to 26)
CMBD (expected)	3825	114279124	3.4 (3.2 to 3.5)	3.4 (3.2 to 3.5)	

BIOBADASER, Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas; CMBD, Conjunto Mínimo Básico de Datos al Alta Hospitalaria (Hospital Discharge Database); SIR, standardised incidence ratio; TNF, tumour necrosis factor.

**Table 3** Incidence of hospitalisations due to chickenpox in population aged  $\geq 18$  years exposed and not exposed to TNF antagonists

	Cases	Person-years	Incidence rate per 100 000 (95% CI)	SIR per 100 000 (95% CI)	SIR (95% CI)
BIOBADASER 2.0					
All rheumatic diseases exposed to TNF antagonist	4	15395	26 (10 to 69)	35 (9 to 91)	19 (5 to 47)
Rheumatoid arthritis exposed to TNF antagonist	0	9066			
CMBD (expected)	2163	114279124	1.9 (1.8 to 2.0)	1.9 (1.8 to 2.0)	

BIOBADASER, Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas; CMBD, Conjunto Mínimo Básico de Datos al Alta Hospitalaria (Hospital Discharge Database); SIR, standardised incidence ratio; TNF, tumour necrosis factor.

# Infezioni virali riattivate dopo terapia con anti TNF o RTX o Infliximab

## Viral infections and biologic agents

HIV – Only few long-term data available. No evidence of worsening  
(Fink DL 2017, Baldazzi F 2017)

CMV - No evidence of reactivation with anti-TNF (Torre-Cisneros J. *Rheumatology* 2005, Mencarini J. *Reumatismo* 2016). Possible reactivation with RTX

EBV – Some reactivations on anti-TNF (case reports) (Park S, *Rheumatol Int* 2009)

HSV - Reactivations are common. Several case reports of disseminated infections. (Skripak JM, *Pediatr Rheumatol Online J*, 2003; van der Klooster JM, *Intensive Care Med* 2003)

MCV, HPV – Some reactivations with Infliximab (case reports)

HHV-6, HHV-8 – Data are scanty

# RITUXIMAB-anti CD20

- **Determina, anche se raramente una riattivazione del virus JC ( PML) ossia della leucoencefalite multifocale progressiva per la quale ad oggi non vi è la terapia.**
- **HPV : modesti aumenti della replicazione virale**
- **TOCILOZUMAB: determina perforazioni intestinali con diverticoliti**

# DMARD ( composti chimici MTX, LFL,SSZ e target tofacitinib,baracitinib Agenti biologici: anti TNF,abatacept,Rituximab (RTX),Tocilizumab,Anankira

**Definition:** reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage and thus interfere with the entire disease process

## DMARD classes:

synthetic chemical compounds (sDMARDs)

- conventional DMARDs (csDMARDs) (MTX, LFL, SSZ, etc)
- **targeted DMARDs (tsDMARDs)** (tofacitinib, baricitinib...)

biological agents (bDMARDs)

- **biological (bDMARDs)** (anti-TNF, abatacept, rituximab, tocilizumab, anakinra)

# Recettori citochinici

Jak members selectively associate with different cytokine receptors

- $\gamma$  family : IL-2, IL-4, IL-7, IL-9, IL-15
- Gp130 family : IL-6, IL-11, OSM, LIF
- Class II cytokine receptor family : IFN  $\alpha/\beta$ , IFN- $\gamma$ , IL-10

Jak 1

Tyk 2

- IFN- $\alpha/\beta$ , IFN- $\gamma$ , IL-12

Jak 2

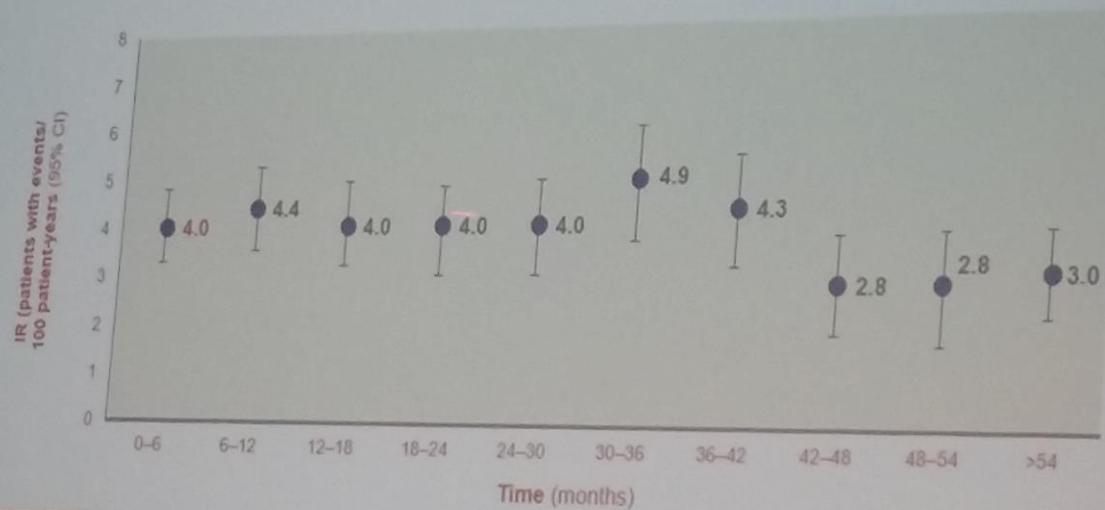
Jak 3

- EPO, TPO, IFN- $\gamma$
- $\beta$ c family : IL-3, IL-5, GM-CSF

- $\gamma$  family : IL-2, IL-4, IL-7, IL-9, IL-15

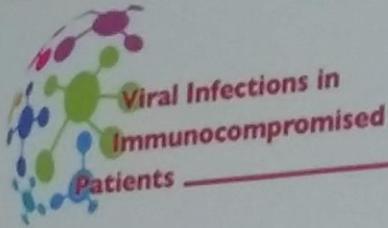
# Tasso di incidenza del VZV per età

Incidence rates for  
herpes zoster infection over time



Total pt exposure (N)	6,194	5,222	4,677	4,217	3,858	3,361	3,043	2,656	2,303	1,727
Patient with HZ (N)	112	106	87	79	71	77	60	34	27	50

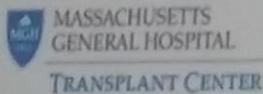
# Nuovi antivirali



## New(er) Antiviral Agents (and approaches)

Jay A. Fishman, M.D.

Professor of Medicine, Harvard Medical School  
Director, Transplant Infectious Disease and Compromised Host  
Program, Massachusetts General Hospital  
Co-Director, MGH Transplant Center, Boston, MA, USA



# Infezioni Virali nei trapiantati

## The Growing Family of Viral Pathogens in Transplantation

- Herpes Simplex
- Varicella Zoster
- Epstein-Barr Virus
- Cytomegalovirus
- HHV6
- HHV7
- HHV8/KSHV
- HIV
- LCMV, Rabies
- West Nile
- Measles, Mumps, Rubella
- Hepatitis B
- Hepatitis C
- Hepatitis E
- Papillomavirus
- Polyomaviruses (BK/JC)
- Community Acquired Respiratory Viruses
  - Adenovirus
  - Respiratory Syncytial Virus
  - Influenza
  - Parainfluenza
  - Metapneumovirus
- SARS coronavirus
- Dengue, Zika
- Parvovirus B19
- Smallpox/Vaccinia

# Monitoraggio non specifico dell'immunodeficit

## Non-specific immune monitoring

- Nutritional status? (generally ignored)
- Absence of circulating virus (BK, CMV, EBV, adenovirus) - Viremia suggests excess immunosuppression relative to host's immune system and viral burden.
- Absence of multiple or recurrent infections (HSV, VZV, pneumonia, others), infections of unusual severity (influenza, RSV), cancers.
- Cell counts (differential, T-cell subsets) – add **growth factors**?
- Antibody levels (worth considering) – replete? With which preparation?
- Immune function assays: Cannot predict risk of graft rejection with reductions.

# IPOGAMMAGLOBULINEMIA

## Hypogammaglobulinemia (HGG)

- Often missed
- Common: ~45% in all recipients, 15% severe levels (IgG 400-700 mg/dL). Up to 63% in lung recipients.
- **Decreased post-transplant IgG predictive of risk for infection**
  - Renal recipients with HGG of any class had higher incidences of overall and bacterial infection at all time points and of bacteremia and acute pyelonephritis beyond 6 months.
  - Odds are increased for respiratory infection, CMV, Aspergillus and other fungal infections for patients with IgG <400 mg/dL.
  - The odds for 1-year all-cause mortality for severe HGG was 21.91 times higher than those for IgG >400 mg/dL.
- **Severe hypogammaglobulinemia during the first year posttransplantation significantly increased the risk of CMV, fungal and respiratory infections, and was associated with higher 1-year all-cause mortality.**
- **Therapeutic trials are lacking.**

Florescu D et al. Am J Transplant 2013; 13:2601-10; Fernandez-Ruiz M et al. Am J Transplant. 2012; 12:2763-73; Yip NH et al. Am J Resp Crit Care Med. 2006;173(8):917-921.

# Immunoglobuline e Ab monoclonali

## Therapeutic Antibodies

- Polyclonocal antibodies
  - IVIG, CMV immunoglobulin
  - Useful: ganciclovir intolerant, prolonged leukopenia/neutropenia, refractory disease, hypogammaglobulinemia
- Monoclonal antibodies
  - RG7667, a combination of 2 monoclonal antibodies, 3% vs 16% in high-risk kidney transplant recipients
  - MSL-109 (Merck)

# Efficacia Ig

## Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of RG7667, a Combination Monoclonal Antibody, for Prevention of Cytomegalovirus Infection in High-Risk Kidney Transplant Recipients

Julia H. Iriburu,\* Aneta Ptasik,\* Anwesha K. Bhattacharya,\* Philippe Gatzert,\* Jacqueline M. Whitford,\* Tracy Burgess,\* Michael A. Darby,\* David R. Snydman,\* Brenda Ross,\* Becket Festerbach,\* Ashley E. Turchi,\* Maritza Mata,\* Hong Deng,\* Carlo W. Rosenberger,\* Lynn A. Gettings,\* Natalie S. Striano,\*  
X. Charlene Lian,\* Jorge A. Tarr\*  
\* denotes equal contribution

TABLE 2 Efficacy endpoints

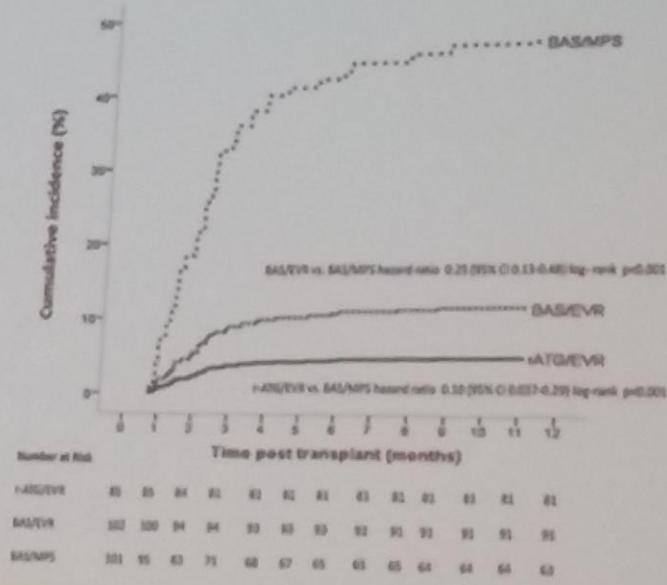
Endpoint <sup>a</sup>	Value(s) for:	
	RG7667 (n = 59)	Placebo (n = 57)
CMV viremia within 12 weeks posttransplant	27 (45.8)	35 (61.4)
n (%)	15.3 (-2.8-32.2)	
Stratum-adjusted difference, % (95% CI)	0.100	
P value		
CMV viremia within 24 weeks posttransplant	30 (50.8)	40 (70.2)
n (%)	19.3 (1.4-35.6)	
Stratum-adjusted difference, % (95% CI)	0.040	
P value		
Median time to viremia (days)	139	46
HR (95% CI)	0.53 (0.33-0.86)	
P value	0.009	
Median viral load at initial detection, copies/ml (IU/ml)	342 (311)	1051 (956)
Median peak viral load, copies/ml (IU/ml)	2,965 (2,698)	6,397 (5,821)
Receipt of preemptive anti-CMV therapy, n (%)		
Within 12 weeks posttransplant	29 <sup>b</sup> (49.2)	36 <sup>b</sup> (63.2)
Within 24 weeks posttransplant	32 (54.2)	40 (70.2)
CMV disease within 24 weeks posttransplant		
n (%)	2 (3.4)	9 (15.8)
P value	0.030	

# Citomegalovirus

## Differential Risk of CMV: *mTOR* Inhibitors

- CMV late phase-induced mTOR activation is essential for efficient virus replication in polarized human macrophages. (Poglitsch M et al. Am J Transplant. 2012 Jun;12(6):1458-68.)
- Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses (H. Tedesco-Silva et al, Am J Transplant 2015, 15, 2655-2664)
- However, data are inconsistent and may reflect strain variation (Clippinger et al, J Virol 2011,85: 9369-9376, Human Cytomegalovirus Infection Maintains mTOR Activity and Its Perinuclear Localization during Amino Acid Deprivation)

Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses



# Valutazione immunologica

How to assess *intensity of immunosuppression* relative to organ rejection and the risk for infection?  
Immune Function Assays?

- Phytohemagglutinin (PHA) as nonspecific mitogen to stimulate cell division in CD4 T-lymphocytes **regardless of their antigenic specificity or memory status**. .... The **production of intracellular ATP** is one of the first steps in cellular activation. (e.g., Immuknow Assay)
- May be a global marker of immune function and response to immunosuppression at the cellular level
- CMS: ~\$200 reimbursement in USA.
- **Is such information actionable?**

# Monitoraggio Immunologico CMV

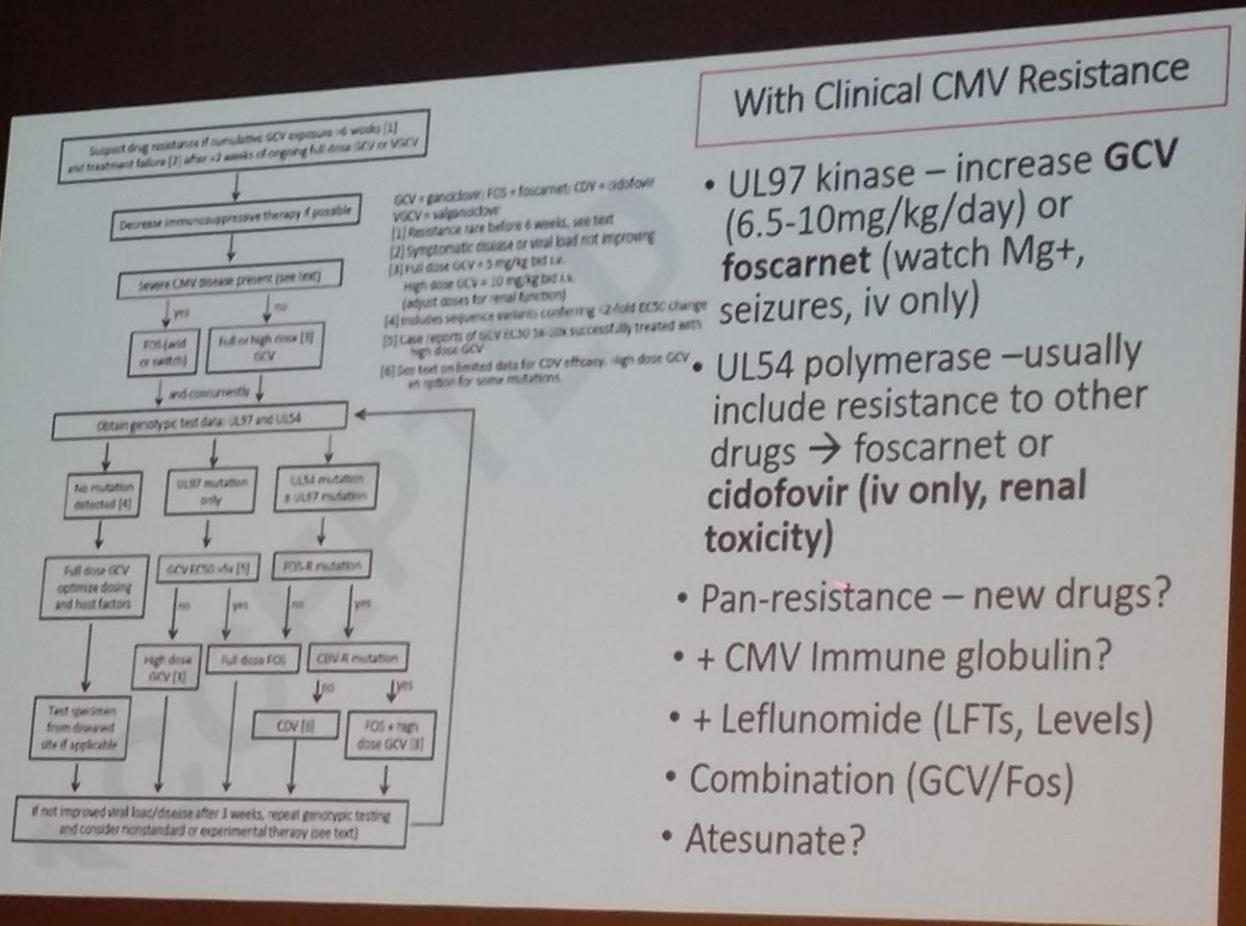
**TABLE 2.**

Advantages and limitations of various assays for immune monitoring of CMV

Assay	Advantages	Limitations	Comments	Predict viremia	Predict disease
ICS	Whole blood assay with low blood volume (1 mL) or PBMC Short incubation time Results available after 8 hours Identification of CD4+ and CD8+ T cells Knowledge of HLA not necessarily required Quantitative and qualitative characterization	Needs access to a flow cytometer Not standardized	Most data available with this technique Potential to freeze PBMCs and ship to reference lab for testing	Yes	Yes
QuantiFERON-CMV (Diagn, USA)	Whole blood assay with low blood volume (3 mL) Simple to perform Results available after 30-40 hours Can be done in any center and stimulated plasma can be sent to reference lab	CD8+ responses only Sensitive to lymphopenia Rare patients whose HLA types are not covered in assay	Approved in Europe	Yes	Yes
ELISpot	Identifies both CD4+/CD8+ T cells Knowledge of HLA not necessarily required Results available after 30-40 hours	Need for purified PBMC from 10 mL blood (in reality 5-10 mL) Cannot differentiate CD4+ and CD8+ T cells Not standardized	Potential to freeze PBMCs and ship to reference lab for testing; Commercial availability (T-Track CMV, Lophius CE marked in Europe; T-SPOT.CMV is LDT in U.S.)	Yes	Yes
MHC multimer staining	Fast assay (1-2 h) Whole blood assay with low blood volume (0.5-1 mL) or PBMC	CD8+ responses only Needs access to a flow cytometer HLA and epitope-specific; No information about function unless combined with ICS Not standardized	Unlikely to be used on a widespread basis	No, Only in combination with functional or phenotypical markers	No

2018 – CMV Guidelines  
(Transplantation, in press)

# CMV resistenza



## With Clinical CMV Resistance

- **UL97 kinase** – increase **GCV** (6.5-10mg/kg/day) or **foscarnet** (watch Mg+, seizures, iv only)
- **UL54 polymerase** – usually include resistance to other drugs → foscarnet or **cidofovir** (iv only, renal toxicity)
- Pan-resistance – new drugs?
- + CMV Immune globulin?
- + Leflunomide (LFTs, Levels)
- Combination (GCV/Fos)
- Atesunate?

# Nuovi farmaci per CMV

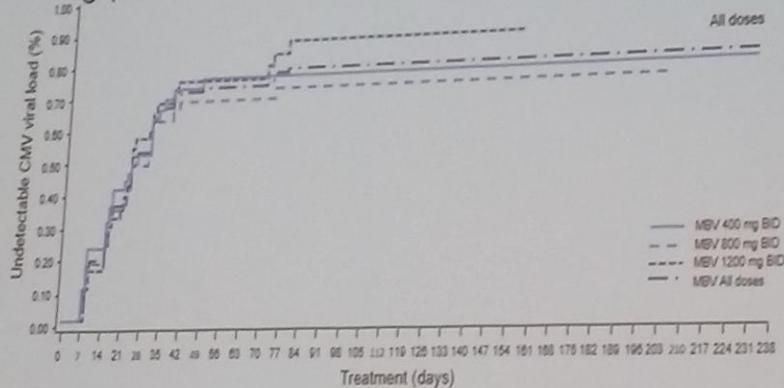
## CMV Newer Options – the basics

- Maribavir (UL97 – viral maturation and egress) – failed prophylaxis study in SOT (wrong dose?)
  - Does not cover HSV/VZV
  - Mixed results in therapy
  - Failed in liver SOT and HSCT Prophylaxis (but low dose)
  - Effective in small trials at higher doses but relapse occurred ~37%
  - Unique resistance mutations in UL97 (not cross reactive with GCV)
- Letermovir (viral terminase) UL56, oral and intravenous (studied in HSCT)
  - Prophylaxis only trials
  - Does not cover HSV/VZV
  - Easy resistance in vitro
  - Activity for treatment is unknown
- CMX001 (Brincidofovir) lipid cidofovir prodrug (oral only), covers herpesviruses
  - GI toxicity
  - Iv under development
  - Expected UL54 mutations (like cidofovir)

# Maribavir per CMV

## Maribavir R/R Phase II Trial: Time to Undetectable Plasma CMV DNA

- Median estimated time to confirmed undetectable plasma CMV DNA at any time (days [95% CI]) were similar: 24 (15, 31), 28 (15, 38), 22 (19, 30), and 23 (21, 29) for MBV 400 mg, 800 mg, 1200 mg (BID), and MBV all doses, respectively



Slide courtesy of M. Pereira, presented at The Joint Annual Congress of the American Society of Transplant Surgeons and The American Society of Transplantation Wednesday May 3, 2017 ClinicalTrials.gov Identifier: NCT01611974

# Adenovirus

## Adenovirus Diagnosis: PCR in SOT

- Adenoviremia may occur frequently after solid organ transplantation
  - 8.3% Liver
  - 6.5% Kidney
  - 6.7% Heart
  - 22.5% Lung
  - Associated with few to no symptoms
  - Recovery without sequelae
  - 5% with subsequent rejection

Humar et al. *Am J Transplant.* 2005;10:312-319.

Humar et al. *J Heart Lung Transplant.* 2006;25:1441-1446.

# Adenovirus: antivirali

## Management: Available Agents

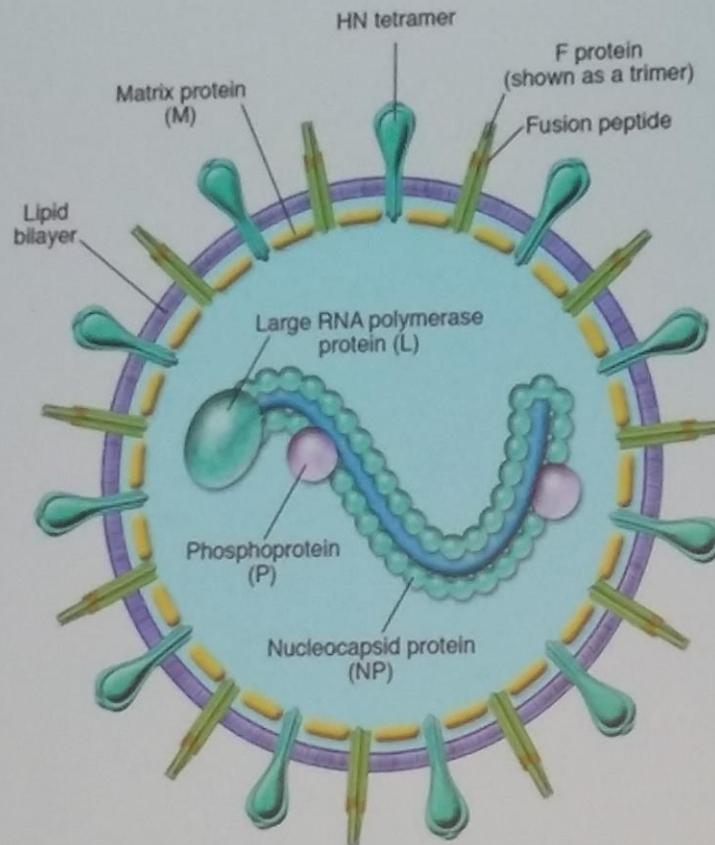
Compound	FDA Status	IC <sub>50</sub> *	Achievable Concentration
Ribavirin	Approved	3 - >250 µg/mL	10.75-18 µg/L
Cidofovir	Approved	8.5 - 100 µM	7.3-19.6 µg/mL
Lipid Esters of Cidofovir	Investigational	0.5 - 2.0 µM	
MMF	Approved		3.7-24.1 µg/mL
Ganciclovir	Approved	4.5 - 33 µM	5.5-9 µg/mL
ddC	Approved	0.05 - 0.83µM	7.6-25.2 ng/mL
Vidarabine	Approved	50 - 200 µg/mL	

\*Cell line and virus type dependent. Acyclovir & foscarnet are not active.

**Courtesy of Michael Ison who tried to teach me !**

# PIV: virus parainfluenzali

## PIV in Transplantation



# HUMAN POLYOMA VIRUS

## Human Polyomavirus Infections in Immunocompromized Hosts

Hans H Hirsch

Transplantation & Clinical Virology  
Department Biomedicine (Haus Petersplatz)

Infectious Diseases & Hospital Epidemiology  
University Hospital Basel  
Basel  
Switzerland



# HUMAN POLYOMA VIRUS

## Discovery of Human Polyomaviruses

1953

MPyV



*Poly-* = multiple  
*-oma* = tumors

1960

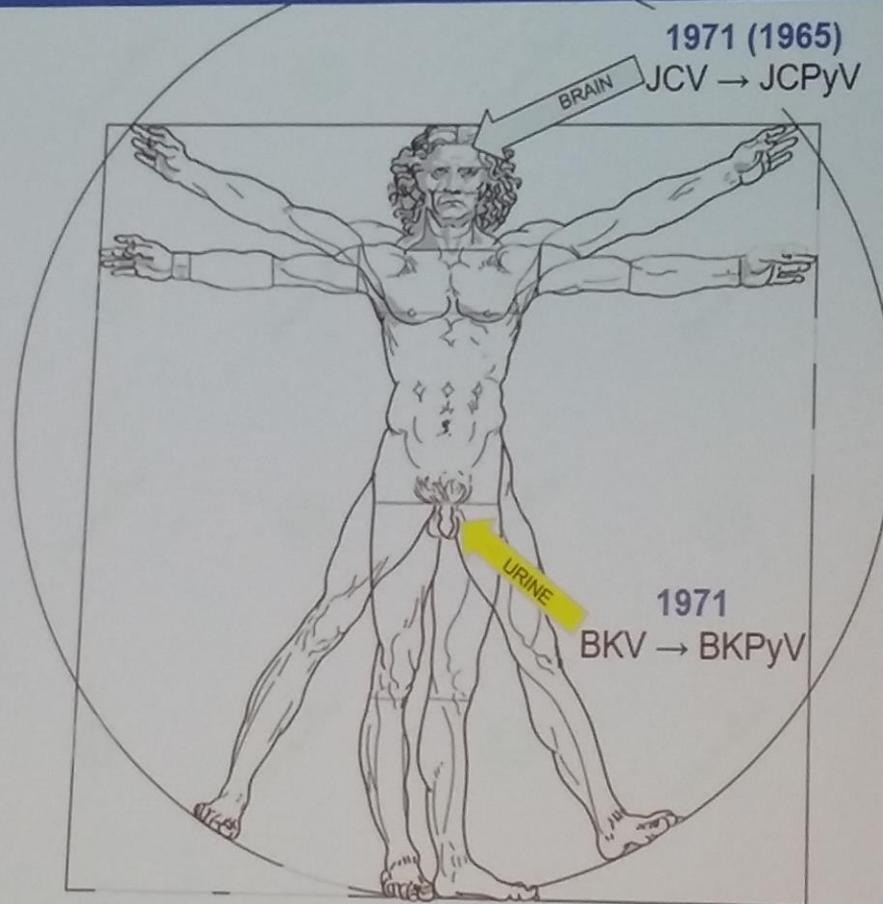
SV40



1971 (1965)

JCV → JCPyV

BRAIN



1971

BKV → BKPyV

URINE

# HUMAN POLYOMA VIRUS

## Discovery of Human Polyomaviruses

1953

MPyV



Poly- = multiple  
-oma = tumors

1960

SV40



2018

*Ailuroopoda melanoleuca*

2010 (1999)

TSPyV

1971 (1965)

JCV → JCPyV

2014  
NJPyV



2010

HPyV6

HPyV7

2011

HPyV9

2012 2013

MWPyV\_STLPyV

HPyV12

BRAIN

SKIN

RESPIRATORY

SKIN

BLOOD

URINE

STOOL  
GI-TRACT

2007  
KIPyV

WUPyV

2008

MCPyV

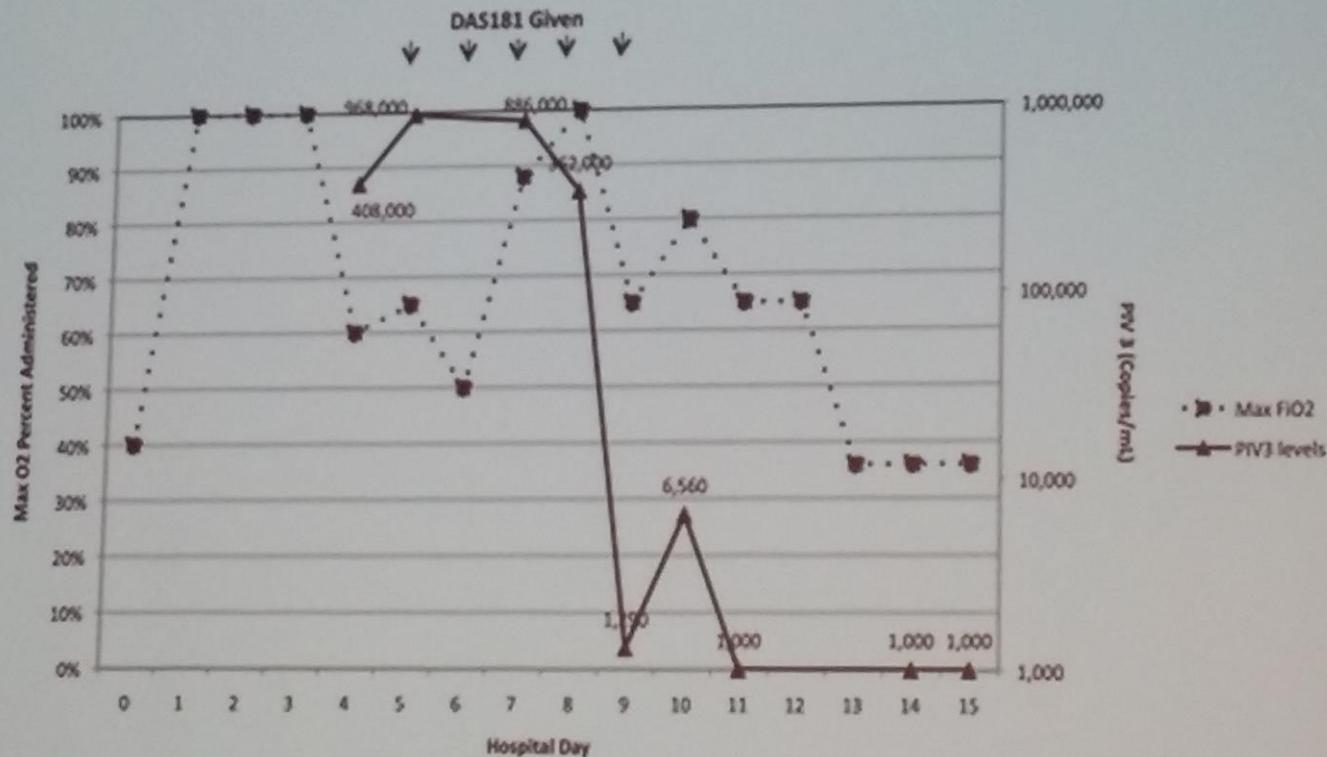
1971

BKV → BKPyV

# PIV: virus parainfluenzali

## PIV: New Treatment Options

- DAS181
  - Sialidase that cleaves the receptor for the virus off cell surface
  - Inhaled or nebulized formulations



# HEV: epatite E

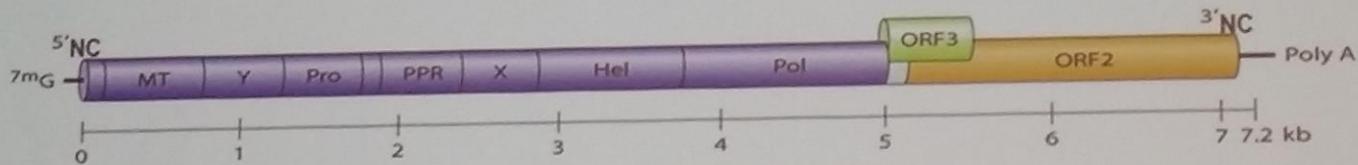
## Hepatitis E virus (HEV)



non-A non-B hepatitis  
with enteric transmission  
Khuroo, Am J Med 1980



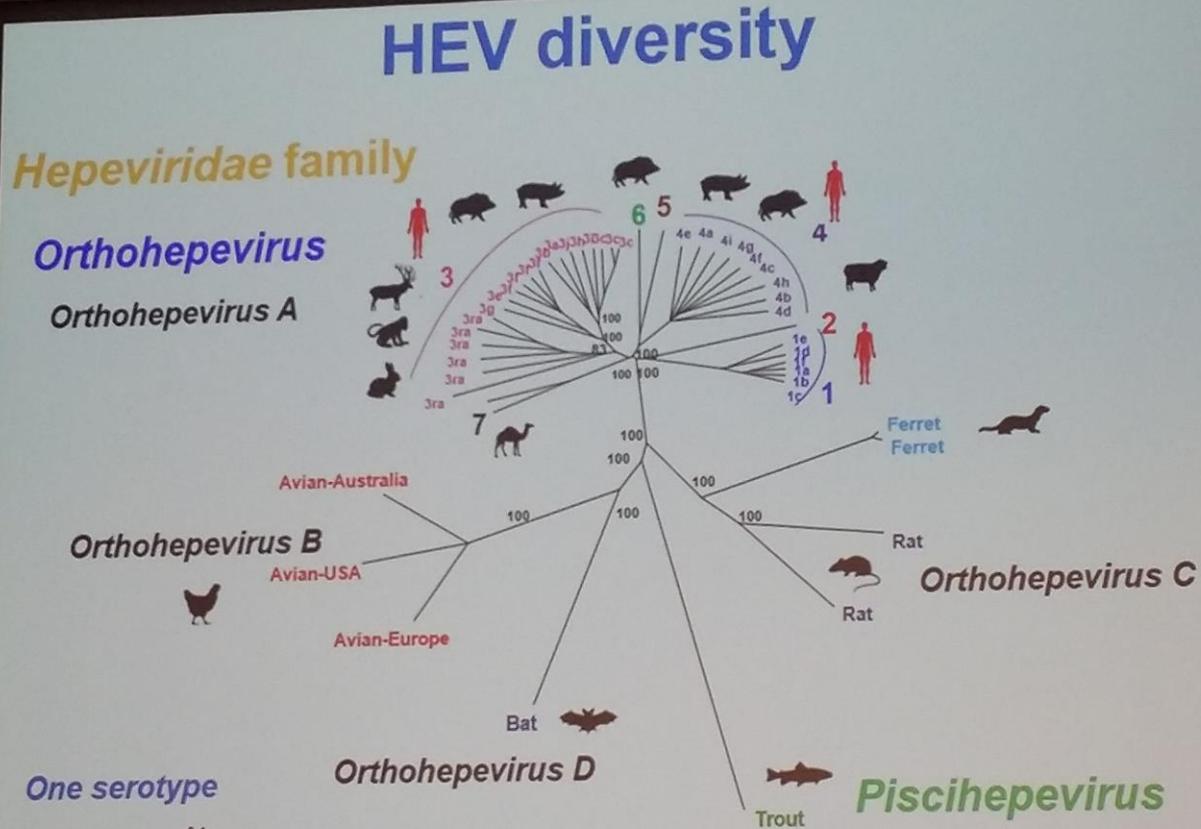
Unenveloped virus with  
icosahedric capsid  
Balayan, Intervirology 1983



Positive sense, single strand RNA

Reyes, Science 1990; Tam, Virology 1991

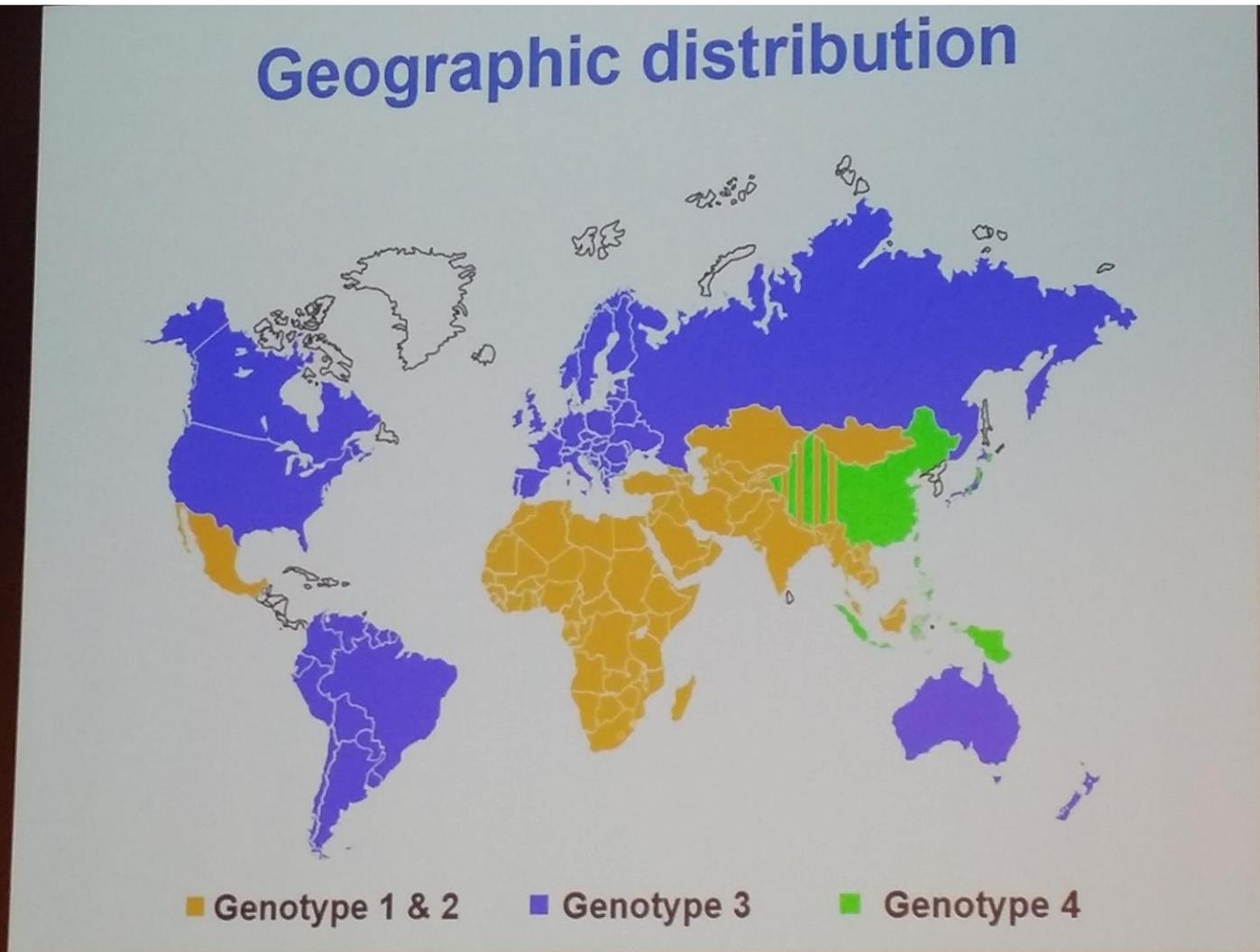
# HEV



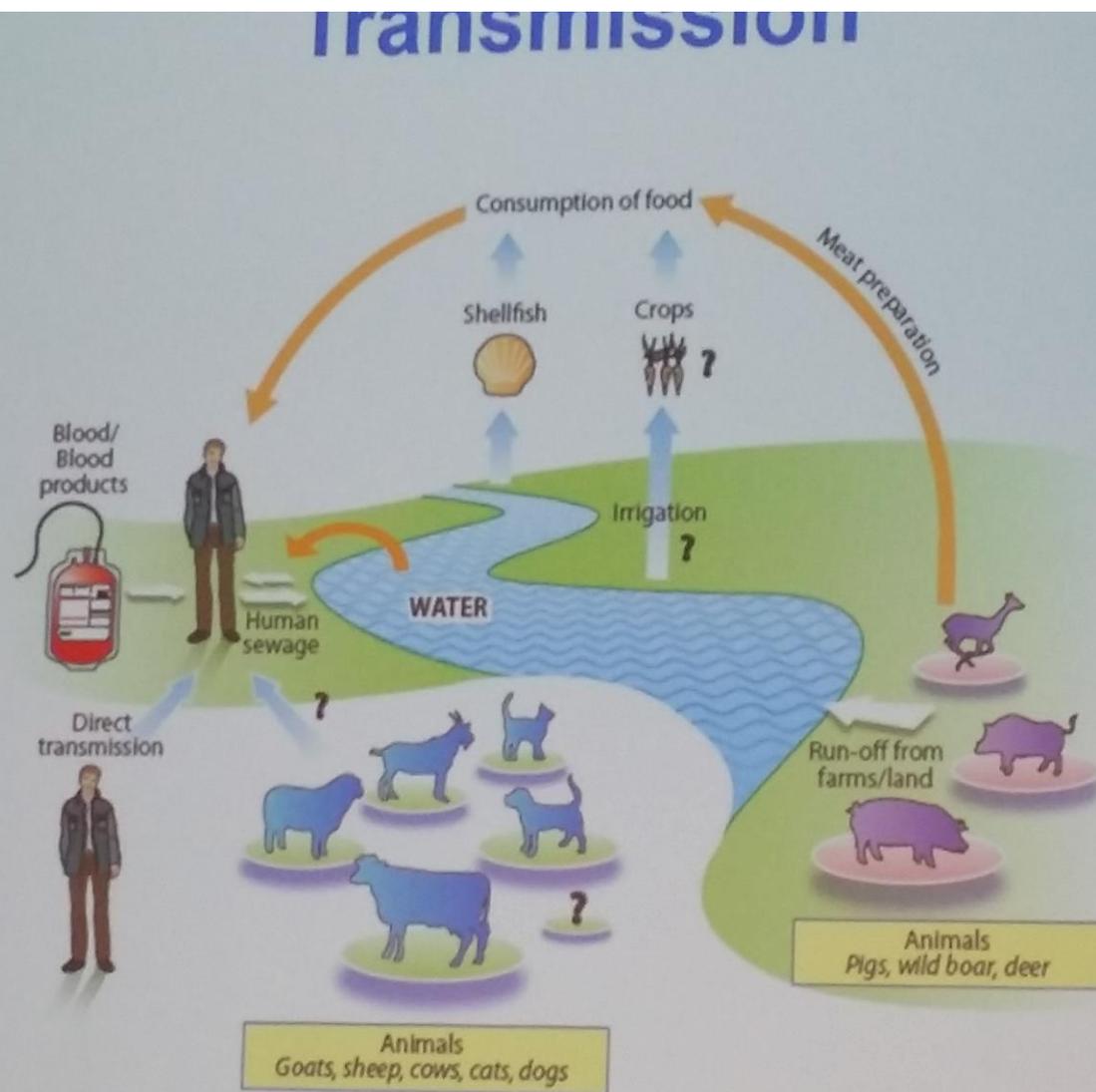
Abravanel et al, Emerg Infect Dis 2009; Izopet et al, Emerg Infect Dis 2012;

Smith et al, J Gen Virol 2014 ; Smith et al, J Gen Virol 2016

# HEV :distribuzione geografica



# Trasmissione HEV



# HEV : contagio trasfusionale

## Transfusion transmitted HEV infection

### ✓ Described in Asia and Europe

- **Japan** : Matsubayashi, Transfusion 2004 & 2008 ; Tamura, Hepatol Res 2007
- **UK** : Boxall, Transfus Med 2006 ; Hewitt, Lancet 2014
- **France** : Colson, Emerg Infect Dis 2007 ; Haim-Boukobza, J Hepatol 2012 ;  
Coilly, Transplantation 2013 ; Hauser, Blood 2014 ;  
Mallet, Ann Intern Med 2016 ; Loyrion, Emerg Infect Dis 2017
- **Germany** : Bettinger, Ann Hematol 2015
- **Spain** : Riveiro-Barciela, Transfusion 2017

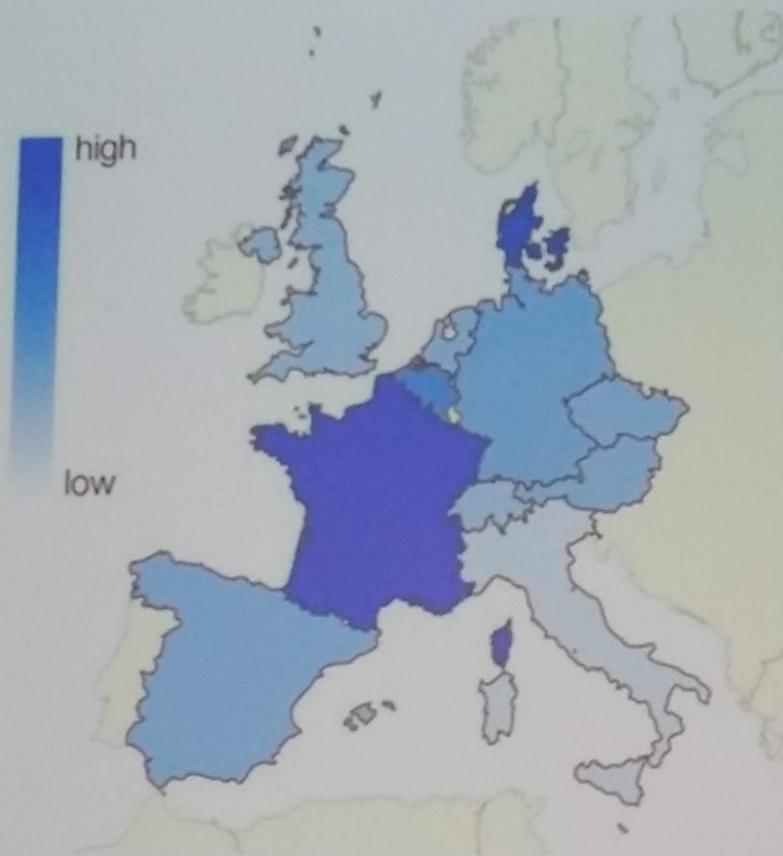
### ✓ HEV detected in plasma pools : 0.7 % - 10 % Ijaz, Vox Sang 2011 ; Baylis, Vox Sang 2011

### ✓ Not the main source of infection

Lhomme, Emerg Infect Dis 2017 ; Tedder, Transfusion 2017

# Prevalenza in Europa di HEV

## Prevalence of anti-HEV IgG



Hartl, Viruses, 2016

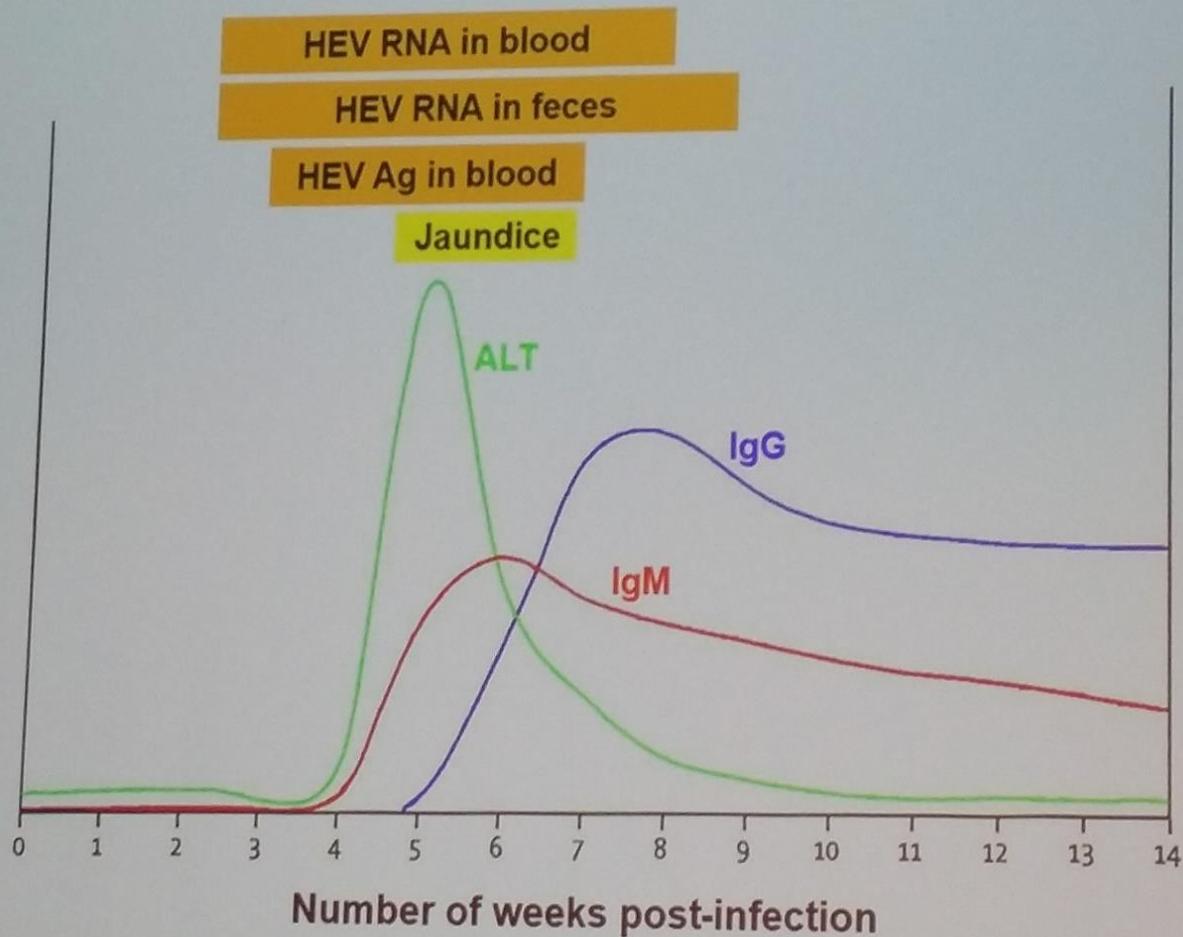
# HEV: fattori legati alla trasmissione

## Factors associated with anti-HEV IgG

Parameter	Multivariate analysis		
	p	OR	CI95%
Age > 45y	< 0.0001	2.51	[2.23-2.51]
Region	< 0.0001	2.28	[2.01-2.59]
Liver sausage	< 0.001	1.30	[1.13-1.50]
Figatellu	< 0.001	1.72	[1.48-1.99]
Game	< 0.01	1.20	[1.05-1.38]
Offal	< 0.0001	1.38	[1.22-1.57]
Bottled water	< 0.01	0.76	[0.61-0.93]

# Infezione acuta da HEV

## Diagnosis of acute HEV infection



# Fattori associati a cronicità negli HEV

## Factors associated to chronicity in solid organ transplant recipients

- ✓ Low platelet counts & use of tacrolimus vs cyclosporine  
Kamar, Gastroenterology 2011
- ✓ Low anti-HEV T cell response  
Suneetha, Hepatology 2011- Abravanel, J infect 2016
- ✓ High genetic heterogeneity of HEV' quasispecies  
Lhomme, J Virol 2012
- ✓ HEV Ag concentrations are higher in chronically infected patients in comparison with acutely infected patients  
Behrendt, J Infect Dis 2016
- ✓ No influence of HEV RNA concentration at the acute phase  
Kamar, Gastroenterology 2011

# HEV nei trapianti

## In solid organ transplant recipients

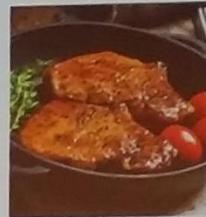
- ✓ Low platelet counts & use of tacrolimus vs cyclosporine  
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- ✓ Low anti-HEV T cell response  
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Behrendt, J Infect Dis 2016
- ✓ No influence of HEV RNA concentration at the acute phase  
Kamar, Gastroenterology 2011

# Prevenzione HEV

## Preventing HEV infection

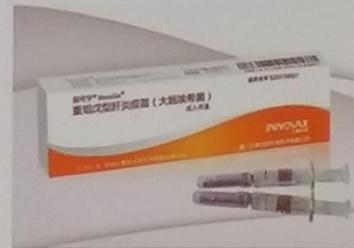
- Cook thoroughly meat at risk ( $>70^{\circ}\text{C}$  at least 2 min)

Johne, *Appl Environ Microbiol.* 2016



- Vaccine available in China

Zhang, *New Engl J Med* 2015



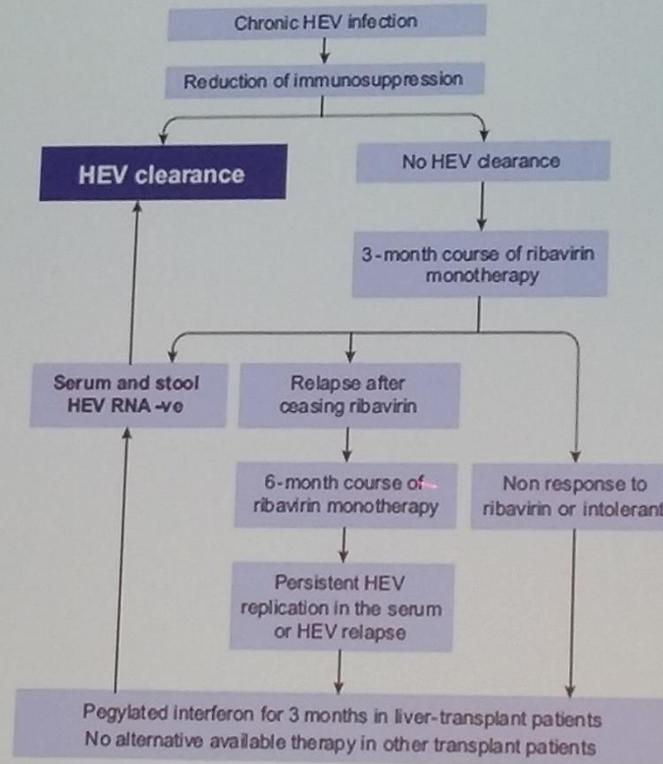
# Ribavirina o Sofosbuvir: fattori predittivi di guarigione

## Predictive factors of sustained virological response

- ✓ No influence of ribavirin trough level at day 7 or month 2
- ✓ Influence of early viral response on sustained viral response  
→  $\geq 0.5 \log \text{ c/ml}$  at day 7  
Kamar, Transplantation 2015
- ✓ Detection of HEV RNA in the stools after 3 months predicts relapse  
Abravanel, Clin Infect Dis 2014
- ✓ No influence of the 1634R mutation on ribavirin treatment outcome  
Lhomme, Antimicrob Agents Chemother 2016

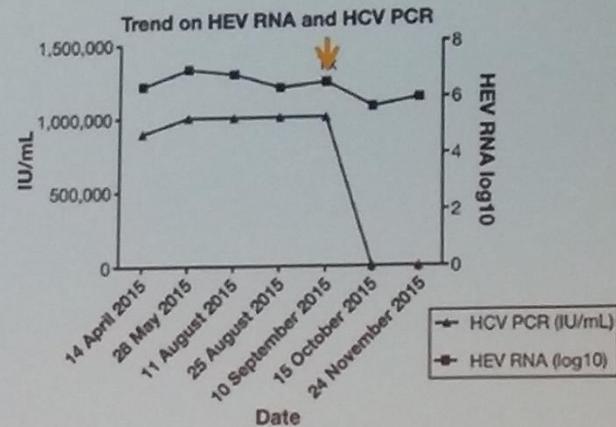
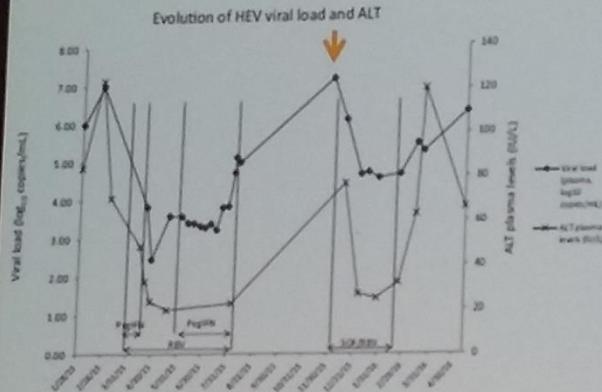
# HEV: management

## Management of chronic HEV infection

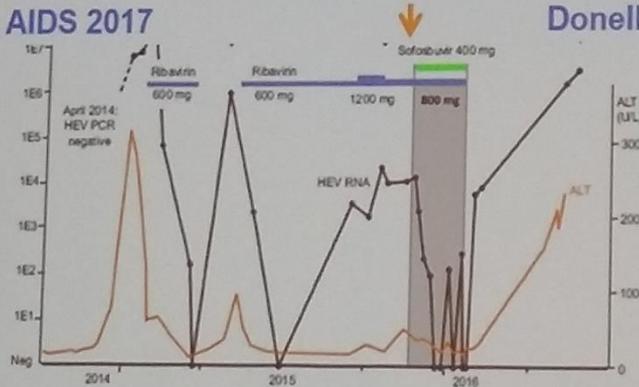


# Sofosbuvir in HEV

## Sofosbuvir shows antiviral activity but is not fully efficient



Todesco, AIDS 2017



Donelli, Gastroenterology 2017

Van der Valk, J Hepatol 2017

# HEV: sommario

## Summary

- ✓ The true burden of HEV infection and disease worldwide is still underestimated
- ✓ There is a better knowledge on the clinical spectrum :
  - extra-hepatic manifestations
  - chronic hepatitis in immunocompromised patients
- ✓ Ribavirin treatment and HEV vaccine are major breakthrough for the management of infection
- ✓ Management of failure to ribavirin therapy needs further research
- ✓ Cell culture systems and animal models will be helpful for future scientific advances

# Virus sinciziale respiratorio

## Epidemiology of RSV

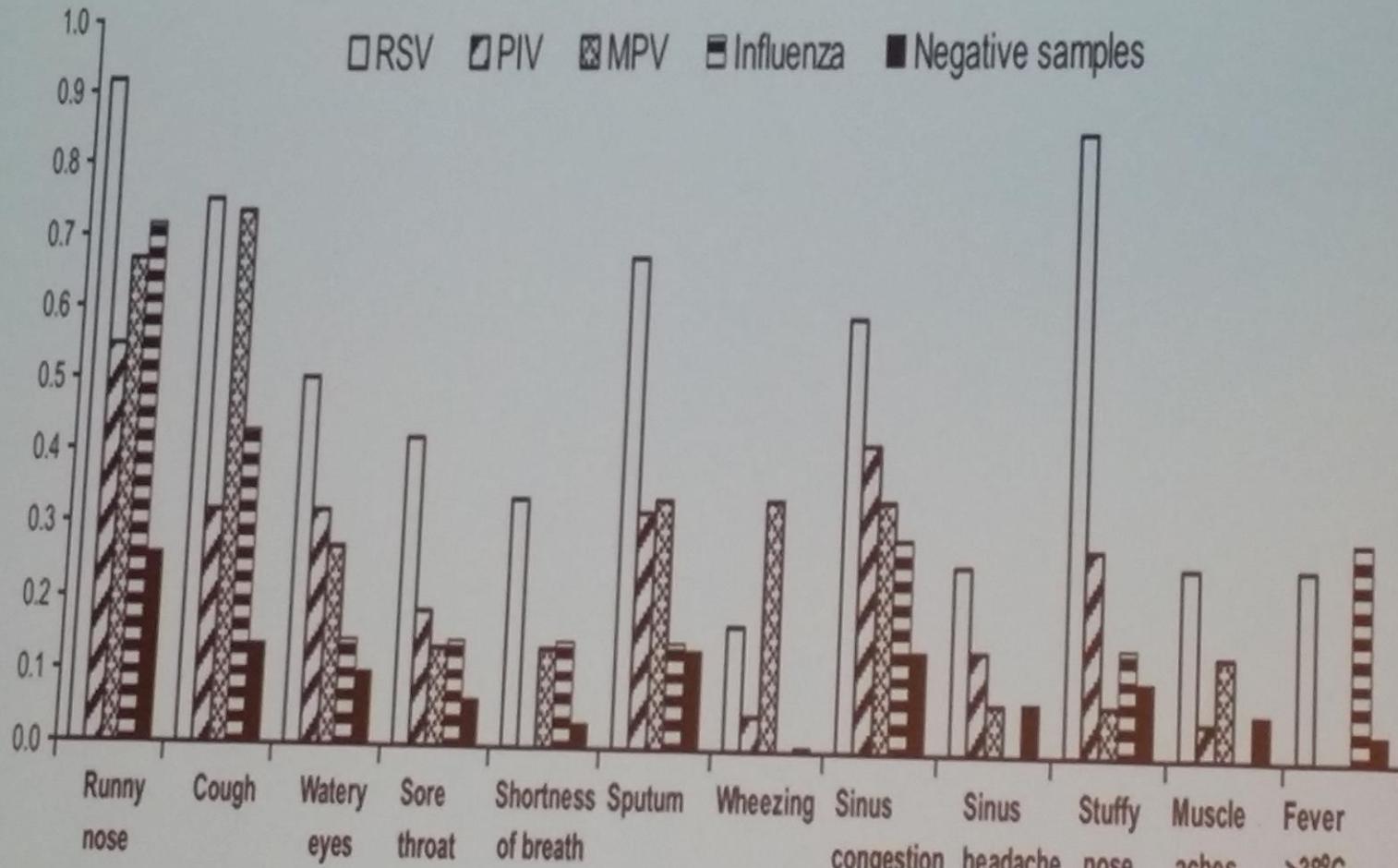
- Virus types and timing are similar to what you would expect in the general population



# RVIs: virus sinciziale respiratorio

## Epidemiology of RVIs

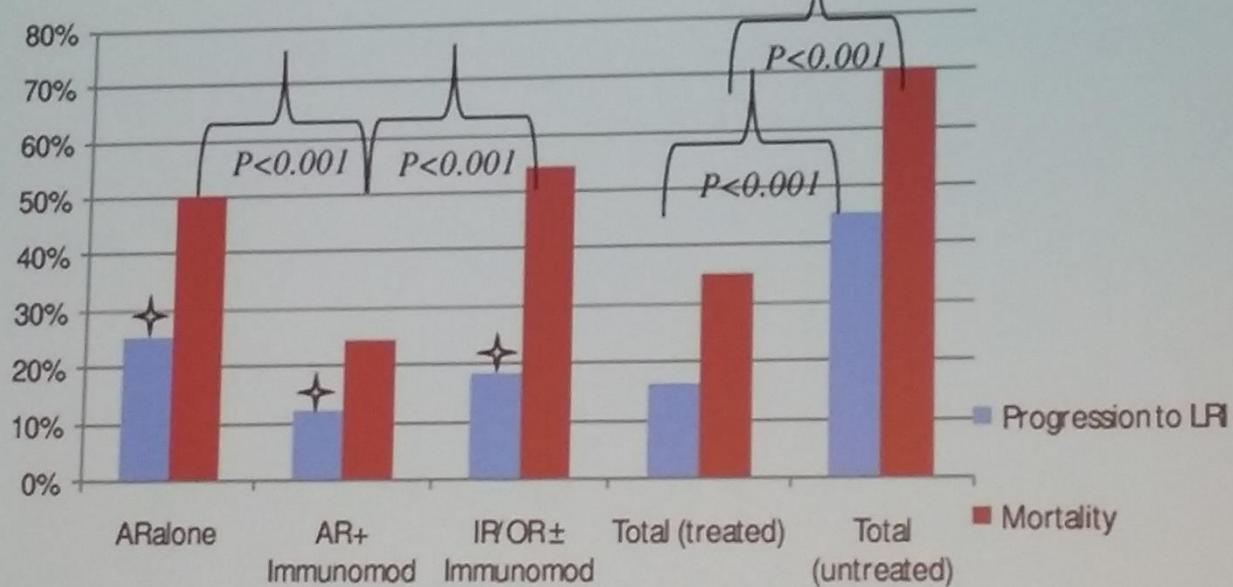
- Symptoms: Few at presentation and resolve quickly



# RSV : terapia con immunomod

## RSV in Hematopoietic Stem Cell Transplantation

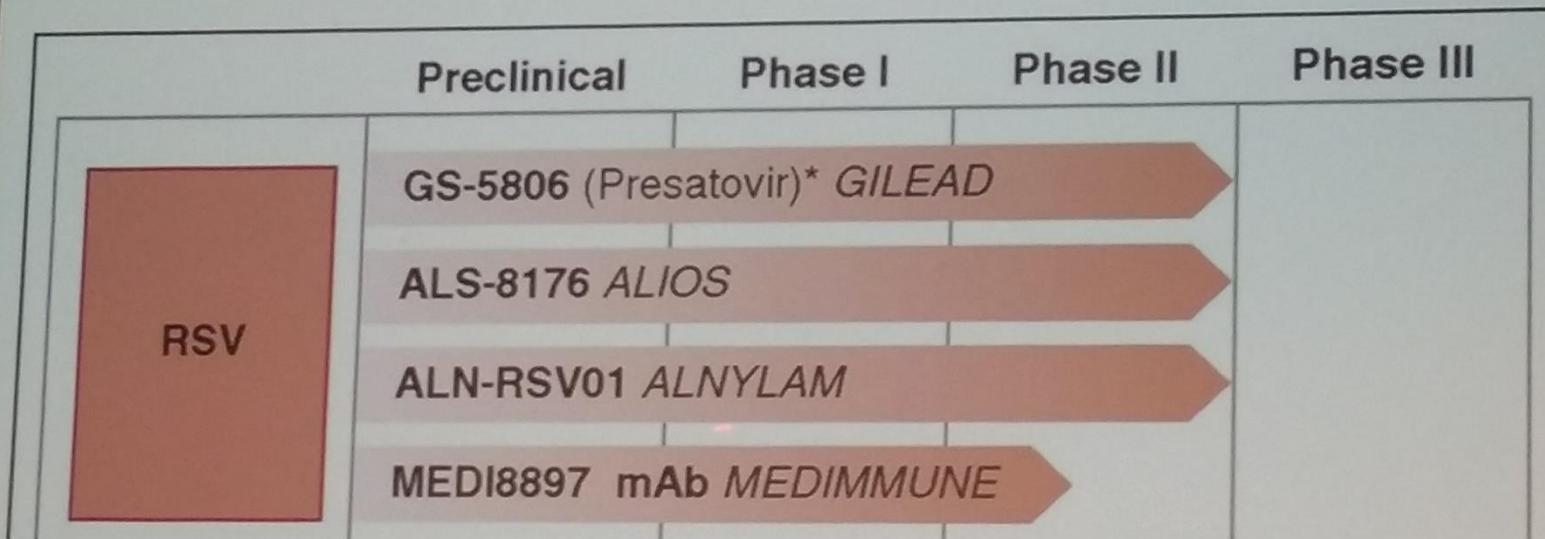
Figure: Summary of outcome data by type of regimen received



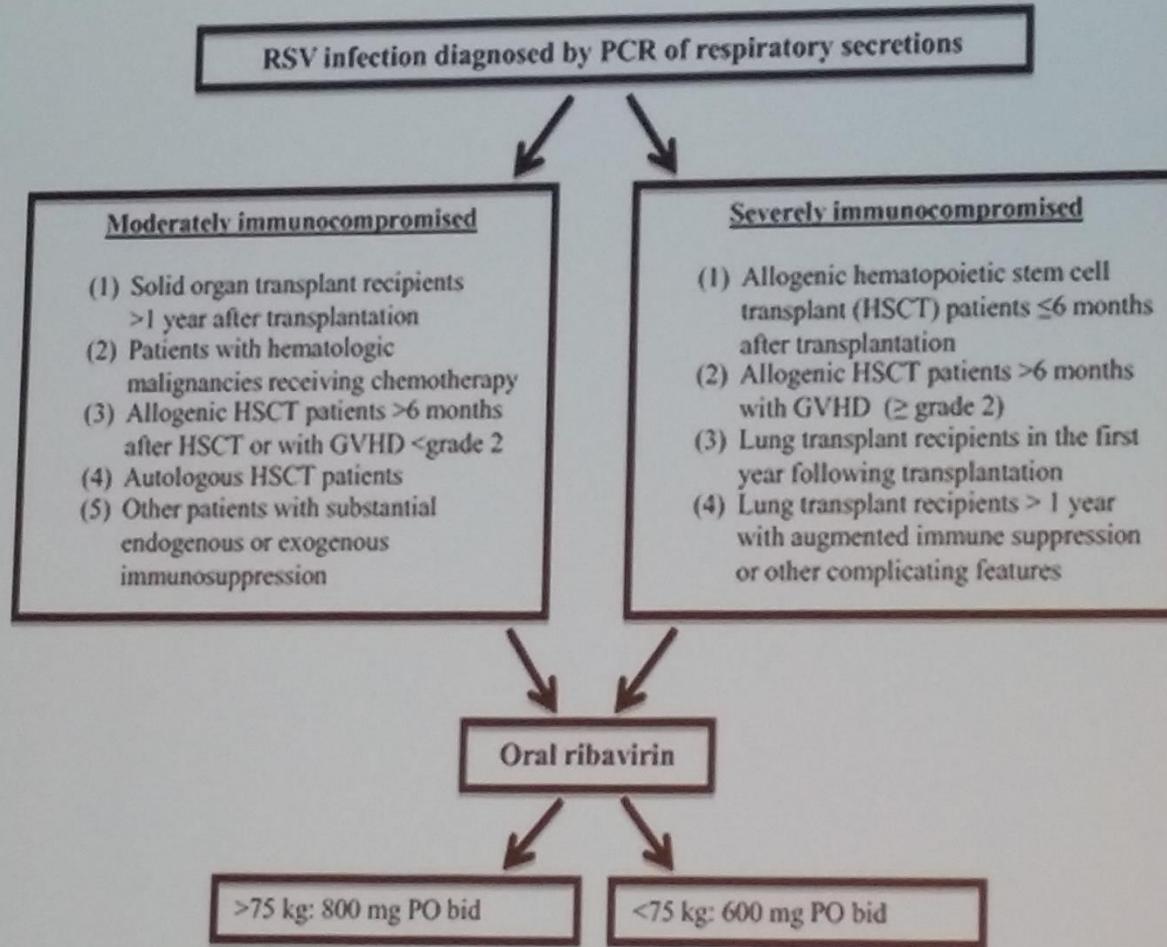
✦ For progression to LRI: ARalone vs. ARplus immunomodulators or IR or OR with or without immunomodulators;  $P=0.13$

# RSV: altre terapie sperimentali

## Treatment of RSV: *Experimental Approaches*



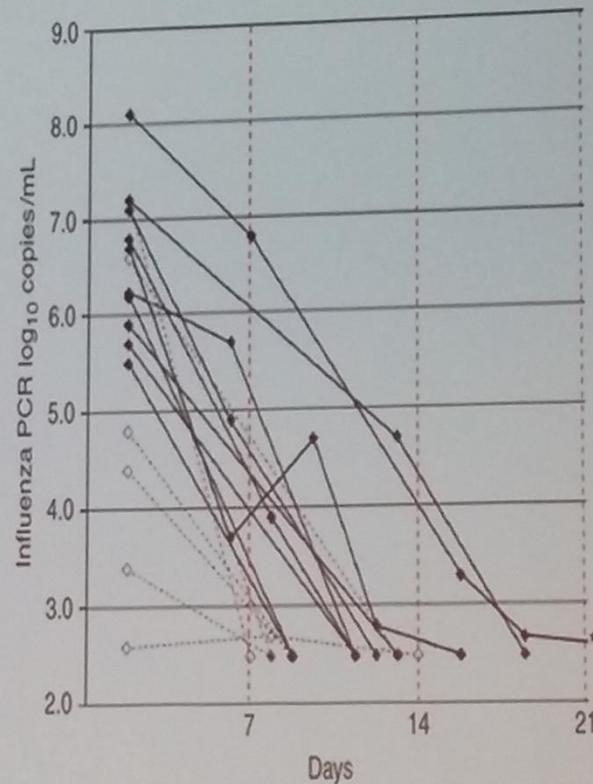
# Virus Sinciziale respiratorio - RSV



# Virus Influenzale : terapia in trapiantati

## Treatment of Influenza

- Antiviral Therapy and Outcomes
  - No prospectively collected data
  - Most data with NAIs > M2 Inhibitors
  - Reduced mortality
    - M2 Inhibitors: 60% vs. 70%
    - NAI: Few deaths reported with use
  - Reduced viral shedding at day 10
    - M2 Inhibitors 20% vs. 50%
  - Lower rate of pneumonia
    - M2 inhibitors: 11% vs. 21%
    - NAI: 0-5% vs. 21%
  - Reduced risk of BOS
  - Risk of resistance emergence



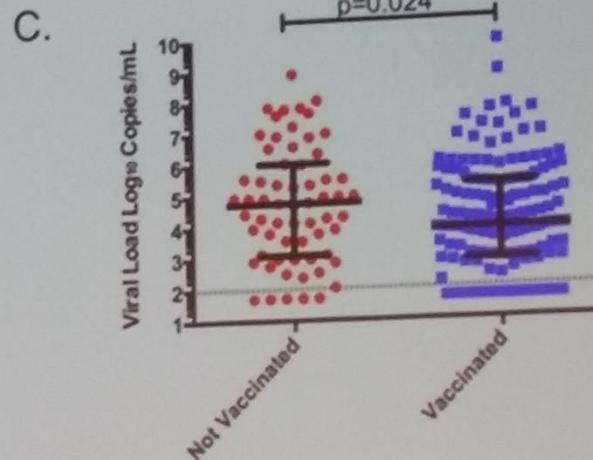
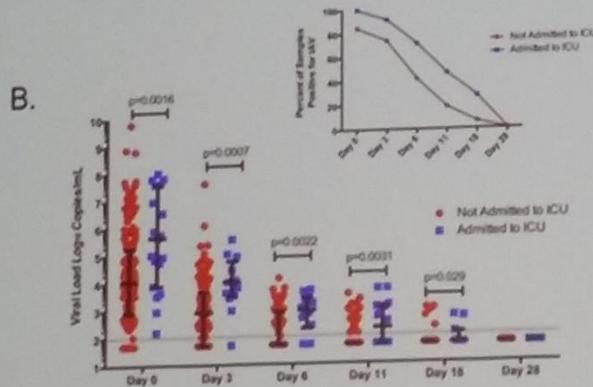
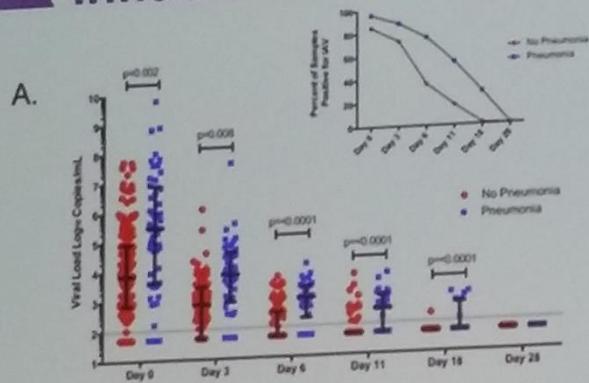
Ison MG. *Antiviral Therapy*. 2007; 12:627-638.

Ison MG et al. *J Heart Lung Transplant*. 2008; 27: 282-288.

Khanna et al. *Transpl Infect Dis*. 2009; 11:100-105.

# Trattamento virus influenzale

## Influenza: Virology in Setting of Treatment



# Influenza: durata terapia

## Treatment of Influenza: *Unanswered Questions*

- Optimal Duration of Antiviral Therapy
  - Patients have prolonged shedding
  - Premature interruption of therapy could result in resistance and clinical decline
  - Many experts recommend a duration > 5 days
    - Many recommend that duration is guided by duration of shedding
- Optimal Dose of Therapy
  - Studies have failed to document improved outcome with high dose oseltamivir
  - 2 of the 3 studies demonstrated a lower rate of resistance with the higher dose
- Role of IV Therapy, Antibodies and Combination
- Management of Resistant Influenza

# Opzioni terapeutiche future per il virus influenzale nei trapiantati

## Future Options for Treatment

### • Polymerase Inhibitors

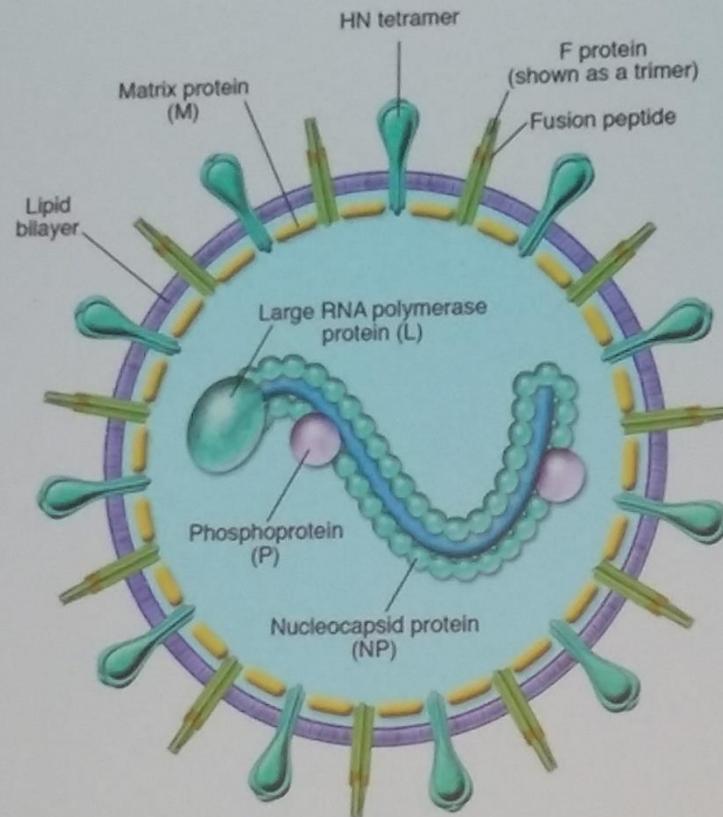
Feature	Favipiravir (T-705)	Pimodivir (JNJ-63623872)	Baloxavir (S-033188)
Target	PB1	PB2	PA
Spectrum	A, B, C	A Only	A and B
M2 and NAI Resistant	Yes	Yes	Yes
Synergy with NAI	Yes	Yes	Yes
Route of Dosing	Oral (IV)	Oral (IV)	Oral
Resistant Variants	None to Date	Yes	Yes
Status	Limited Approval in Japan, Investigational ROW	Phase 2 Ambulatory and Hospitalized Done	Ambulatory Phase 2 Done
Reduction in VL	Modest	> Than NAI	Great (3.5 log reduction)

### • Other Therapies

- Monoclonal Antibodies, Immunoglobulin, Plasma
- Arbidol

# PIV: polyoma virus

## PIV in Transplantation



# HPV

## Human Polyomavirus Infections in Immunocompromized Hosts

Hans H Hirsch

Transplantation & Clinical Virology  
Department Biomedicine (Haus Petersplatz)

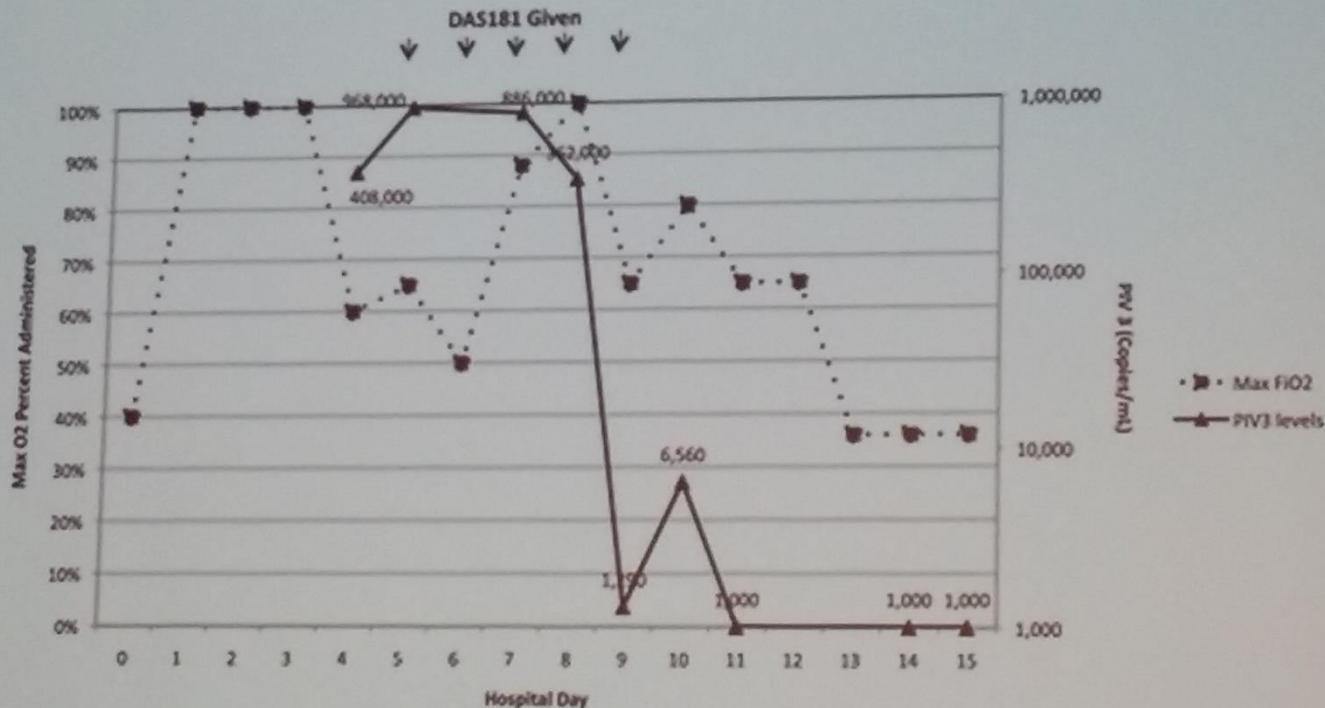
Infectious Diseases & Hospital Epidemiology  
University Hospital Basel  
Basel  
Switzerland



# Trattamento PIV

## PIV: New Treatment Options

- DAS181
  - Sialidase that cleaves the receptor for the virus off cell surface
  - Inhaled or nebulized formulations



# HPV : localizzazioni

## Discovery of Human Polyomaviruses

1953  
MPyV

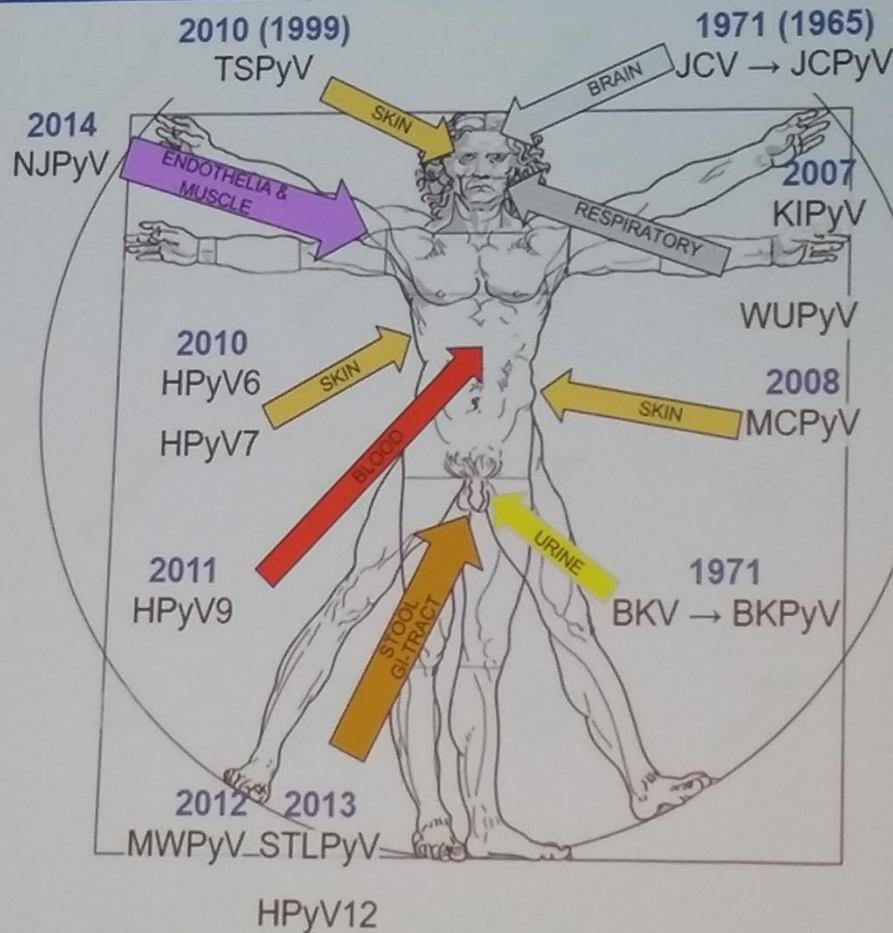


*Poly-* = multiple  
*-oma* = tumors

1960  
SV40



2018  
*Ailuropoda melanoleuca*



# Polyioma virus

## Human Polyomavirus Infections in Immunocompromized Hosts

Hans H Hirsch

Transplantation & Clinical Virology  
Department Biomedicine (Haus Petersplatz)

Infectious Diseases & Hospital Epidemiology  
University Hospital Basel  
Basel  
Switzerland



# Caarcinoma di MERKEL

## Merkel cell carcinoma treatment and prognosis

**Table 1.** Prognosis and treatment for Merkel cell carcinoma (MCC) according to American Joint Committee on Cancer (AJCC) stage (based on references 57, 61–63)

AJCC stage	Prognosis		Treatment				
	OS 2 years*	OS 5 years**	Wide local excision (2 cm)	Lymph node dissection	Radiotherapy (tumoral site)	Radiotherapy (lymph node site)	Chemotherapy
Size < 2 cm (stage I)	67%	81%	+	–	+	–	–
Size > 2 cm (stage II)	59%	67%	+	–	+	±	–
Nodal disease (stage III)	49%	52%	+	+	+	+	–
Systemic metastases (stage IV)	23%	11%	±	±	±	±	+

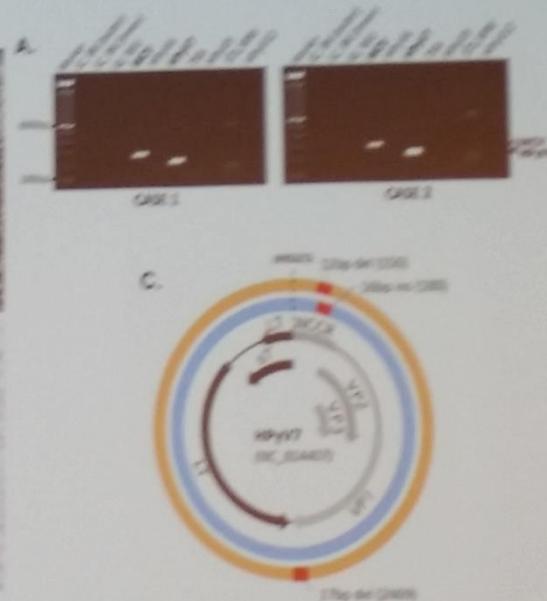
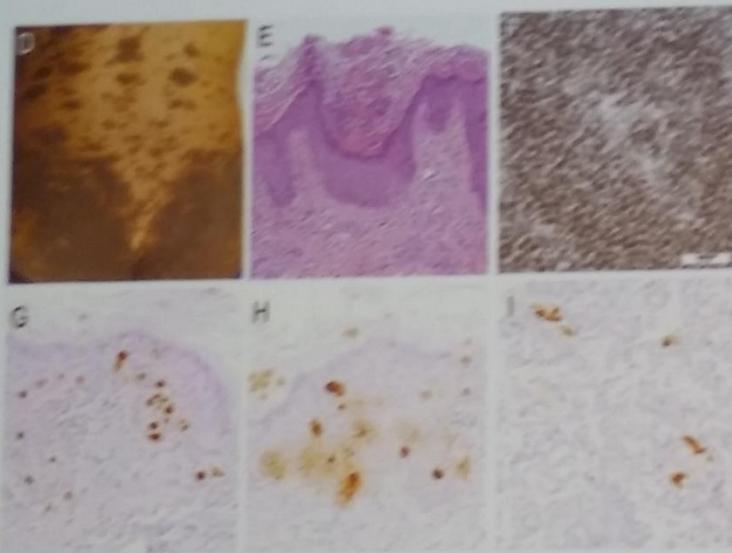
\*Overall survival at 2 years.

\*\*Overall survival at 5 years.

# HPyV.7

## HPyV-7

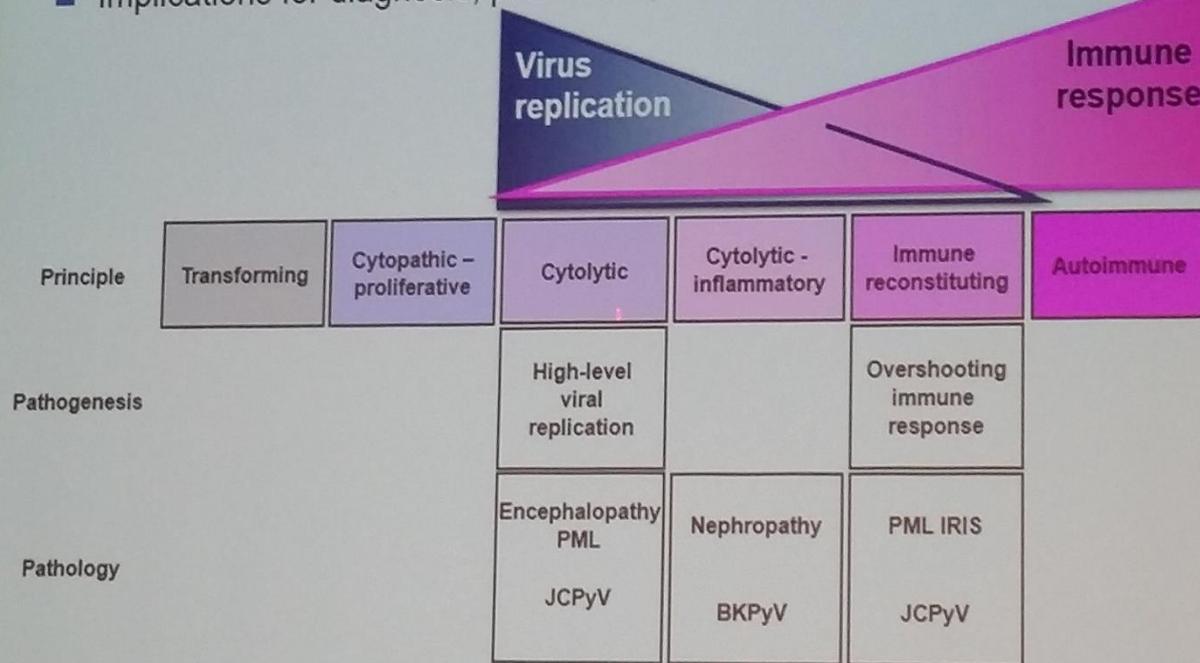
- Lung transplant recipients with brownish-velvety, pruritic plaques
- IHC for SV40 LTag, weakly for HPyV7-VP1, EM particles, DNemia
- Rolling circle and specific NAT reveal HPyV-7 and MCPyV
  - HPyV7 with rearranged NCCRs



# Polyomavirus-pathologia

## Principle Patterns of Polyomavirus Pathology

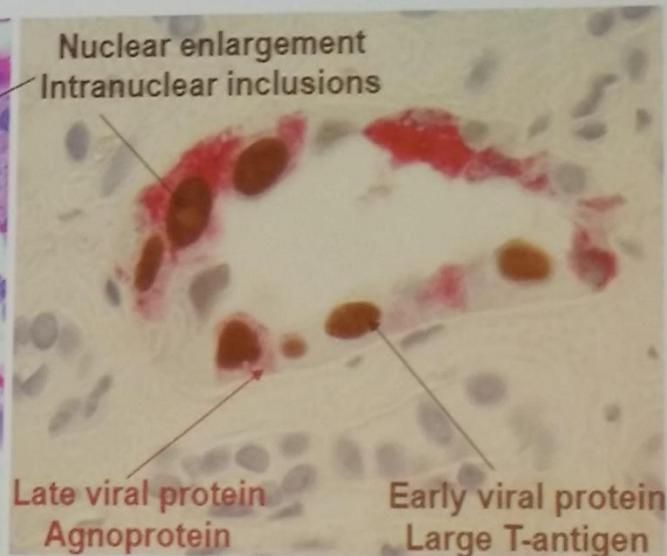
- Replicative and non-replicative pathology in different immunity settings
- Implications for diagnosis, prevention, treatment and outcome?



# Polyiomavirus

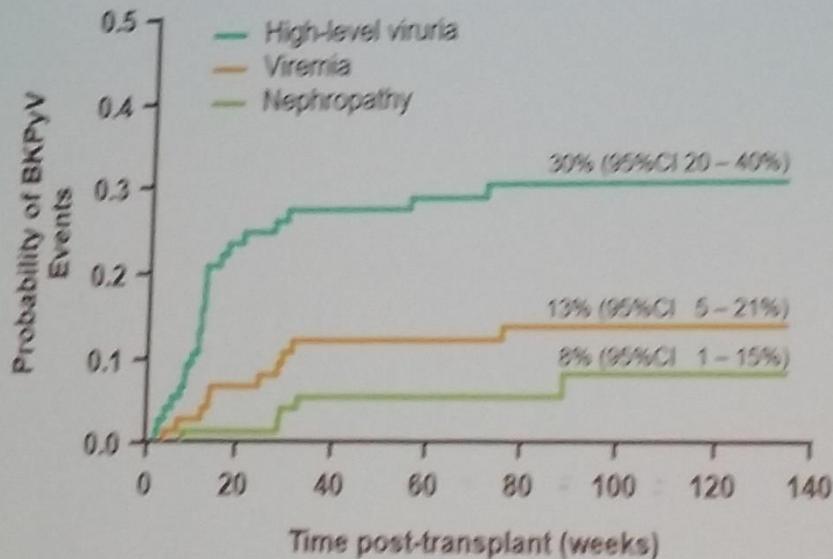
## What is BK Polyomavirus-associated Nephropathy ?

- Proven disease occurring in 5% of kidney transplants (range 1% - 15%)
  - Cytopathically altered renal tubular epithelial cells, cell lysis (necrosis), denudation
  - Secondary inflammation
  - Functional deficits in ~90%, progressive deterioration, graft loss in ~50%



# BK Polyiomavirus in trapiantati di rene

## BK Viruria and Viremia precede Nephropathy in Kidney Transplant Recipients



Decoy Cells



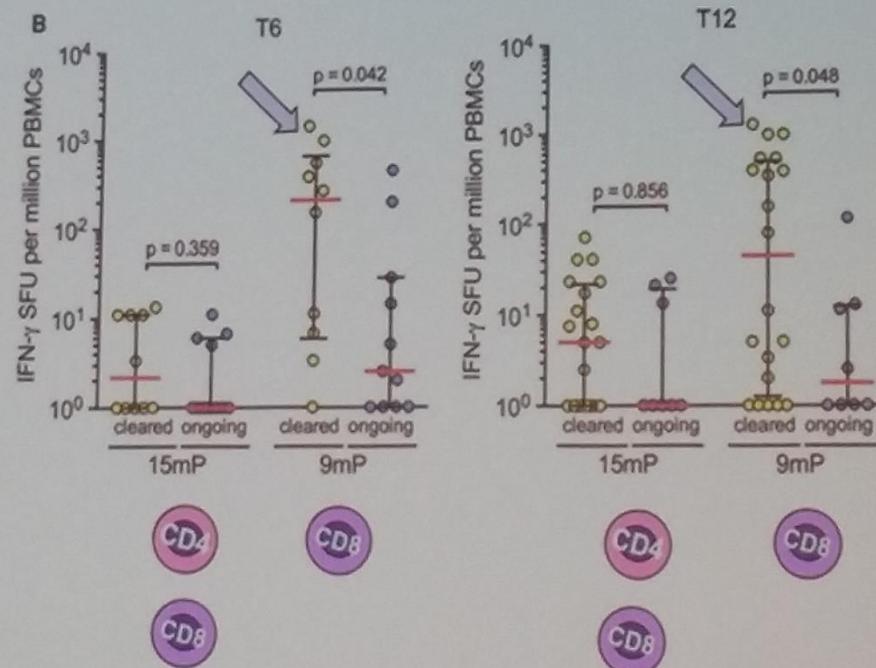
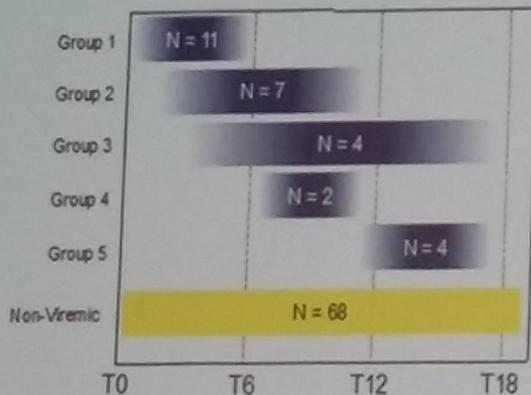
Nephropathy



# BKPyV

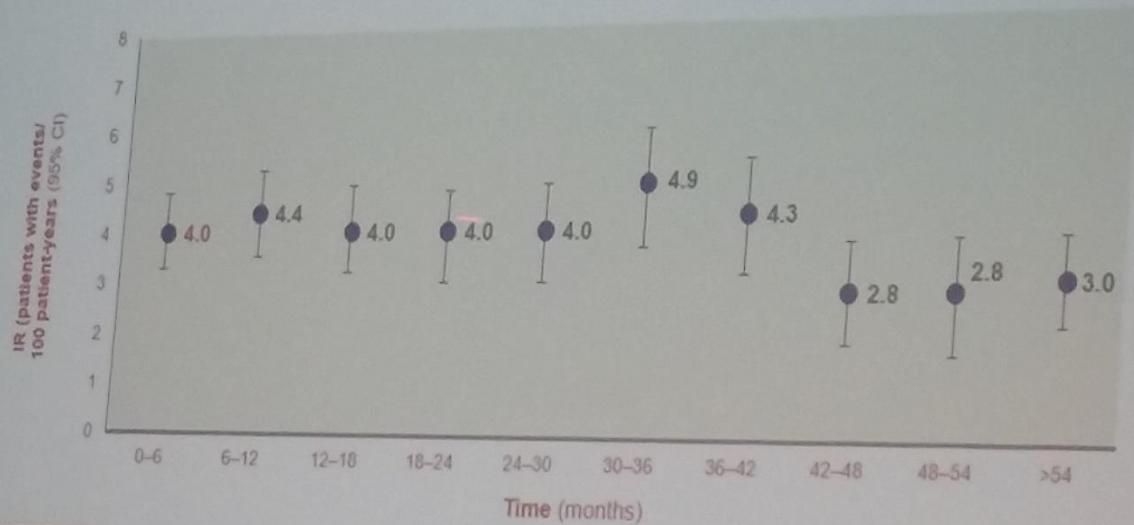
## BKPyV T-cell Responses and Viremia Clearance

- Characterization of immunodominant 9mer peptides in LTag and sTag
- Increasing CD8 T-cells targeting LTag/sTag in blood when clearance of BKPyV viremia occurs in kidney transplant patients after reducing immunosuppression



# VZV

## Incidence rates for herpes zoster infection over time



Total pt exposure (N)	6,194	5,222	4,677	4,217	3,858	3,361	3,043	2,656	2,303	1,727
Patient with HZ (N)	112	106	87	79	71	77	60	34	27	50

# Adenovirus

## Importance of Early Onset of Therapy

Earliest Rational Employment of Antiviral Treatment?

Adenoviremia

Intestinal HAdV proliferation with loads above the critical threshold

Intestinal HAdV shedding prior to allogeneic HSCT

# Adenovirus :terapia

## Documented Efficacy of Antivirals in HAdV Infections

Cidofovir

- standard of care (SoC) anti-HAdV agent for pre-emptive therapy
- efficacy against all HAdV species > gains time for T-cell recovery
- ✗ → low bioavailability and significant nephrotoxicity  
*(Lindemans CA. Blood 2010;116:5476; Neophytos D. EBMT 2007, 13:74-81, Ljungman P. BMT 2003, 31:481-6)*

Ribavirin

- documented in vitro activity against HAdV-C only
- questionable therapeutic effect in vivo > added value against HAdV-C?  
*(Marfin F. Antivir Ther 2009, 14:55-61; Lankester A. CID 2004, 38:1521-5) ;Abe S. BMT 2003, 32:1107-8*

Ganciclovir

- modest activity due to inefficient phosphorylation (lack of TK in HAdV)  
*(Voessens L. Antimicrob Agent Ther 2003, 49:1010-16; Bruno BT. BMT 2003, 9:341-2)*

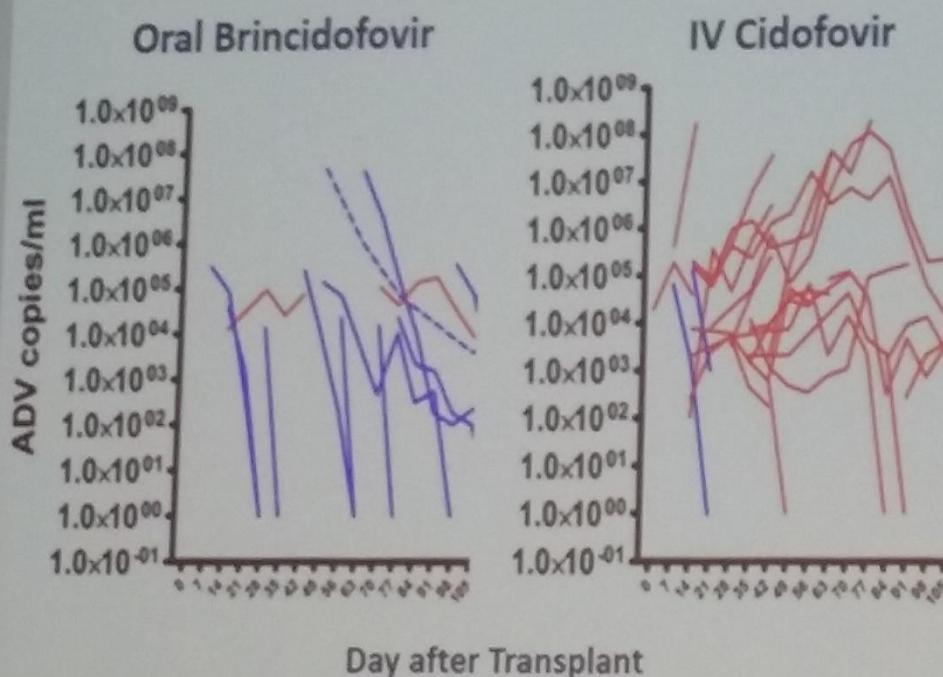
Brincidofovir

- orally bioavailable investigational nucleoside analogue
- active against all HAdV species, no cidofovir-like nephrotoxicity  
*(Box A. BMT Tandem 2016; Tippin T. Ther Drug Monit. 2016;38:777-86)*

# Brincidofovir vs Cidofovir

## Brincidofovir vs cidofovir in pediatric HCST recipients

Hiwarkar P et al. Blood 2017;129(14):2033-2037



- 80% of pediatric HCT patients cleared plasma with BCV (median 4 wks)
  - Only 35% cleared with IV CDV (median 9 wks)
- Unlike CDV, BCV cleared viremia independent of immune reconstitution
- Preemptive therapy safety profile:
  - CDV: renal toxicity observed in 9/23 patients
  - Oral BCV: 1/18 discontinued therapy for GI AEs

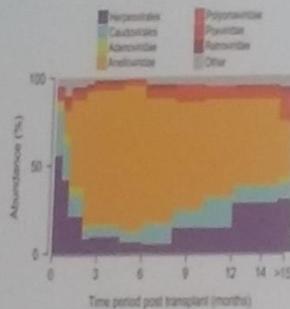
# Viremie in trapiantati di cuore e polmoni

## DNA virome in Heart & Lung transplant recipients

Cell free DNA in plasma (656 samples)

Heart recipients: pediatric (24) and adults (41)

Lung recipients: adults (31)



Anelloviridae	68%
Herpesvirales	13%
Caudovirales	5%
Polyomaviridae	5%
Adenoviridae	2%
Poxviridae	1%
Retroviridae	1%
Other	5%

*J De Vlaminck. Cell. 2013 Nov 21;155(5):1178-87.*

# HSCT transplantato: viremia intestinale

HSCT recipients: the gut virome

Picobirnavirus detected in 41% of all cases, more frequently at baseline  
Multivariate analysis: associated with severe GVHD (HR 2.66, 1.46-4.86)



J. Legoff, *Nature Medicine*, 2017 Sept 23; (9):1080-1085

**I trapiantati hanno ulteriori rischi come la West Nile, Dengue, Chikungunia. In Europa la West Nile è endemica**