Immunologia e infettivologia dei trapianti

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Spec. in Malattie Infettive e Tropicali
Immunologia Clinica e Allergologia
Epatologia

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Biologic agents in rheu

- **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-α Therapy in Patients with Rheumatoid Arthritis and Chronic Hepatitis C Virus Infection

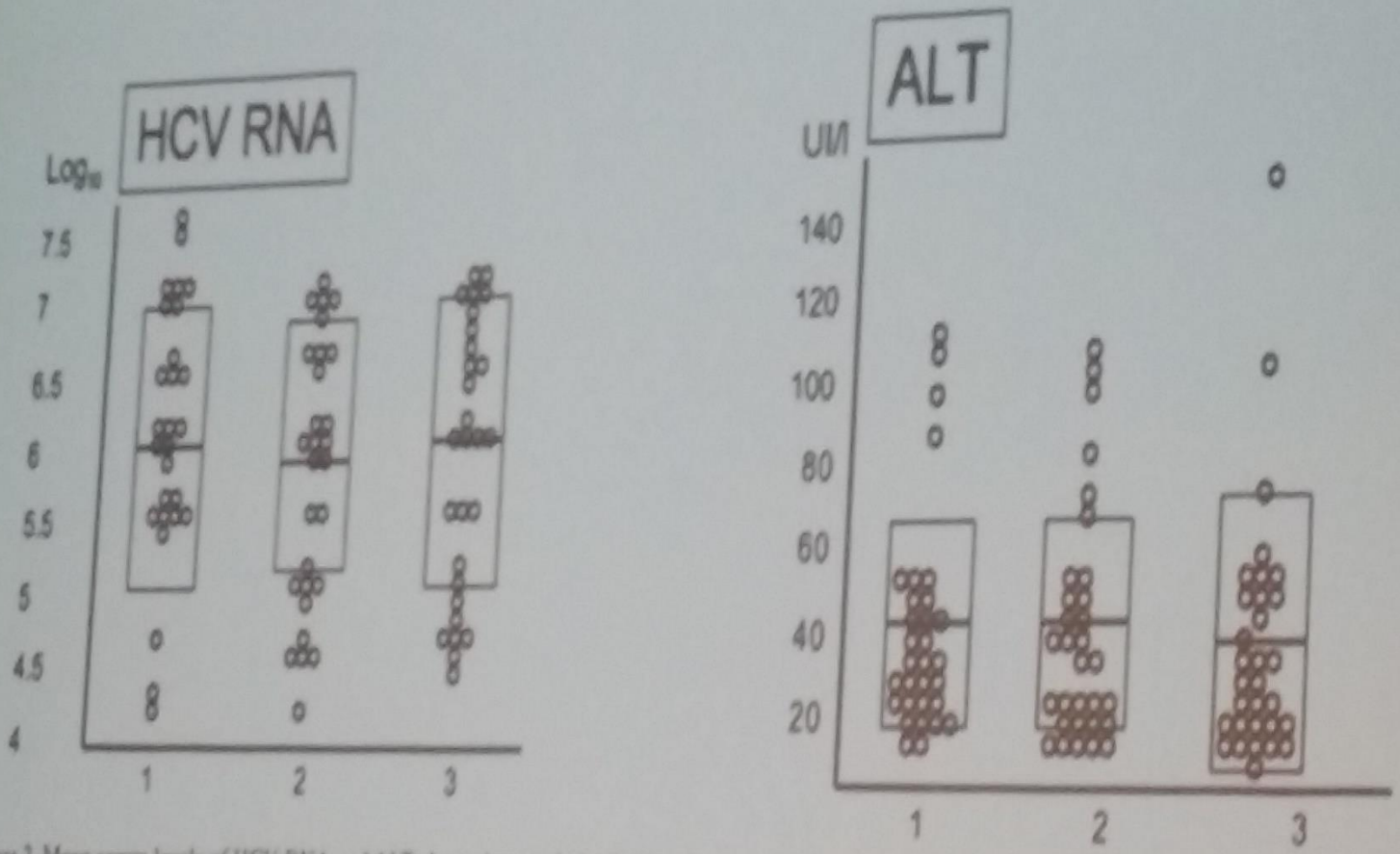


Figure 2. Mean serum levels of HCV RNA and ALT showed no statistically significant variations after the first 3 months of anti-TNF-α treatment (2), and at the last recorded visit (3), compared to baseline (1).

Infezione da HCV con Rituximab

Rituximab in HCV carriers

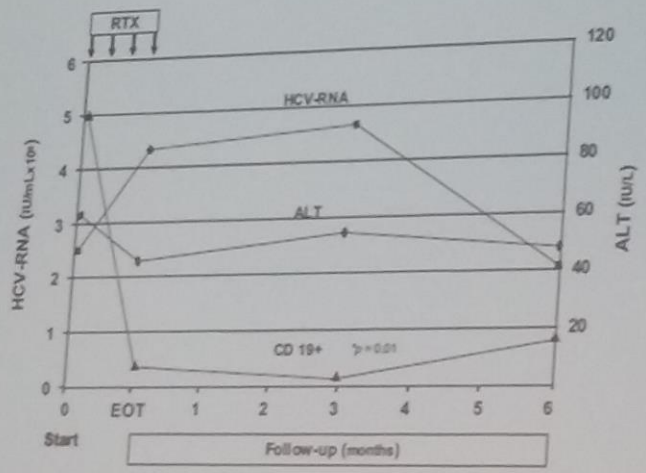


Figure 2. Pattern of HCV RNA, alanine aminotransferase, and CD19 mean values of the 19 patients with HCV-positive MC during the study. RTX indicates rituximab infusions; EOT, end of treatment; and ALT, alanine aminotransferase.

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

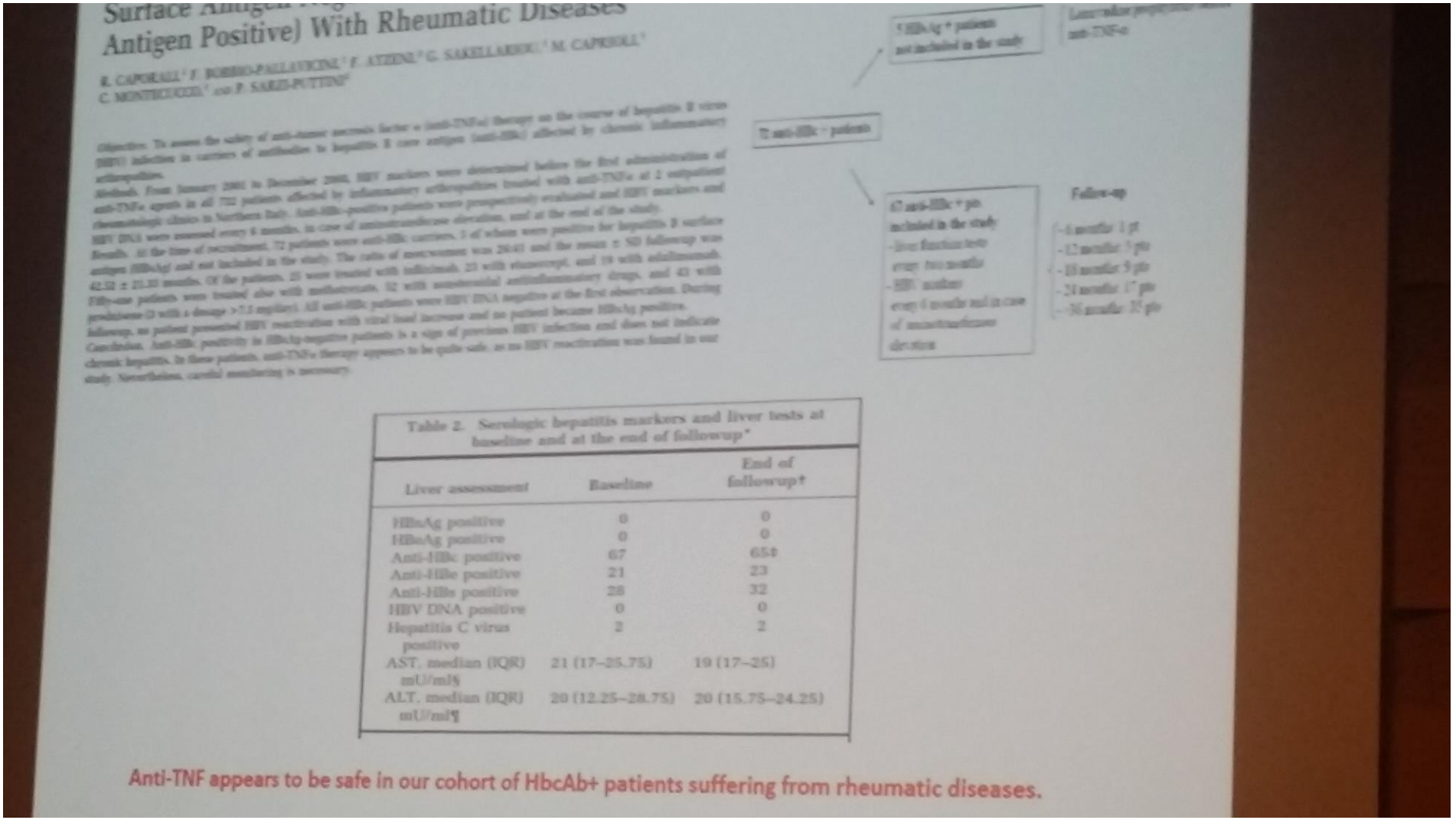
HBV trapiantati epatici

- **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 celluare 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 ... Antigen Positive) With Rheumatic Diseases

R. CAPORALI, F. BOBBIO-PALLAVICINI, F. ATZENI, G. SAKELLARIOU, M. CAPORALI, C. MONTECUCCO, and P. SARZI-PUTTINI

Table 2. Serologic hepatitis markers and liver tests at baseline and at the end of followup*

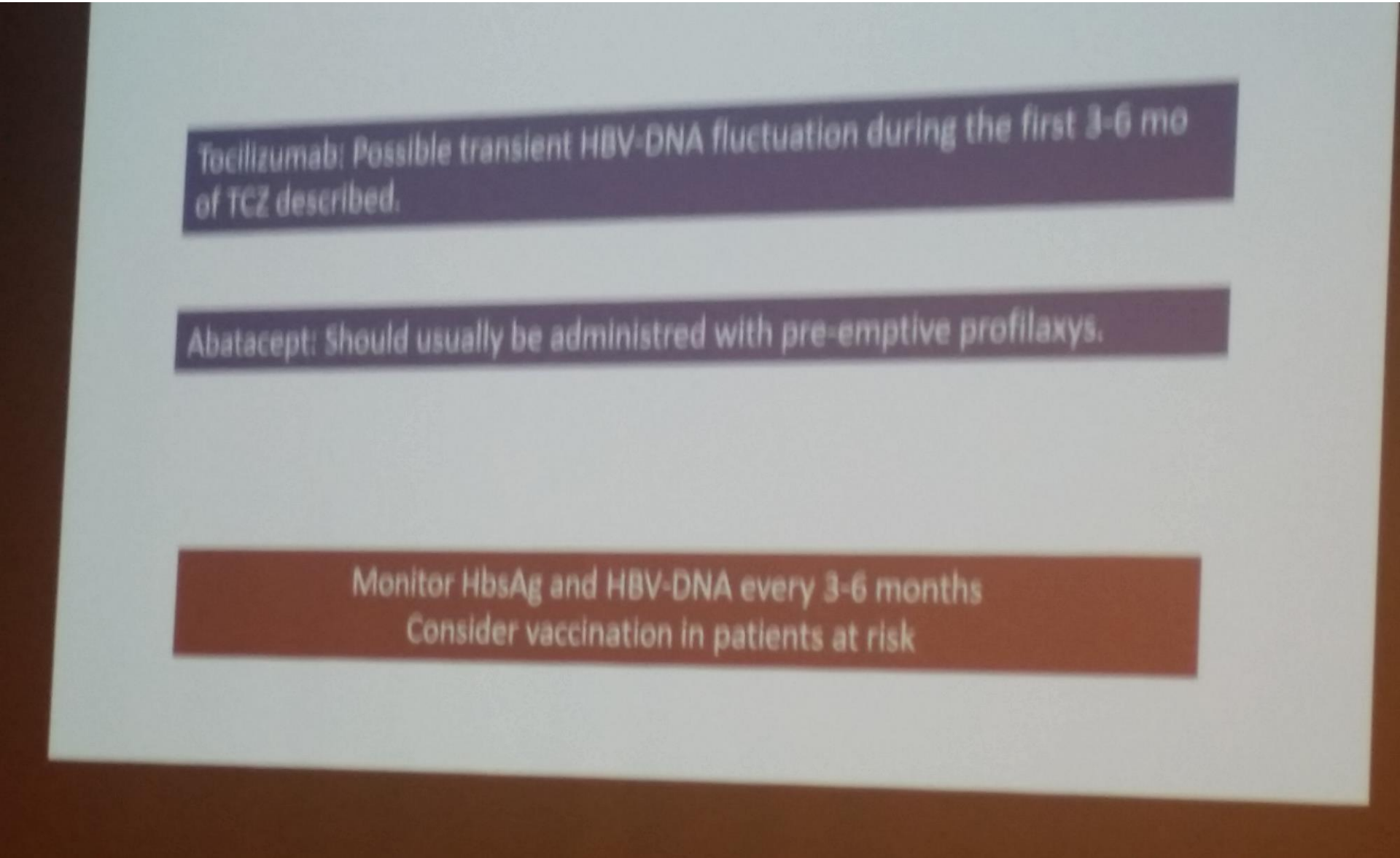
Liver assessment	Baseline	End of followup†
HBsAg positive	0	0
HBsAg positive	0	0
Anti-HBc positive	67	65‡
Anti-HBe positive	21	23
Anti-HBs positive	28	32
HBV DNA positive	0	0
Hepatitis C virus positive	2	2
AST, median (IQR) mU/ml§	21 (17–25.75)	19 (17–25)
ALT, median (IQR) mU/ml¶	20 (12.25–28.75)	20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

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

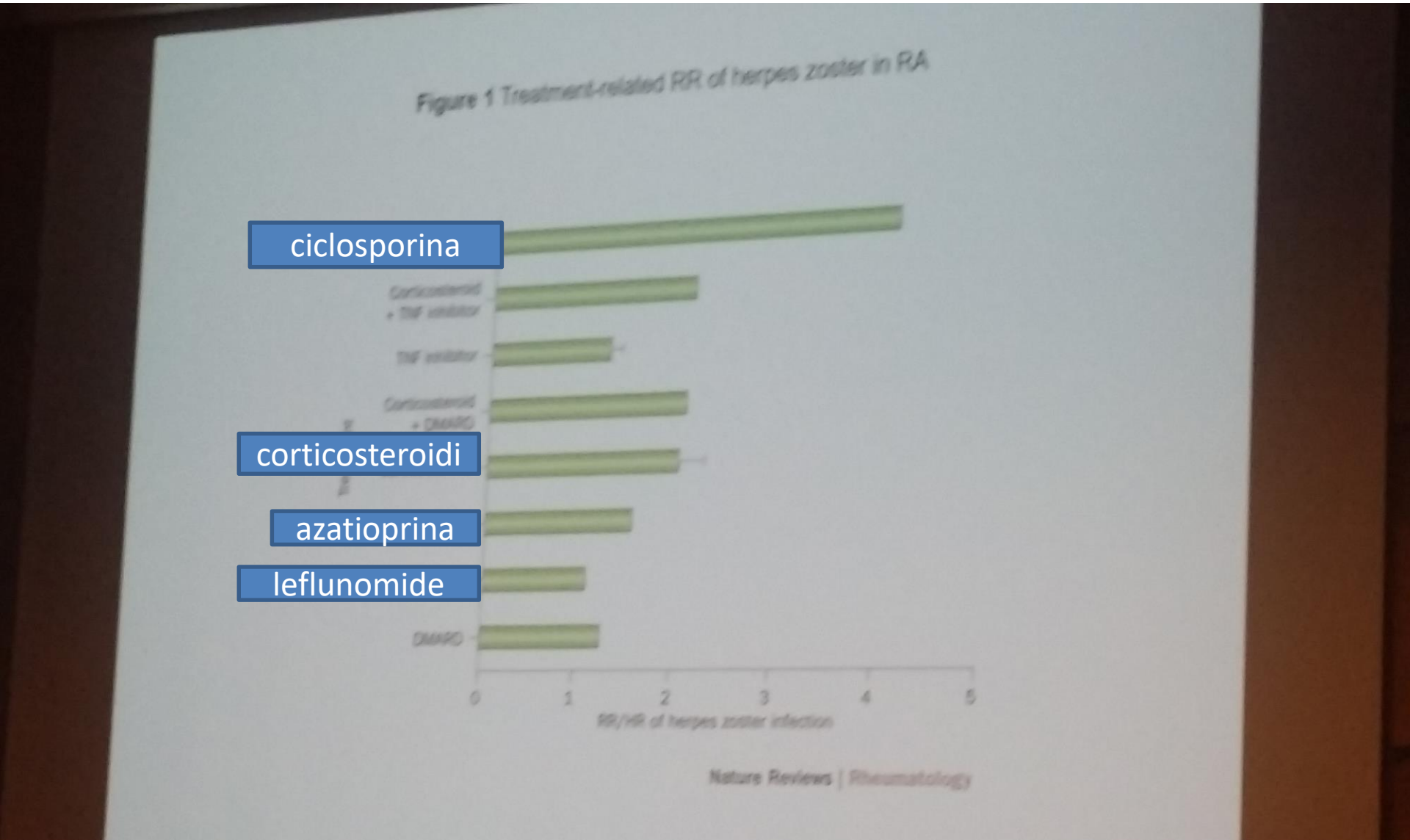
Profilassi

- 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

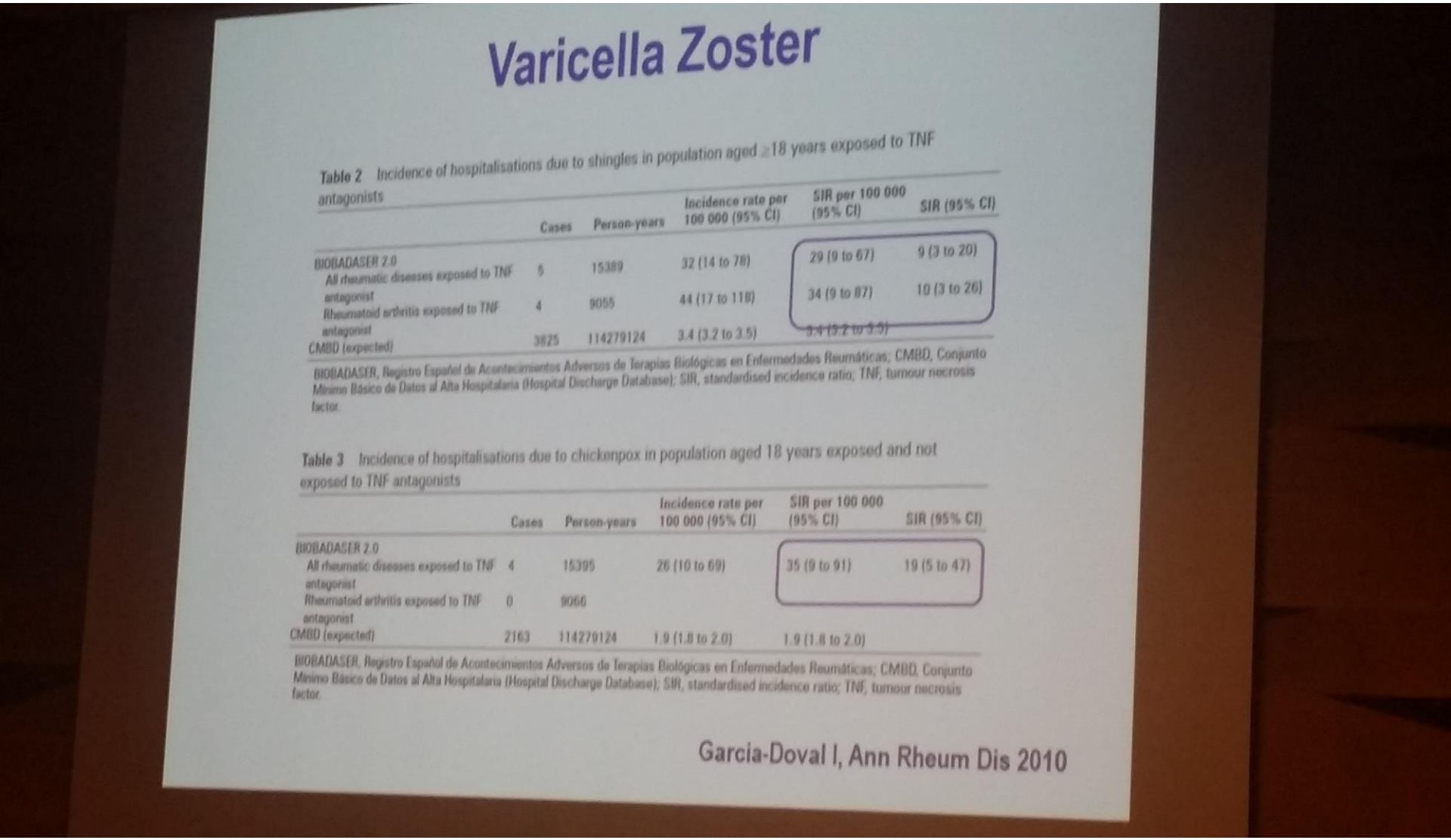
Tacilizumab e abatacept in HBV



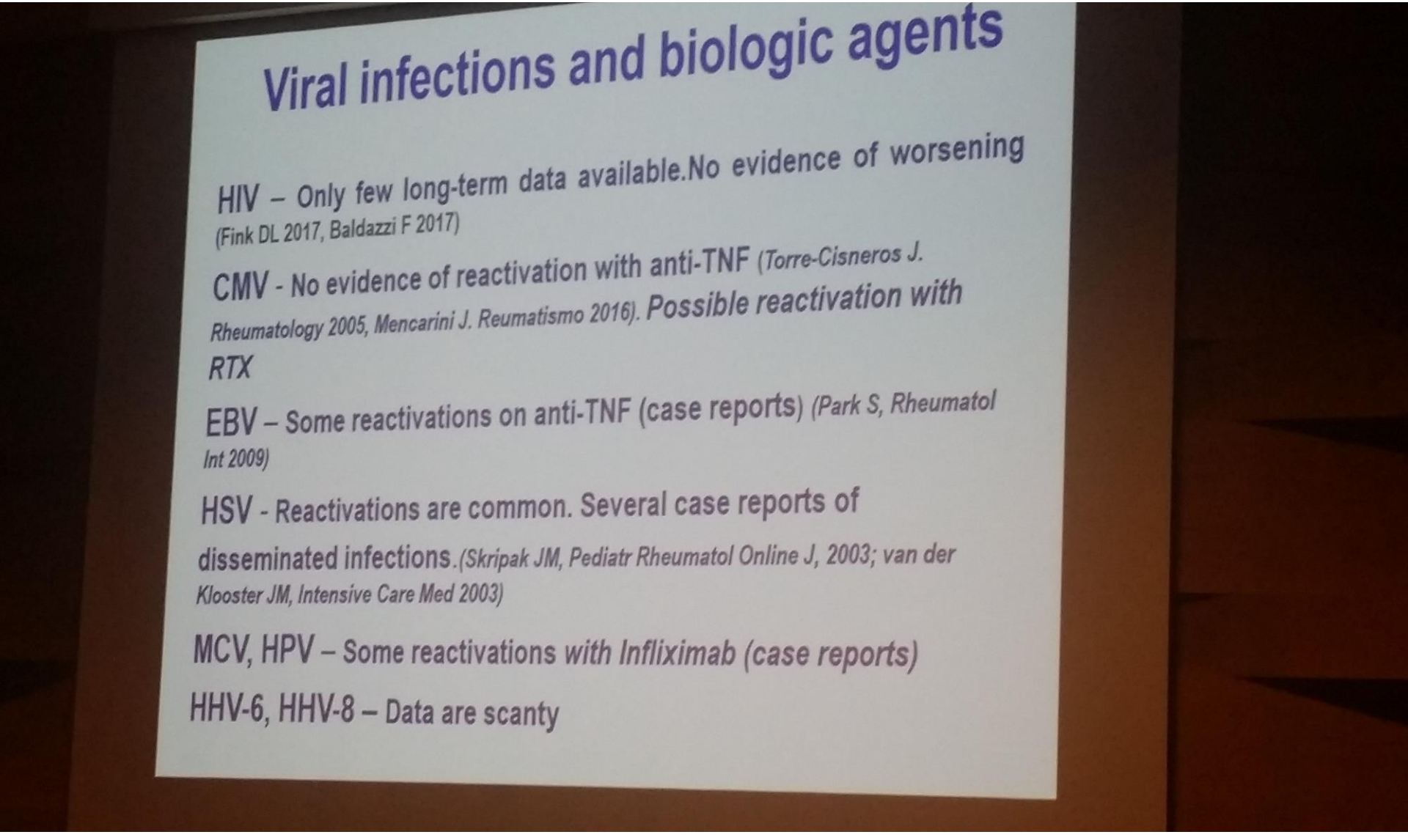
Treatment-related of VZV in RA-numero episodi per tipo di farmaco per paziente



Varicella zoster in terapia con TNF



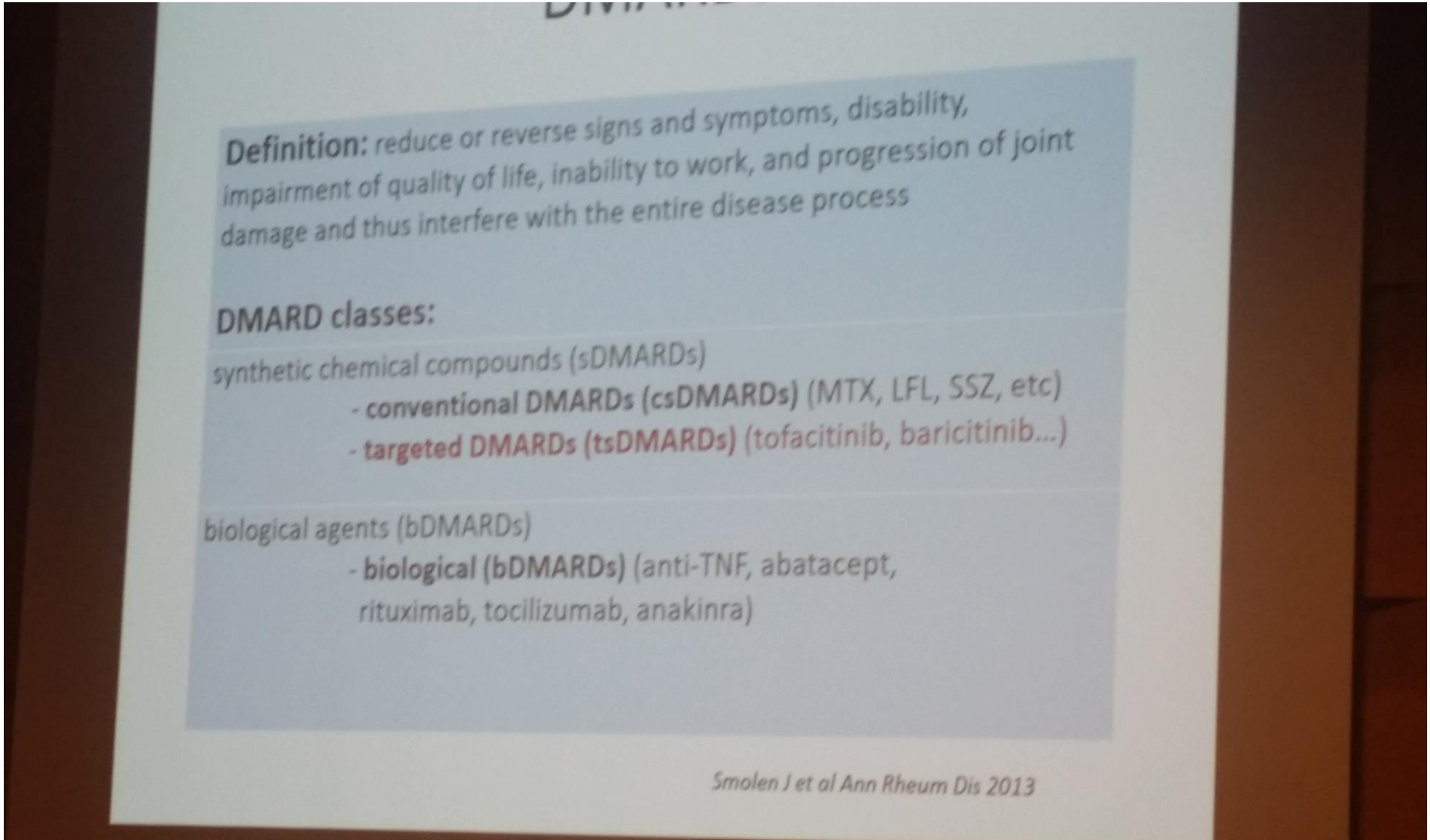
Infezioni virali riattivate dopo terapia con anti TNF o RTX o Infliximab



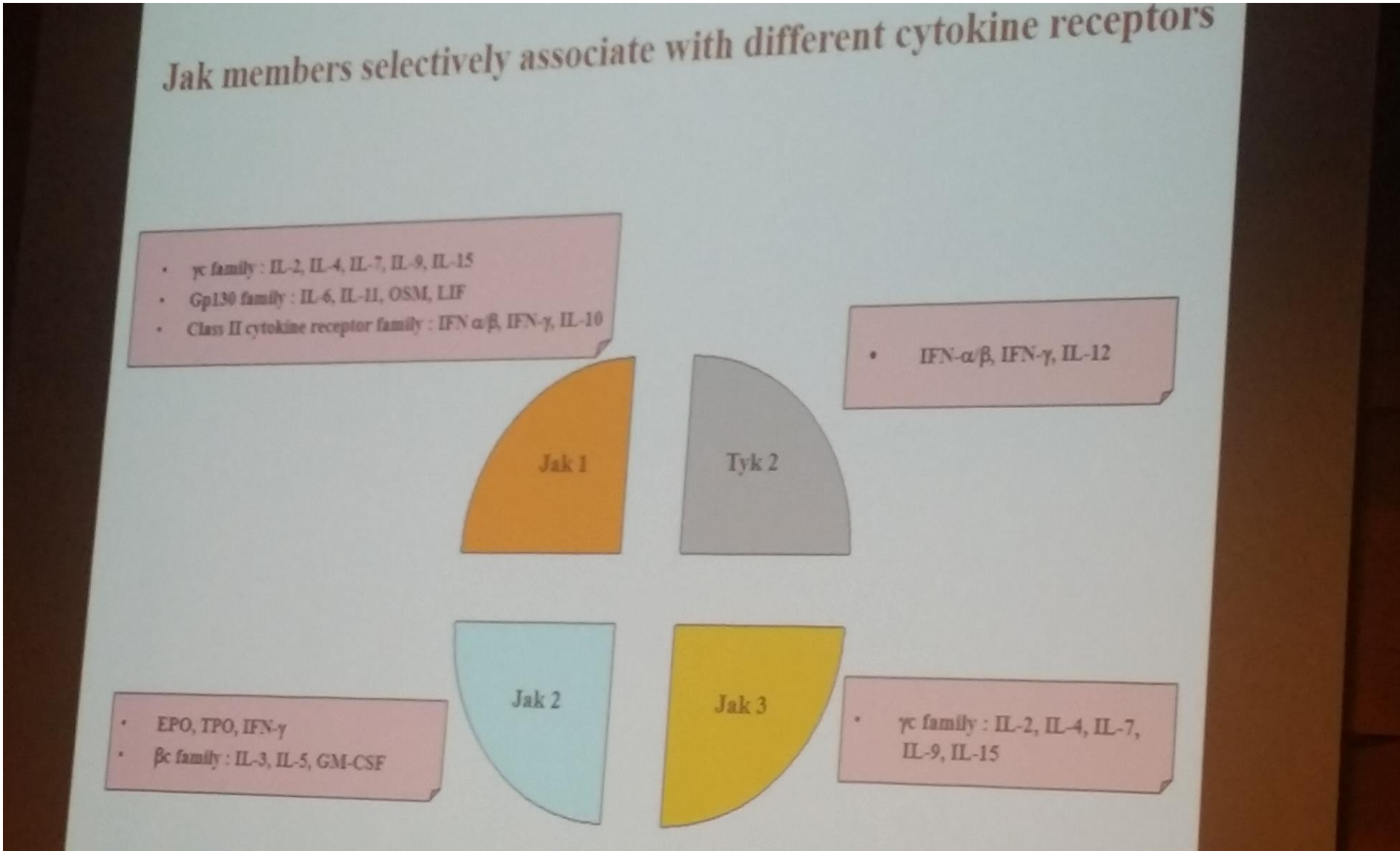
RITUXIMAB-anti CD20

- **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**

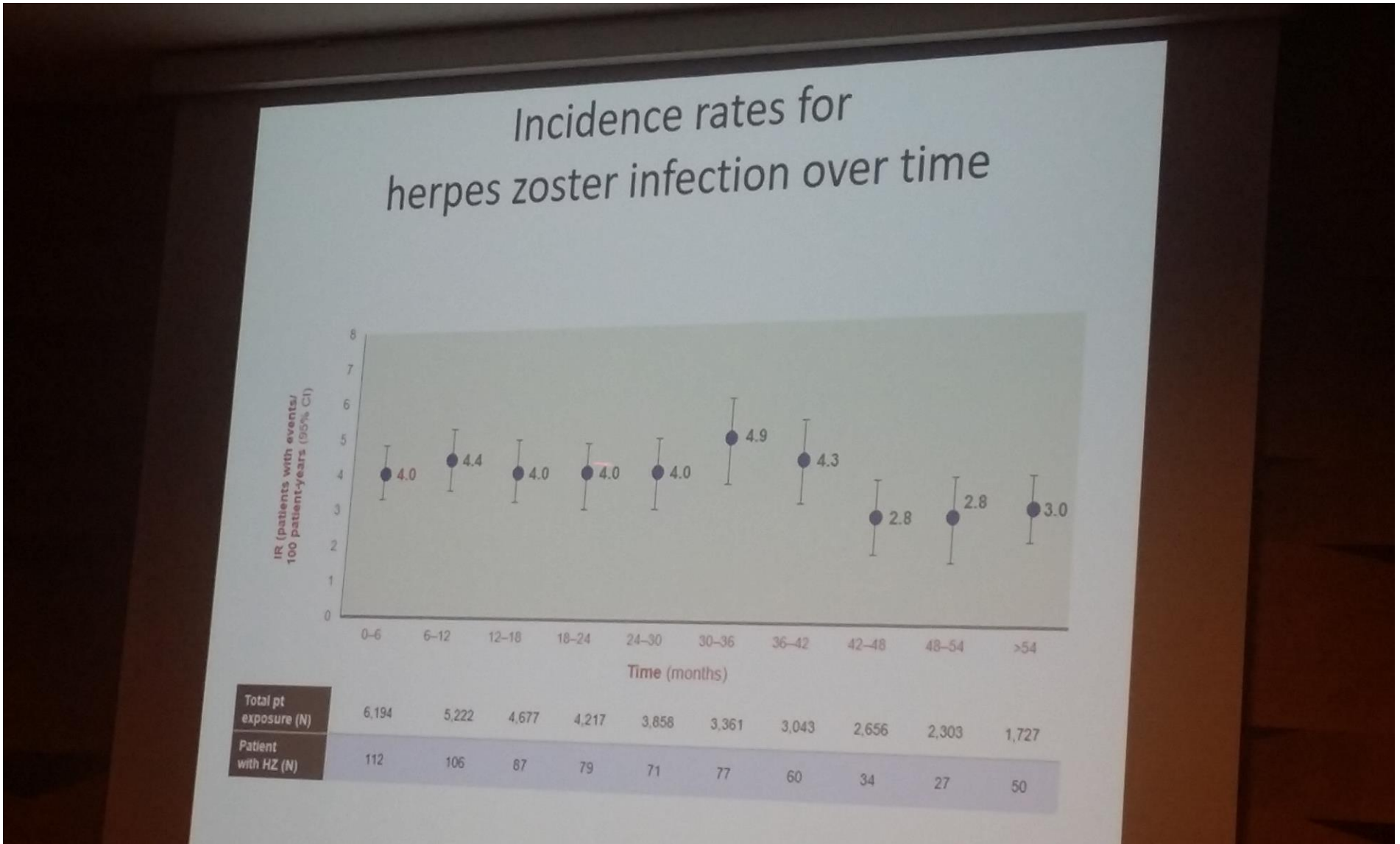
DMARD (composti chimici MTX, LFL,SSZ e target Tofacitinib,baracitinib
Agenti biologici: anti TNF,abatacept,Rituximab
(RTX),Tocilizumab,Anankira



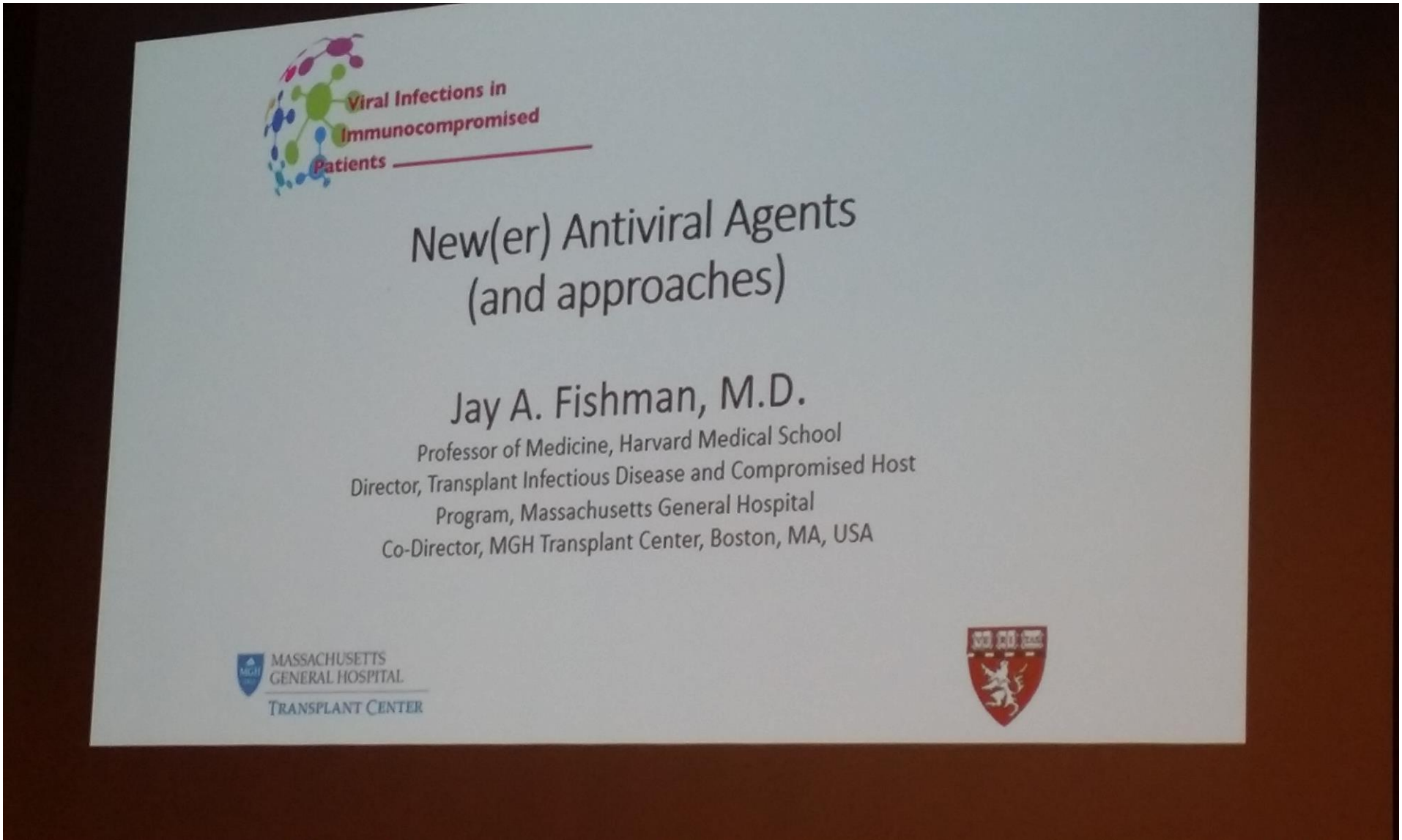
Recettori citochinici



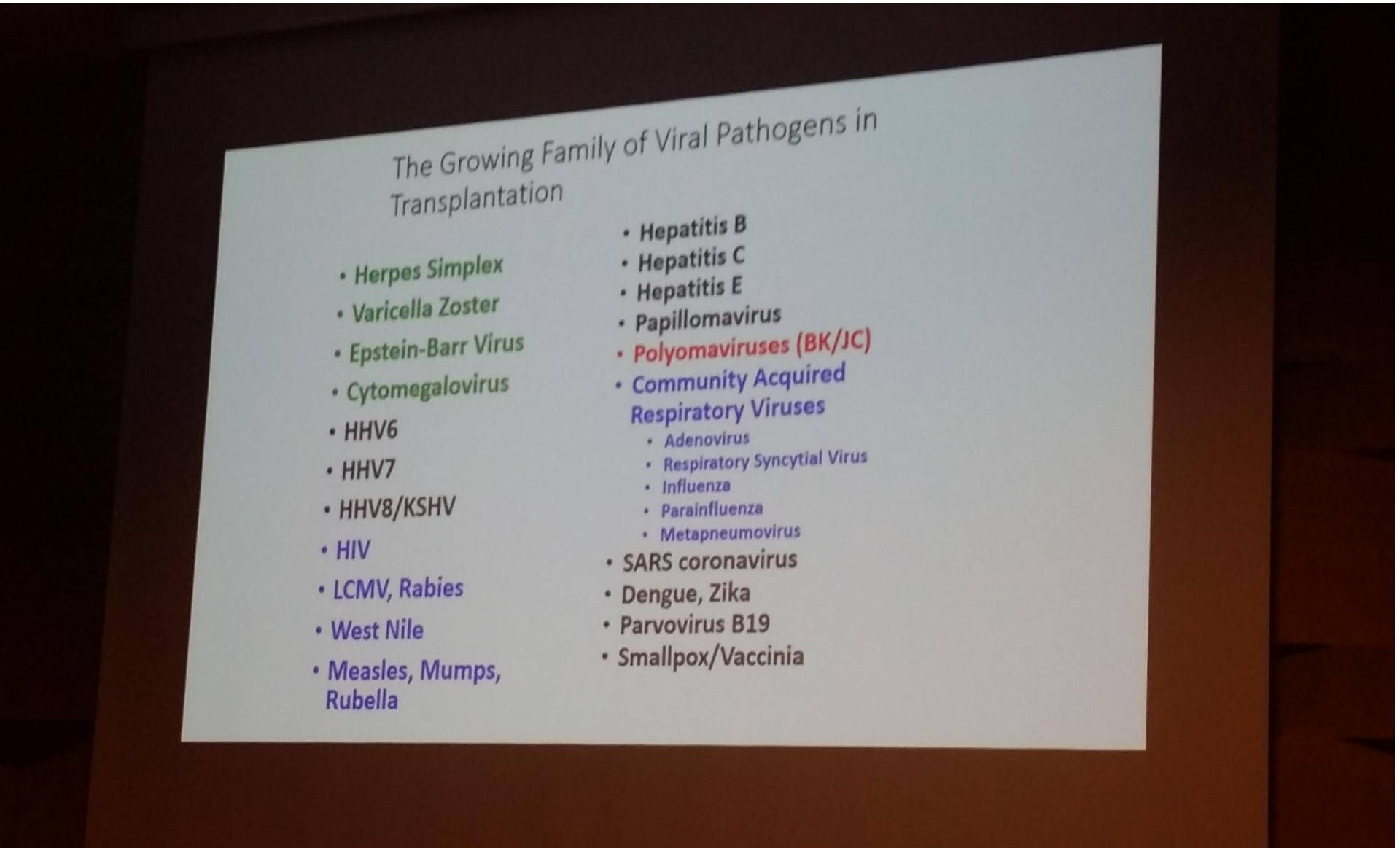
Tasso di incidenza del VZV per età



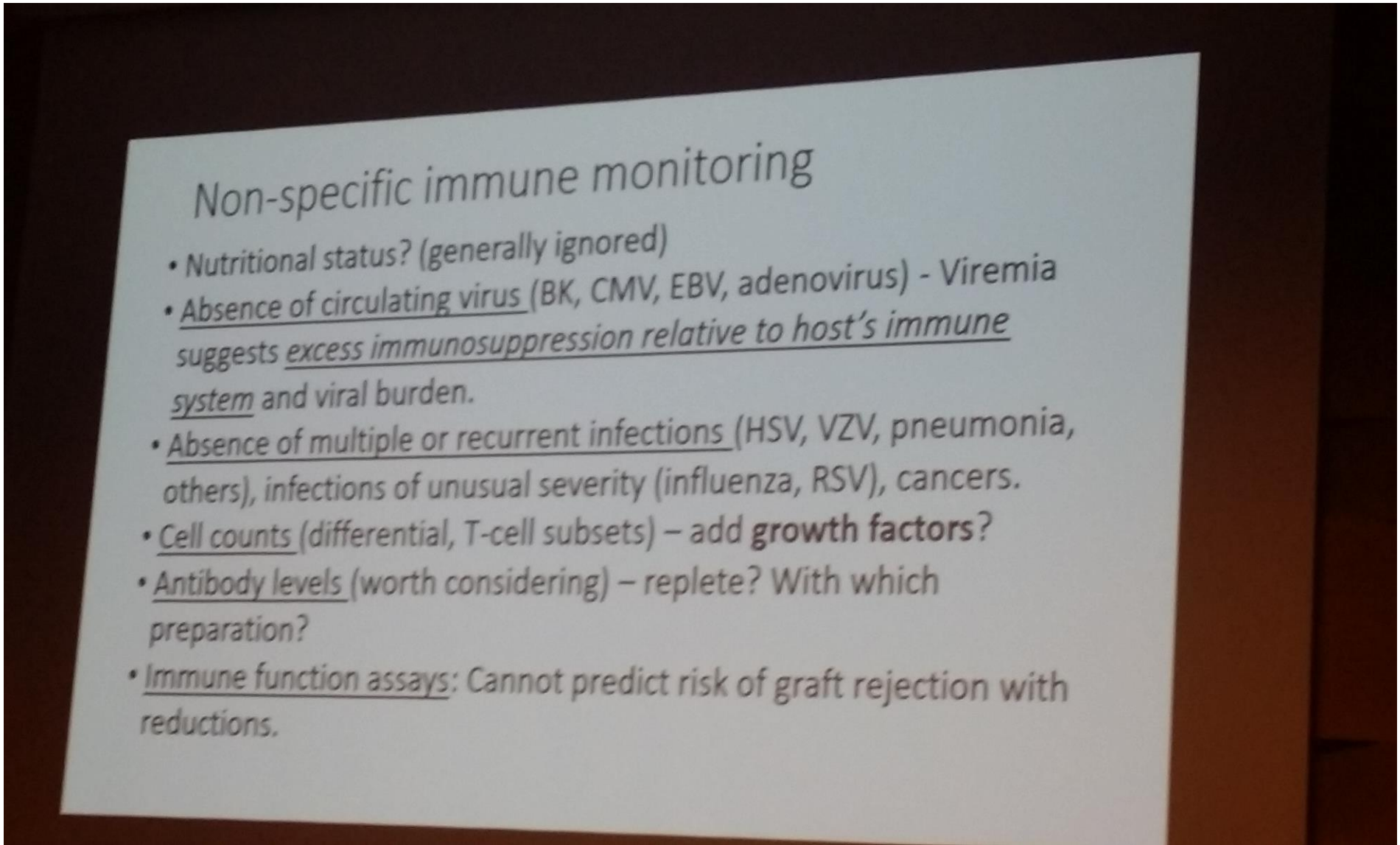
Nuovi antivirali



Infezioni Virali nei trapiantati



Monitoraggio non specifico del-l' immunodeficit



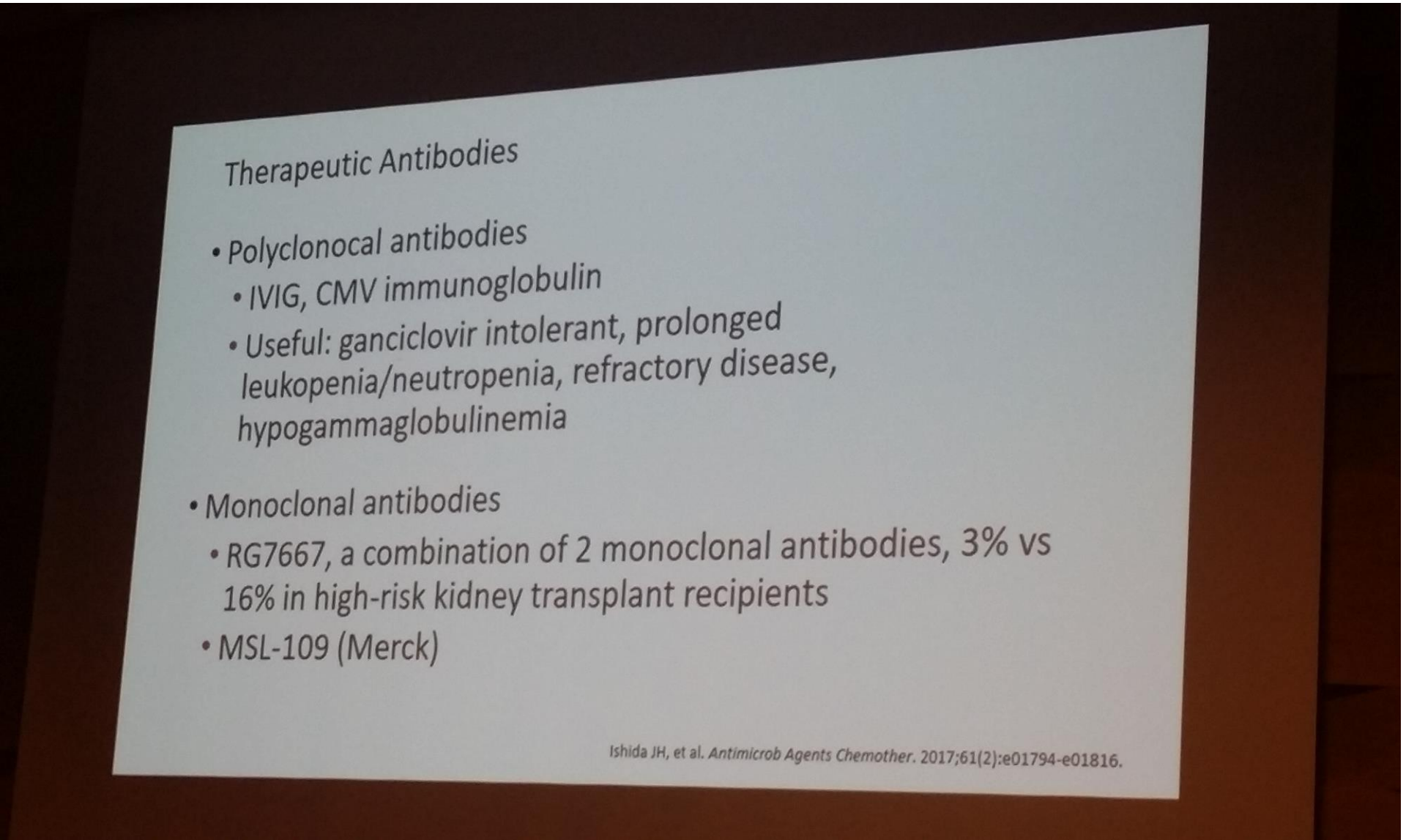
IPOGAMMAGLOBULINEMIA

Hypogammaglobulinemia (HGG)

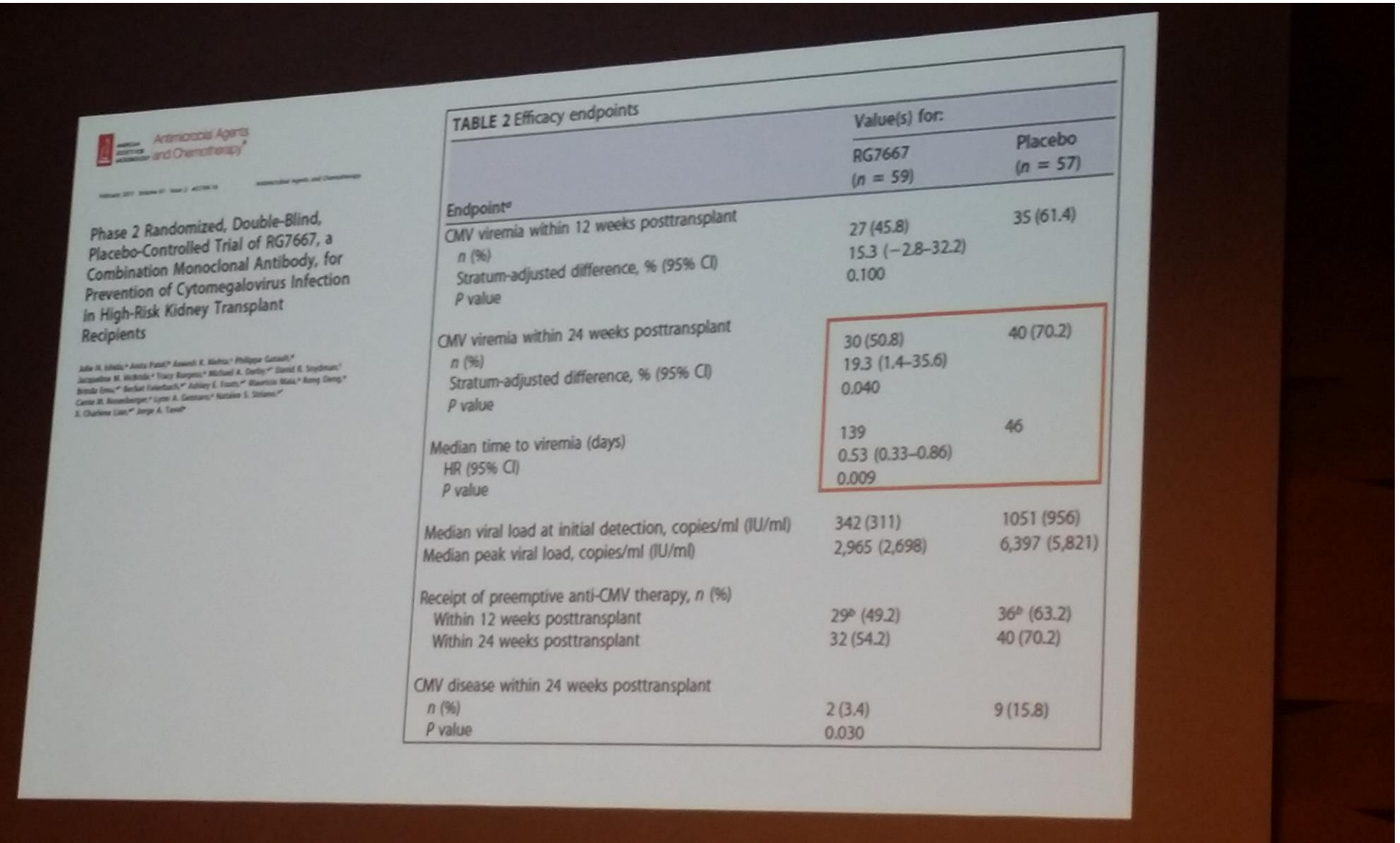
- Often missed
- Common: **~45% in all recipients,** 15% severe levels (IgG 400-700 md/dL). Up to 63% in lung recipients.
- **Decreased post-transplant IgG predictive of risk for infection**
  - Renal recipients with HGG of any class had higher incidences of overall and bacterial infection at all time 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



Efficacia Ig



Antimicrobial Agents and Chemotherapy

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

TABLE 2 Efficacy endpoints

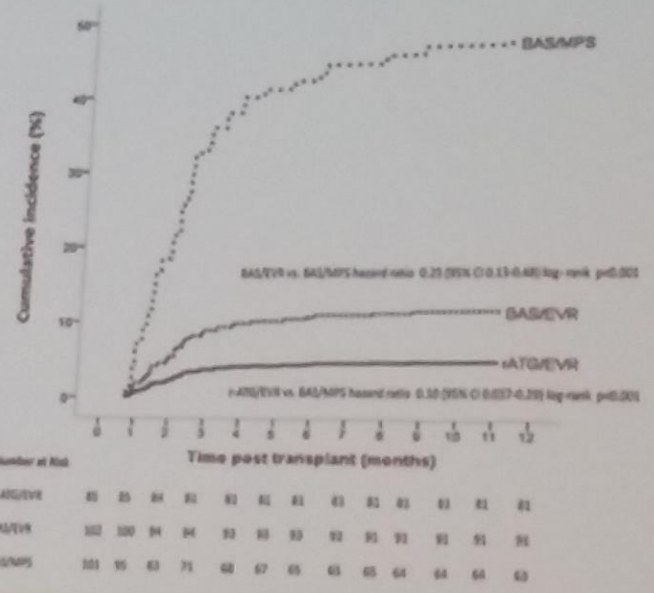
Endpoint[a]	Value(s) for: RG7667 (n = 59)	Placebo (n = 57)
CMV viremia within 12 weeks posttransplant		
n (%)	27 (45.8)	35 (61.4)
Stratum-adjusted difference, % (95% CI)	15.3 (−2.8–32.2)	
P value	0.100	
CMV viremia within 24 weeks posttransplant		
n (%)	30 (50.8)	40 (70.2)
Stratum-adjusted difference, % (95% CI)	19.3 (1.4–35.6)	
P value	0.040	
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[b] (49.2)	36[b] (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 g
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

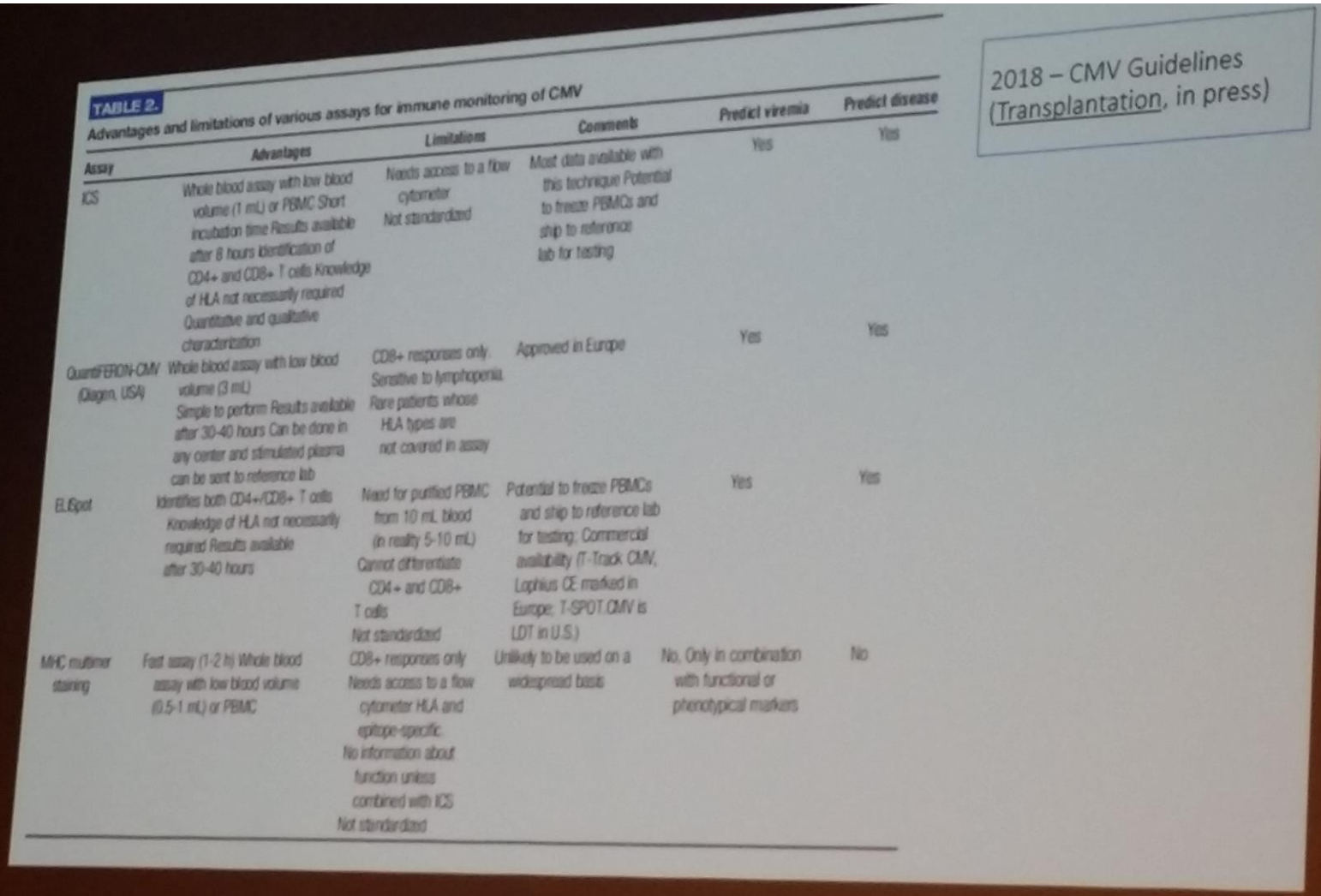
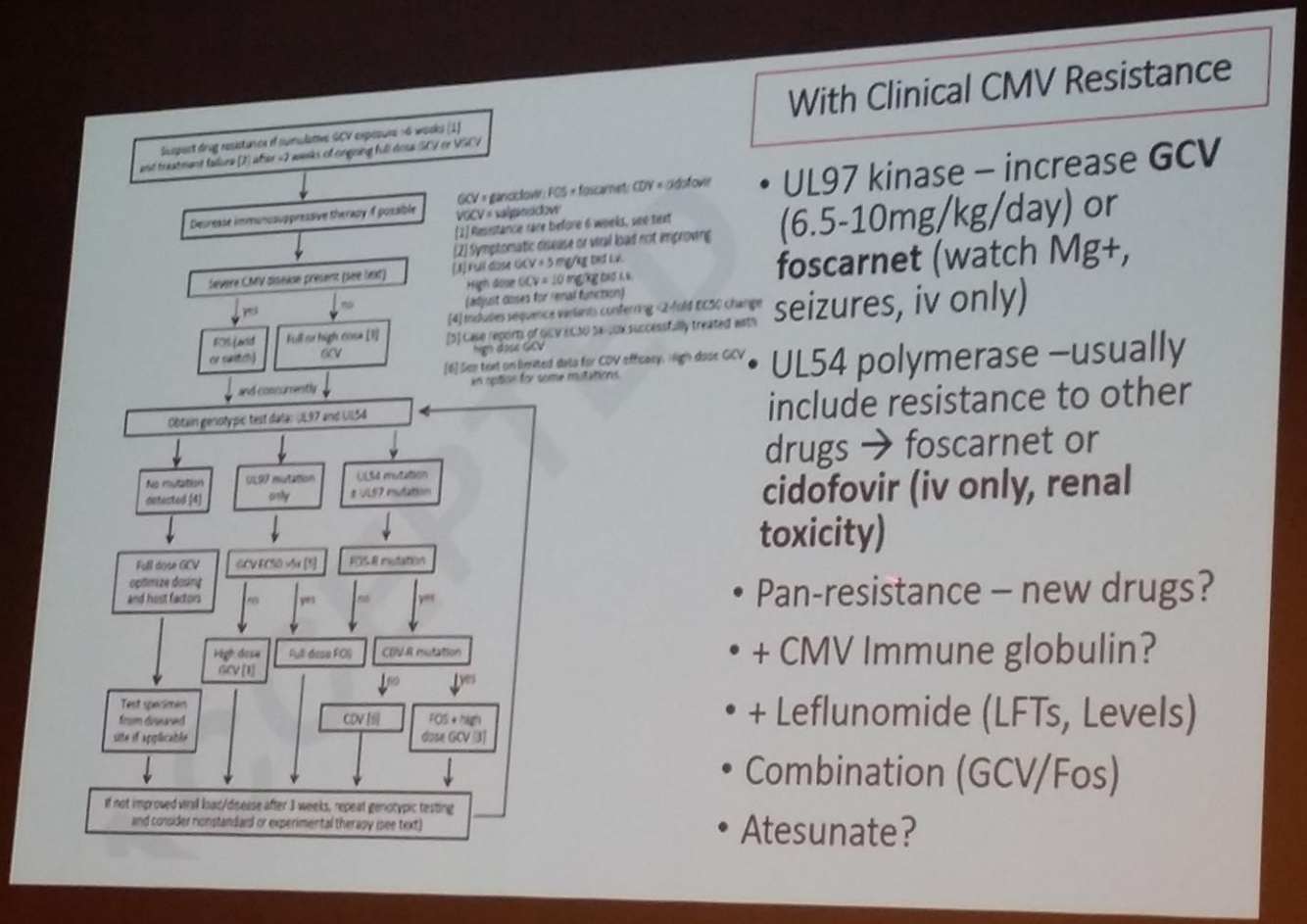


TABLE 2.
Advantages and limitations of various assays for immune monitoring of CMV

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 (Qiagen, 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)

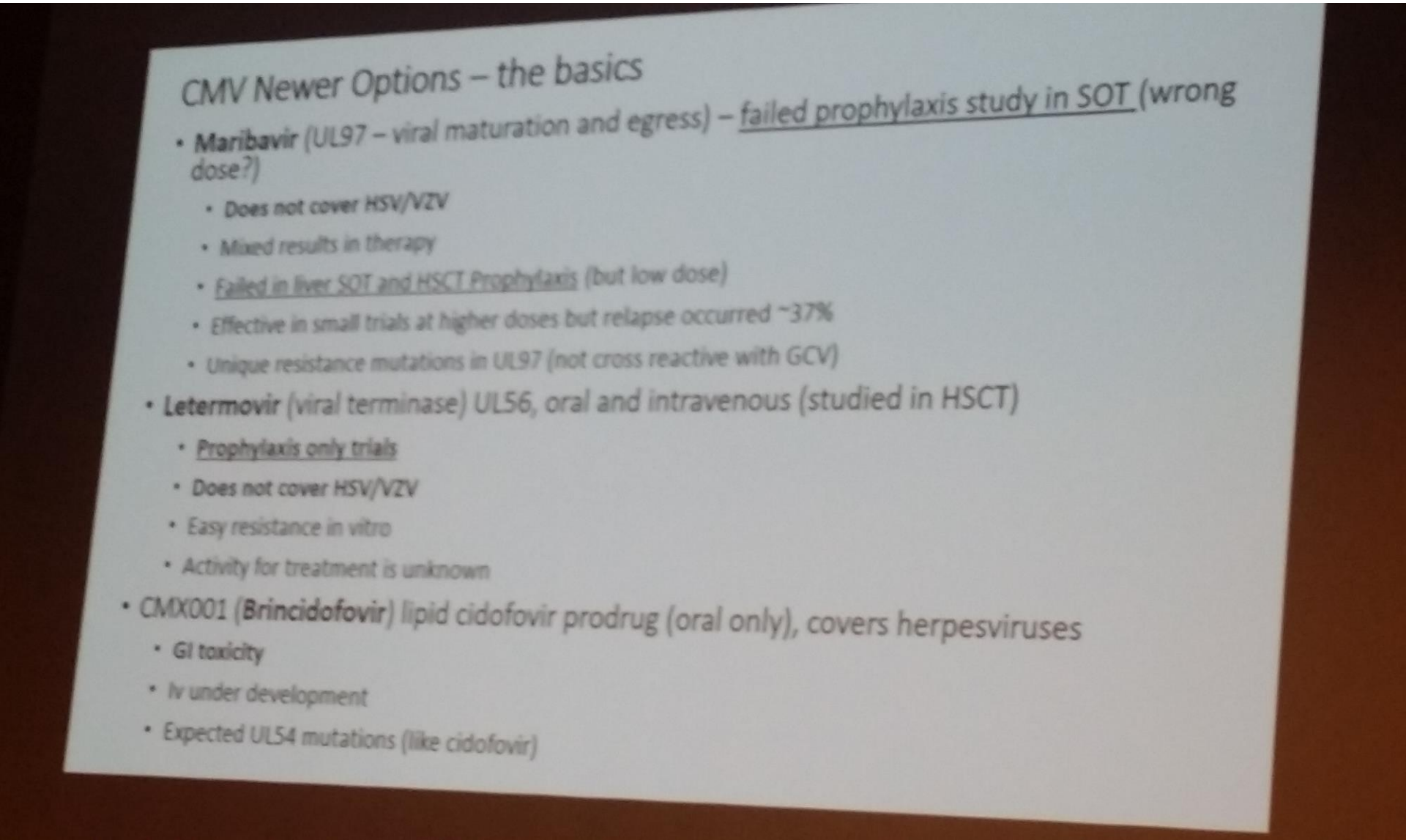
CMV resistenza



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?

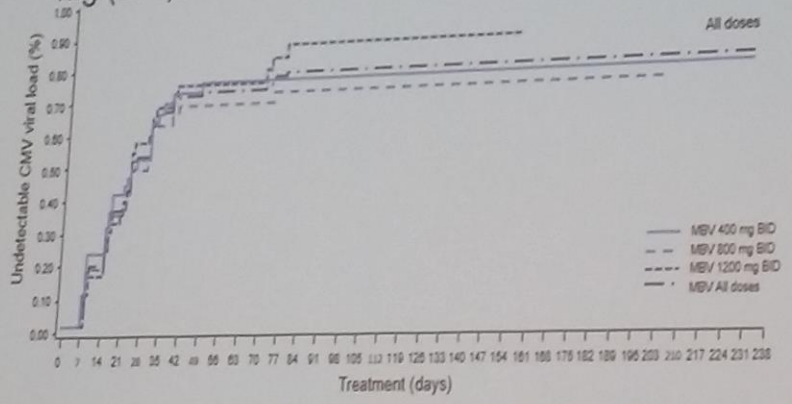
Nuovi farmaci per CMV



Maribavir per CMV

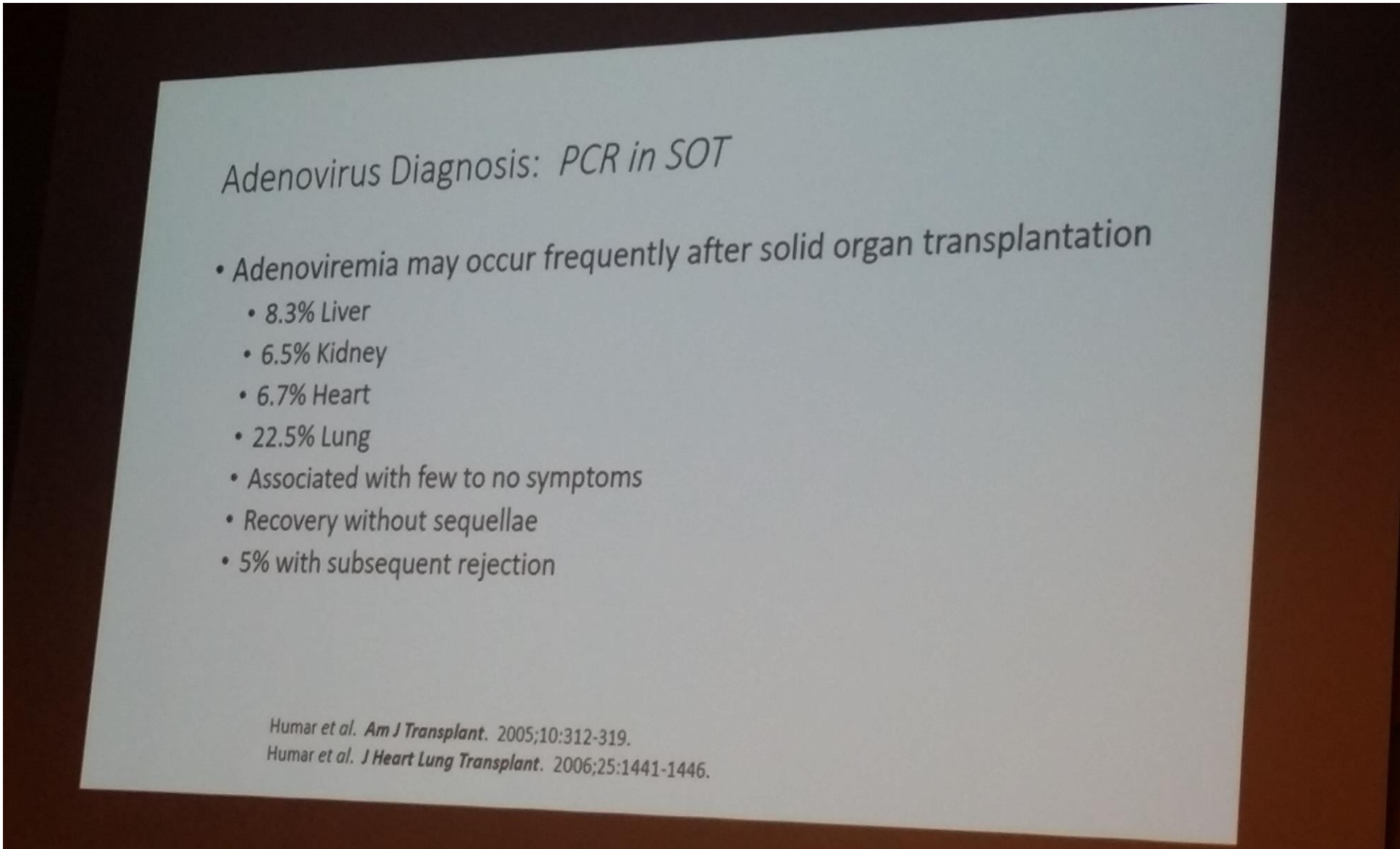
Maribavir R/R Phase II Trial: Time to Undetectable Plasma CMV DNA

- 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

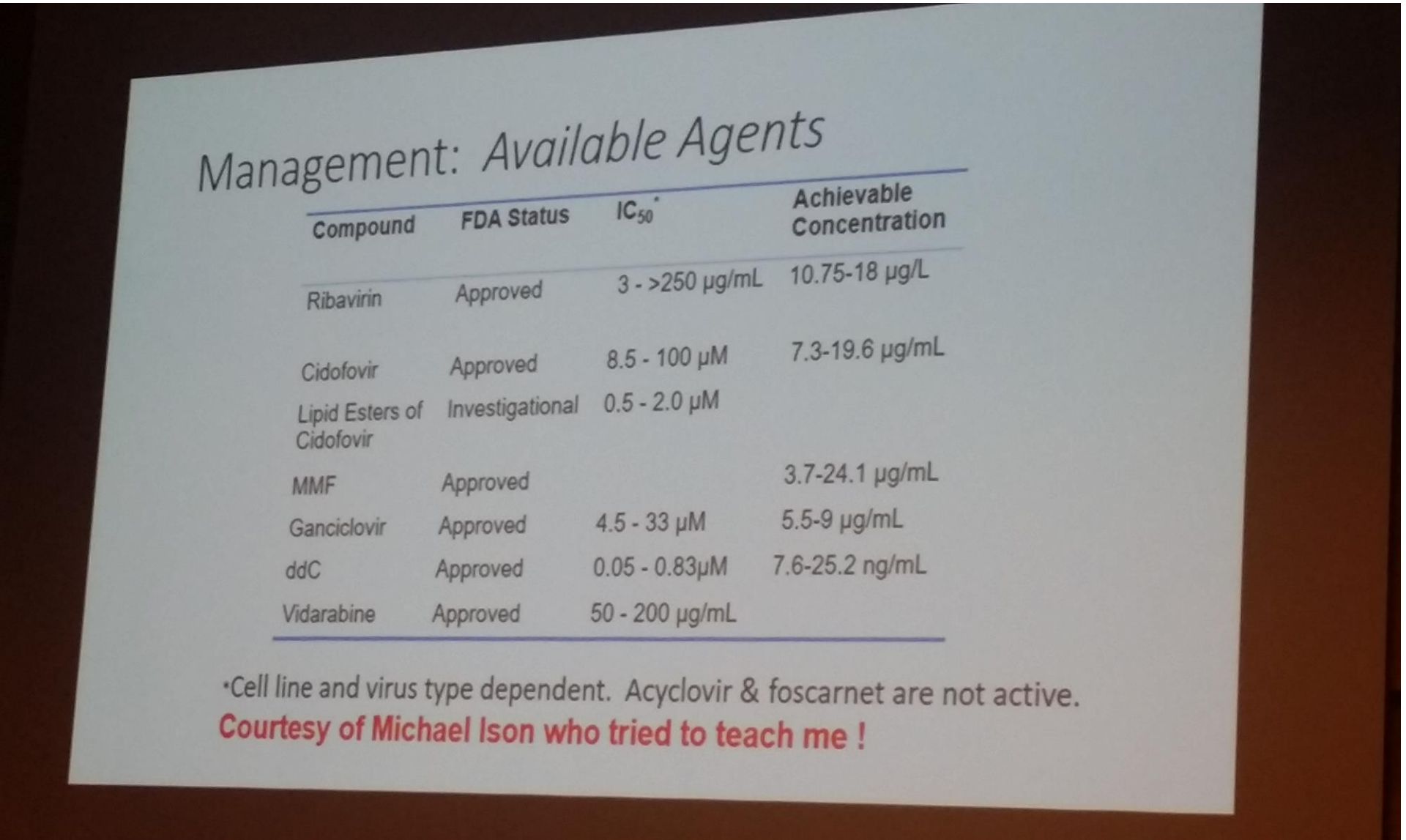


Slide courtesy of M. Pereira, presented at The Joint Annual Congress of the American Society of Transplant Surgeons and The American Society of Transplantation Wednesday May 3, 2017 ClinicalTrials.gov Identifier: NCT01611974

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 sequellae
• 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*

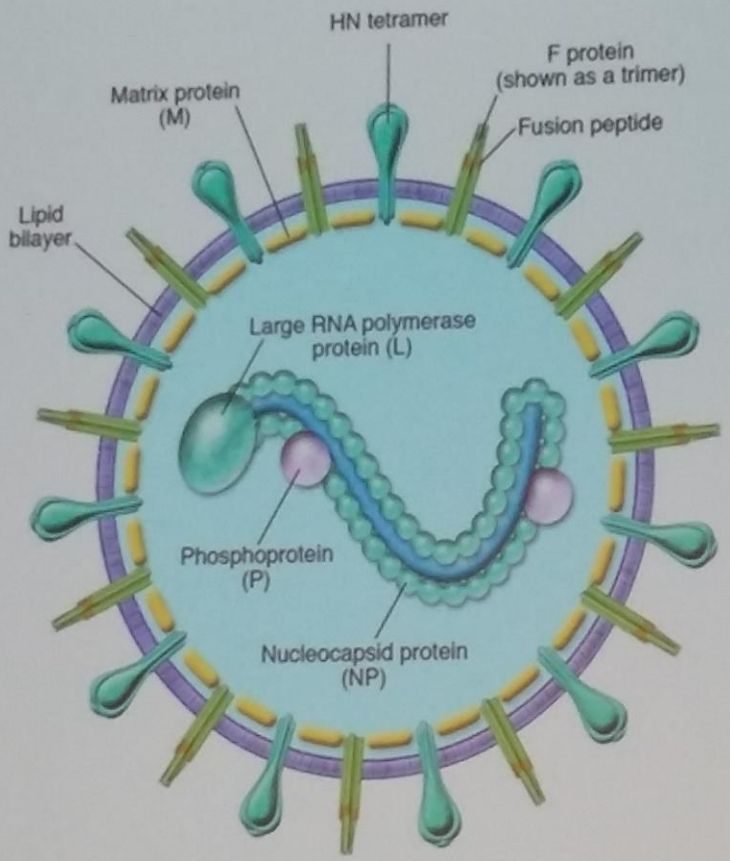
Compound	FDA Status	IC_{50}*	Achievable Concentration
Ribavirin	Approved	3 - >250 µg/mL	10.75-18 µg/L
Cidofovir	Approved	8.5 - 100 µM	7.3-19.6 µg/mL
Lipid Esters of Cidofovir	Investigational	0.5 - 2.0 µM	
MMF	Approved		3.7-24.1 µg/mL
Ganciclovir	Approved	4.5 - 33 µM	5.5-9 µg/mL
ddC	Approved	0.05 - 0.83µM	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



Northwestern

Northwestern University
NUTORC

HUMAN POLYOMA VIRUS

Human Polyomavirus Infections in Immunocompromised Hosts

Hans H Hirsch

Transplantation & Clinical Virology
Department Biomedicine (Haus Petersplatz)

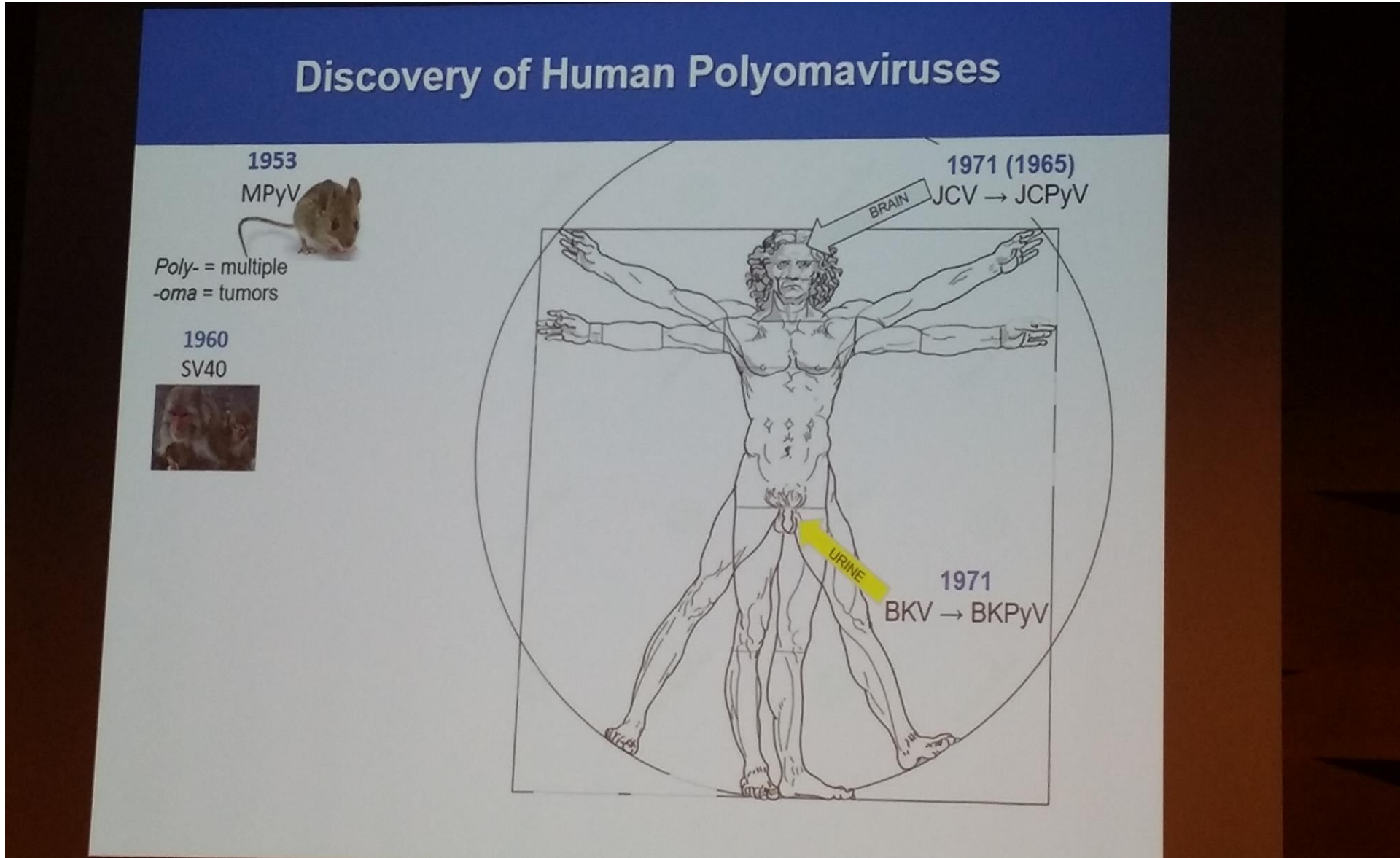
Infectious Diseases & Hospital Epidemiology
University Hospital Basel
Basel
Switzerland

4th INTERNATIONAL CONGRESS
Viral Infections in Immunocompromised Patients
Varese, 17-18 May 2018
Congress President: Paolo A. Grossi, Varese

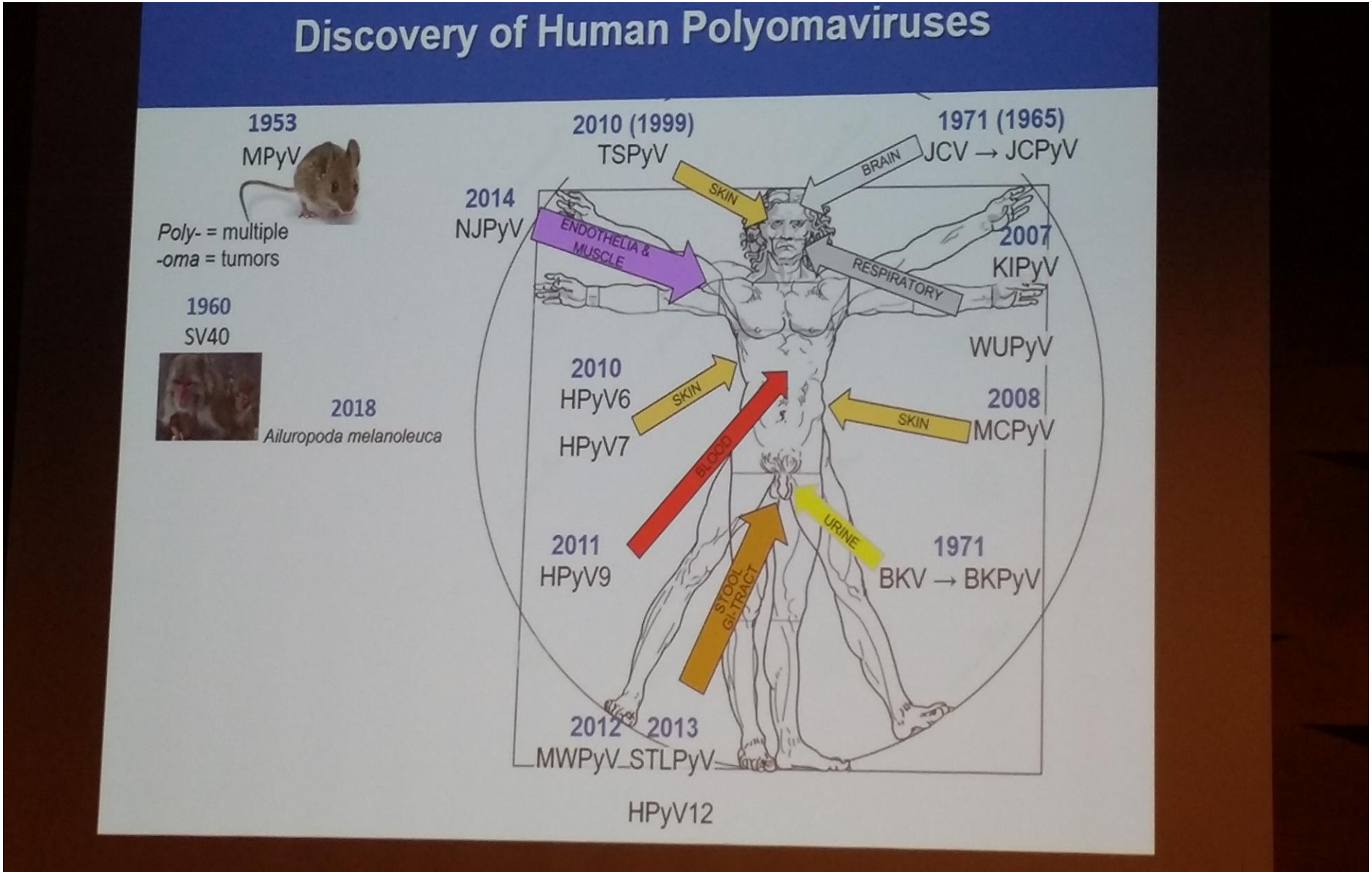
Departement Biomedizin Basel

University Hospital Basel

HUMAN POLYOMA VIRUS



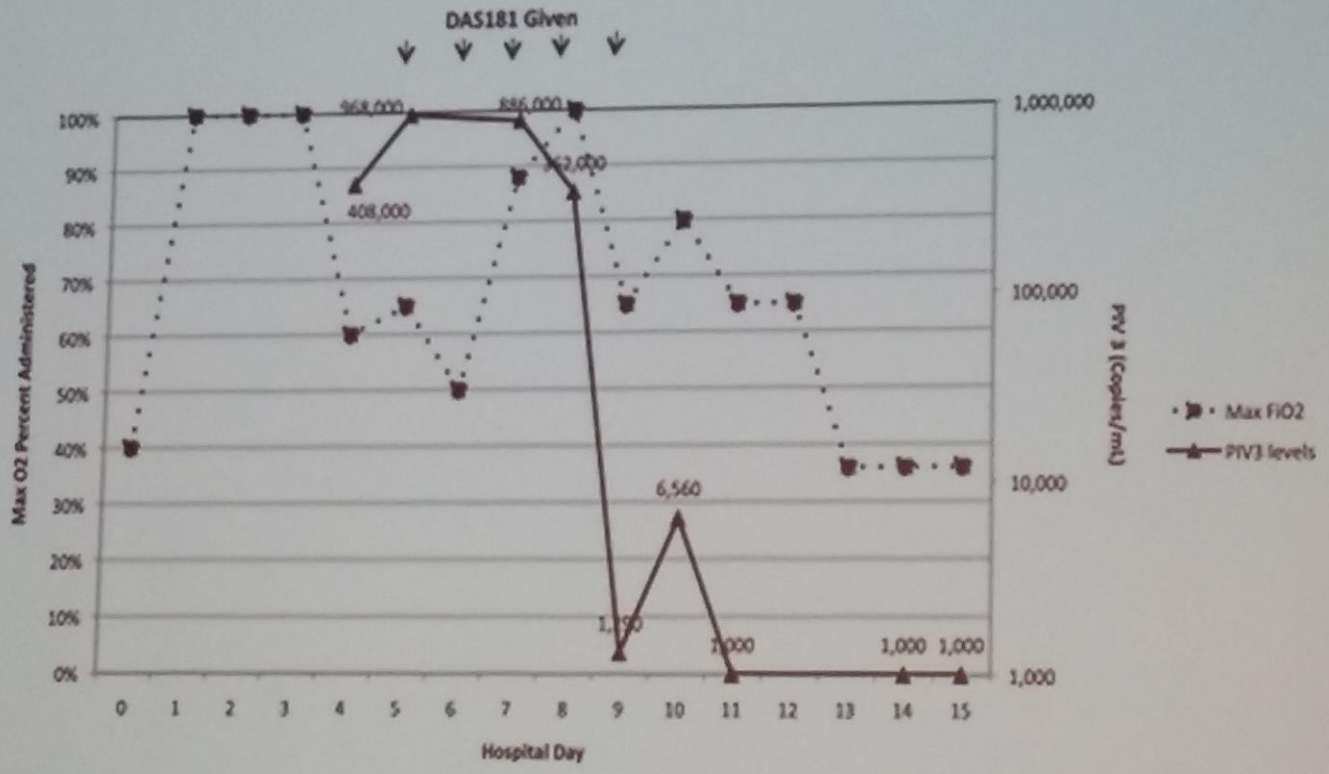
HUMAN POLYOMA VIRUS



PIV: virus parainfluenzali

PIV: *New Treatment Options*

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



Northwestern Medicine

Drozd *et al. Transplant Infect Dis.* 2013; 15: e28-e32.

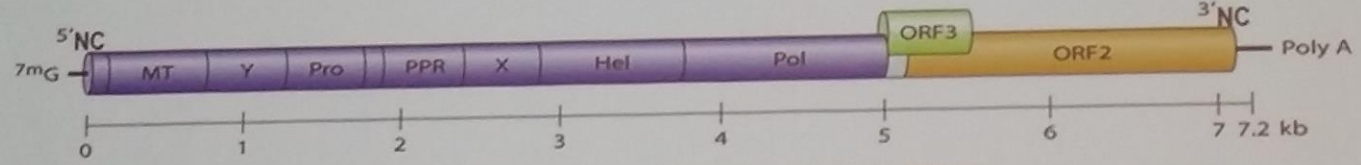
Northwestern University NUTORC

HEV: epatite E

Hepatitis E virus (HEV)

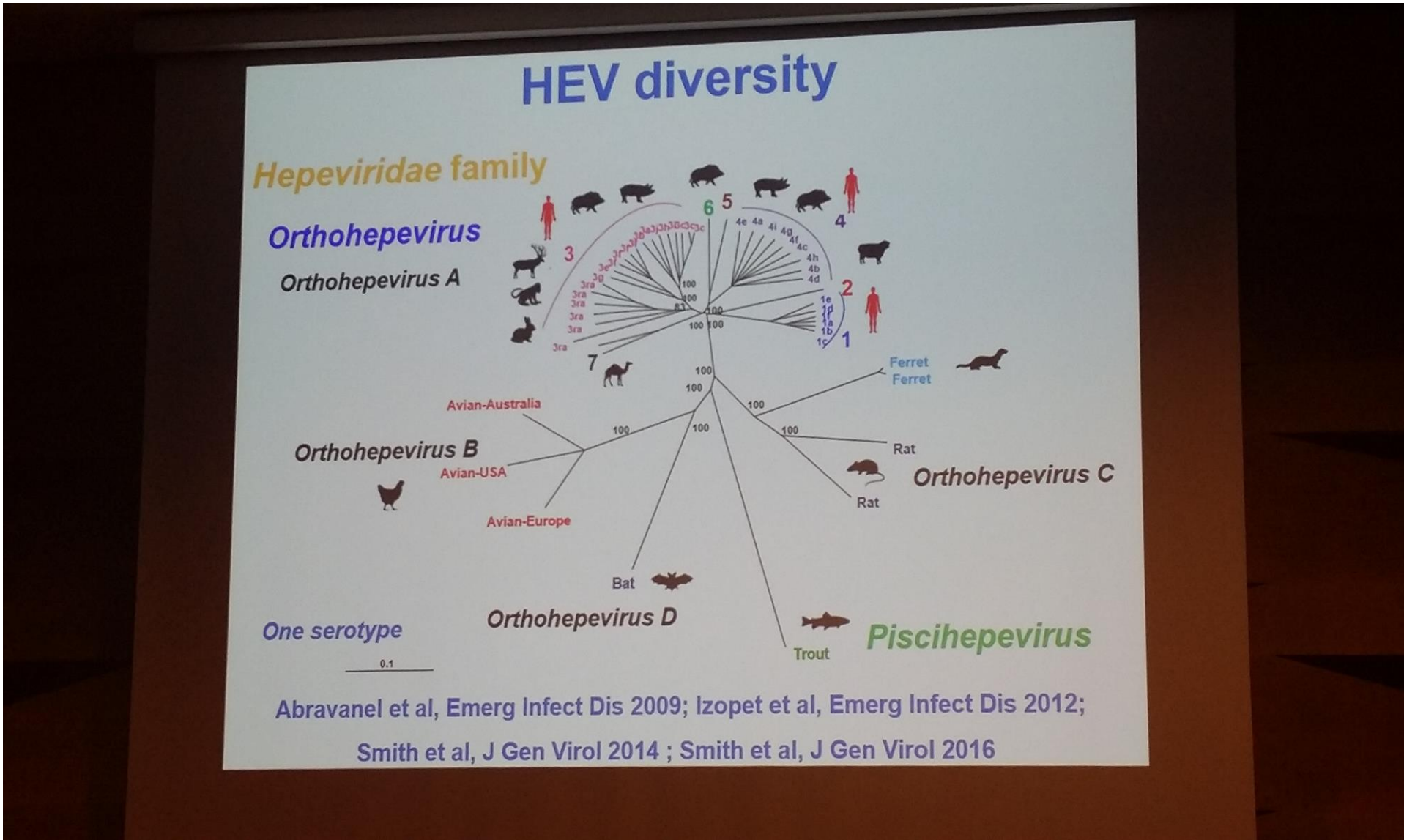
non-A non-B hepatitis
with enteric transmission
Khuroo, Am J Med 1980

Unenveloped virus with
icosaedric capsid
Balayan, Intervirology 1983

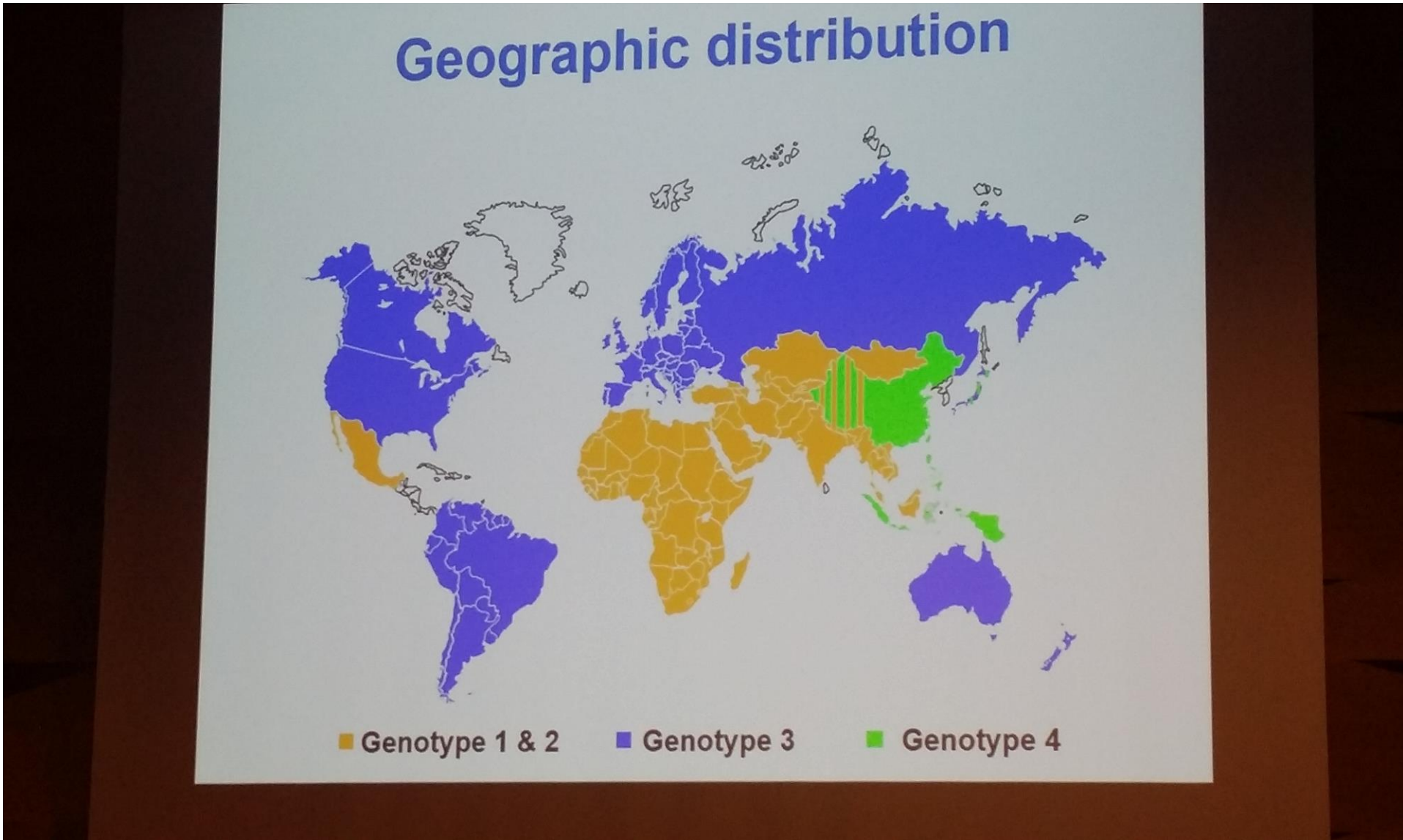


Positive sense, single strand RNA
Reyes, Science 1990; Tam, Virology 1991

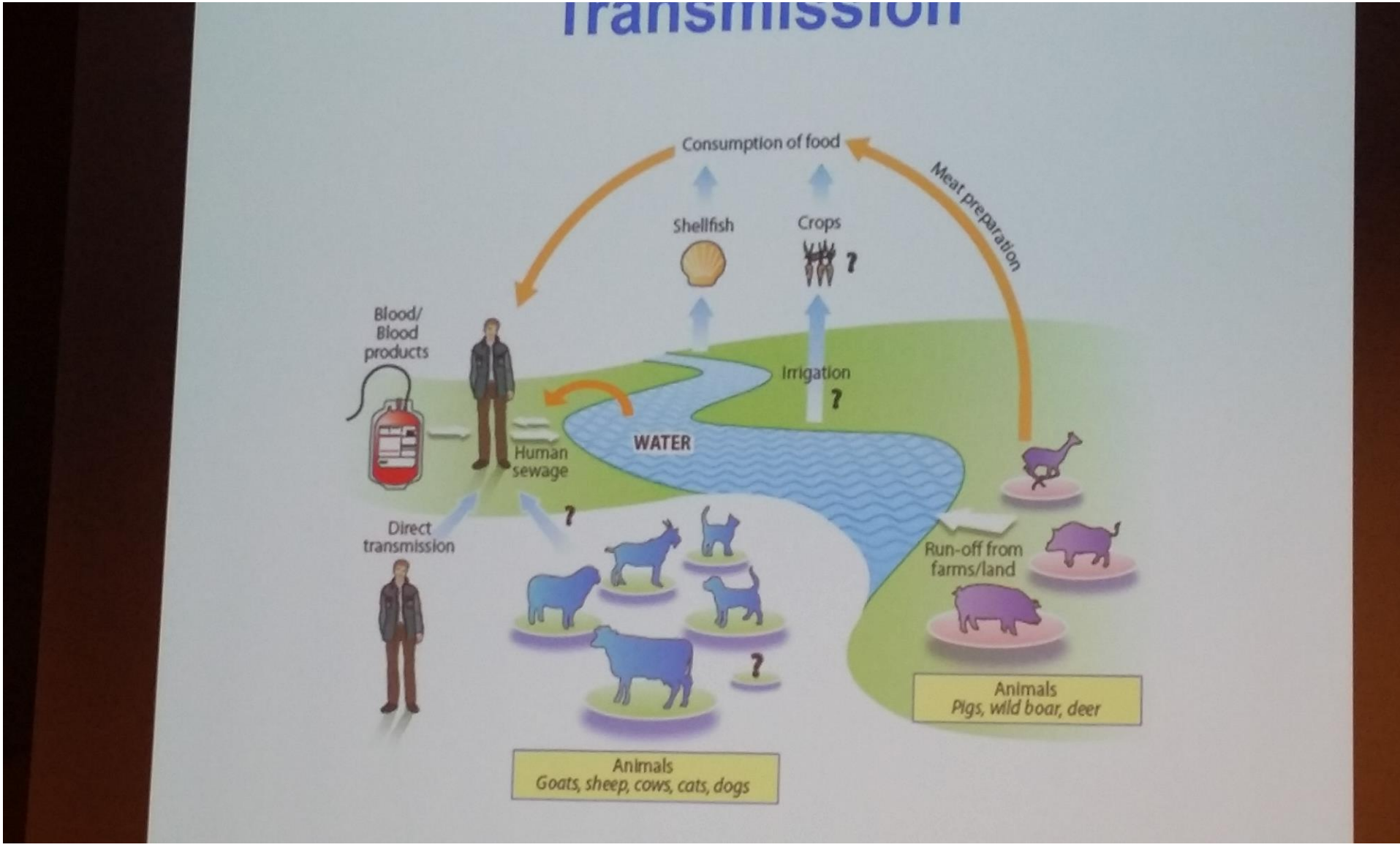
HEV


HEV diversity
Hepeviridae family
Orthohepevirus
Orthohepevirus A
Orthohepevirus B
Orthohepevirus C
Orthohepevirus D
Piscihepevirus
One serotype
0.1
Avian-Australia
Avian-USA
Avian-Europe
Ferret
Ferret
Rat
Rat
Bat
Trout
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

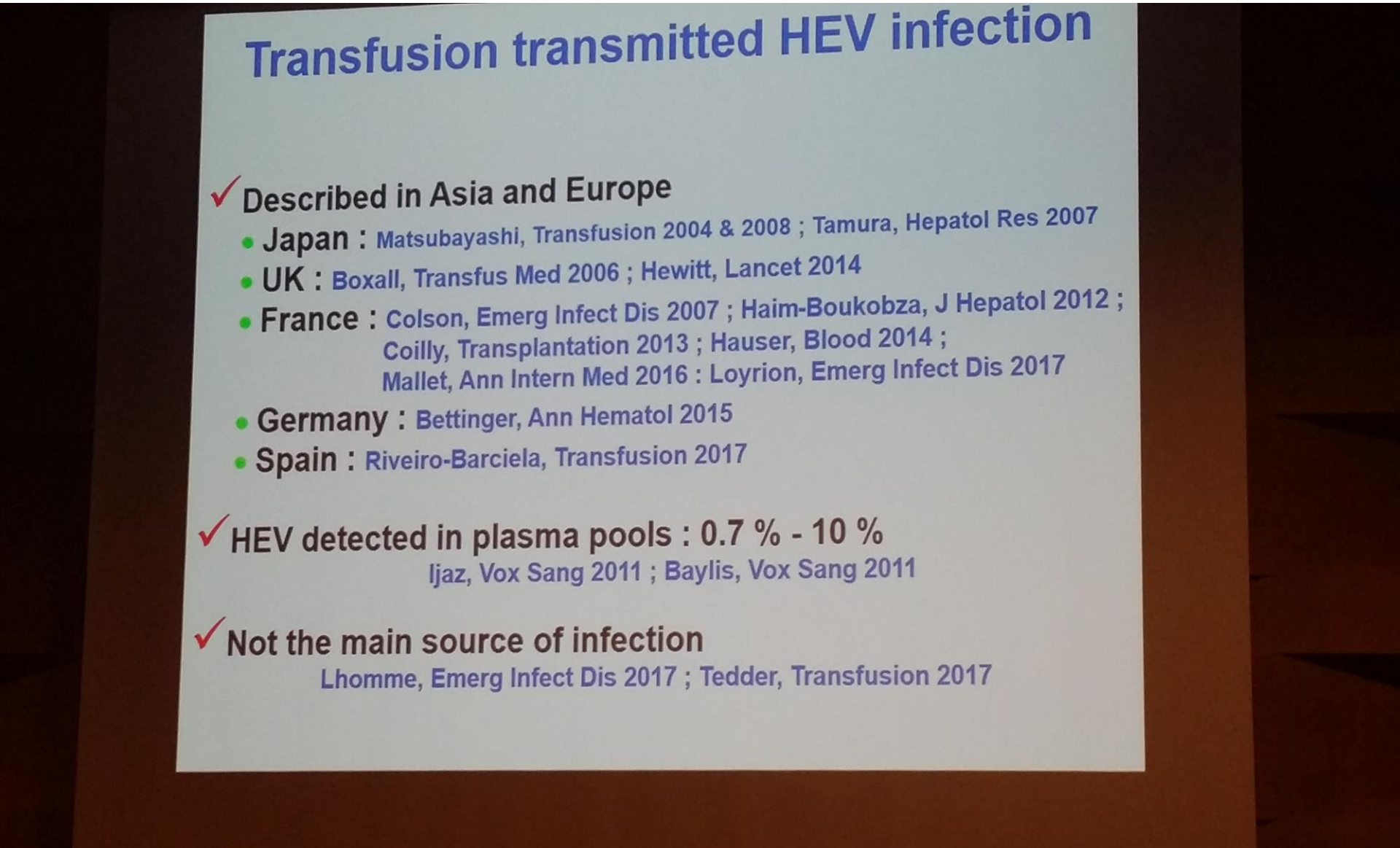
HEV :distribuzione geografica



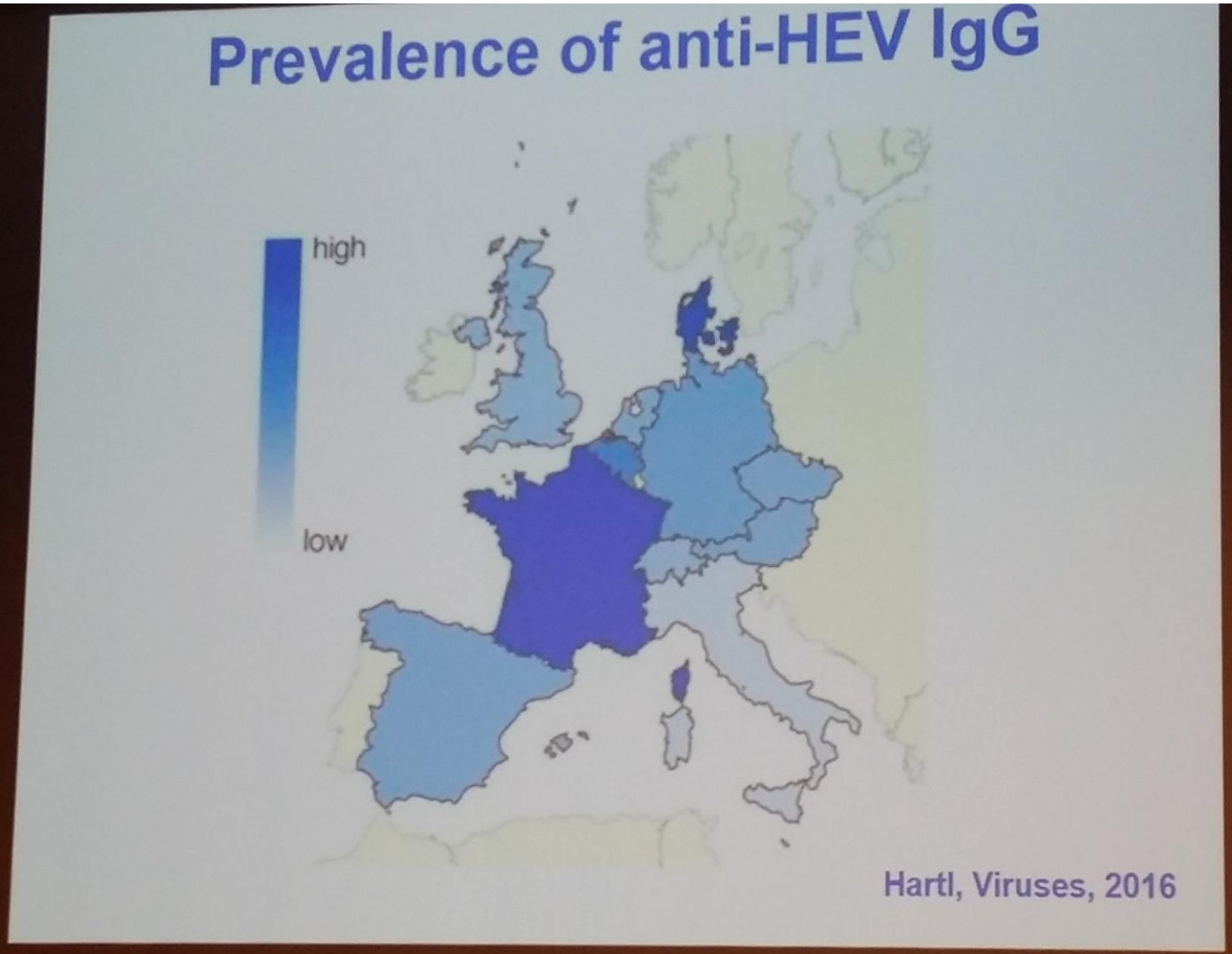
Trasmissione HEV



HEV : contagio trasfusionale



Prevalenza in Europa di HEV



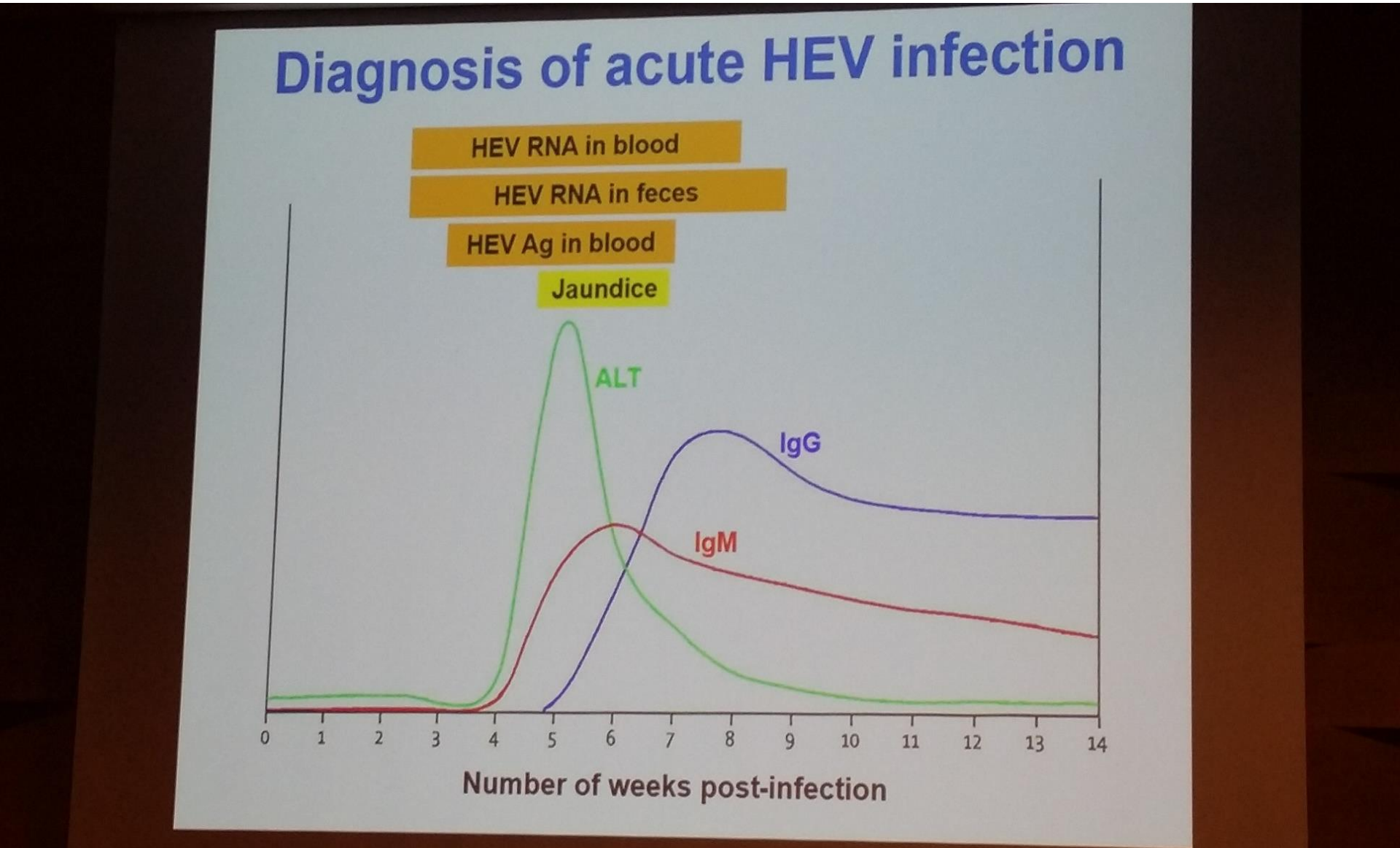
HEV: fattori legati alla trasmissione

Factors associated with anti-HEV IgG

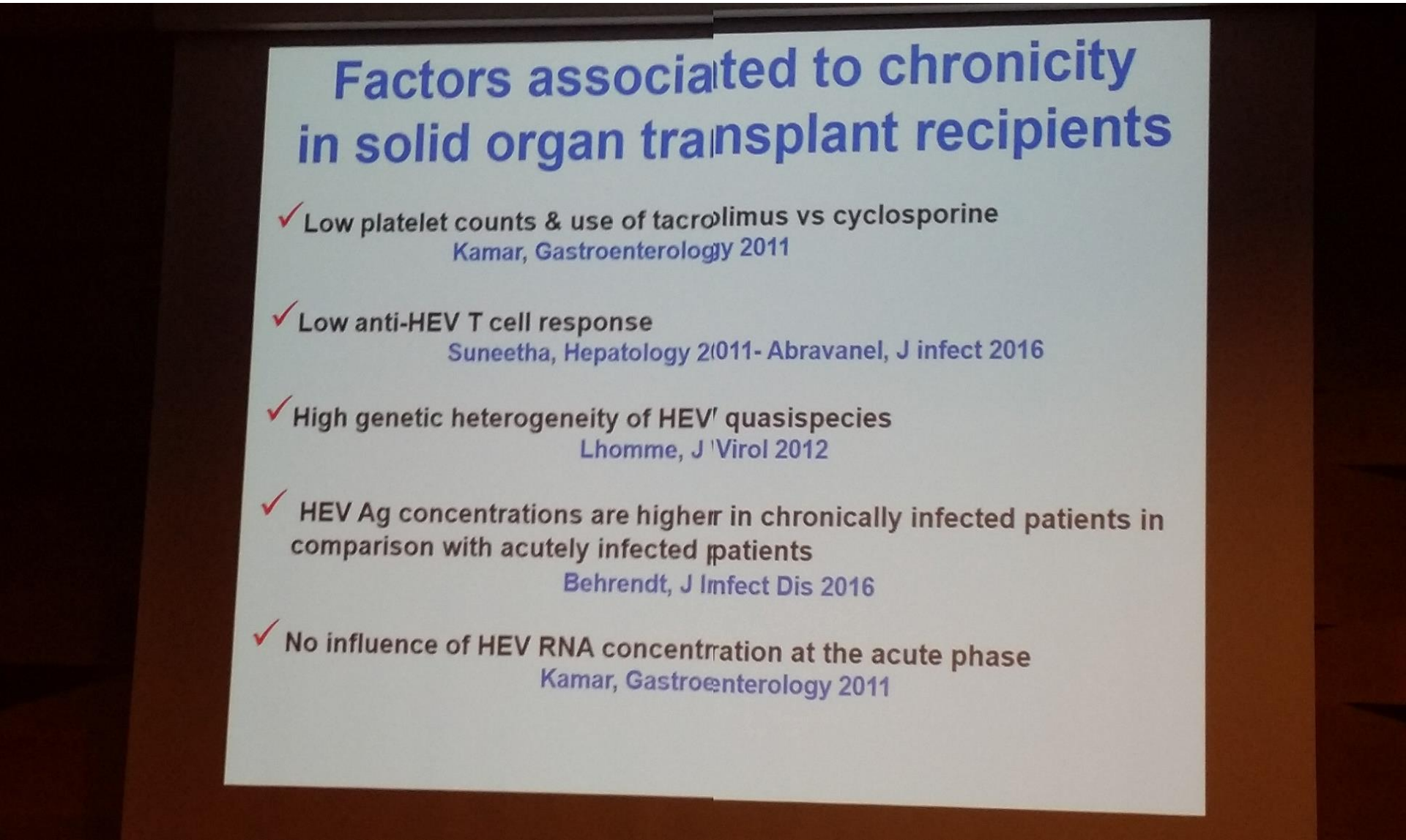
Parameter	Multivariate analysis p	OR	CI95%
Age > 45y	< 0.0001	2.51	[2.23-2.51]
Region	< 0.0001	2.28	[2.01-2.59]
Liver sausage	< 0.001	1.30	[1.13-1.50]
Figatellu	< 0.001	1.72	[1.48-1.99]
Game	< 0.01	1.20	[1.05-1.38]
Offal	< 0.0001	1.38	[1.22-1.57]
Bottled water	< 0.01	0.76	[0.61-0.93]

Mansuy, Hepatology 2016

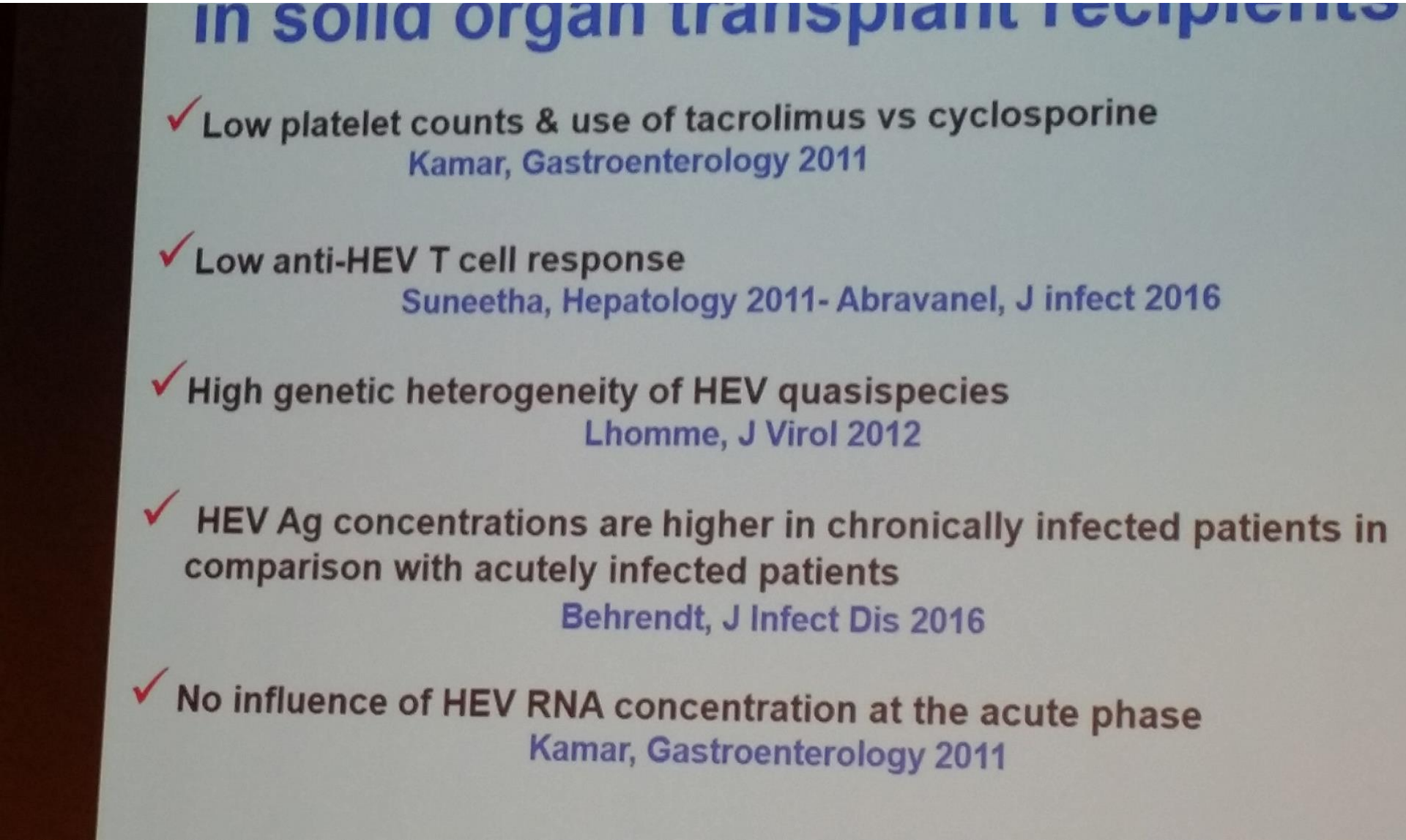
Infezione acuta da HEV



Fattori associati a cronicità negli HEV



HEV nei trapianti

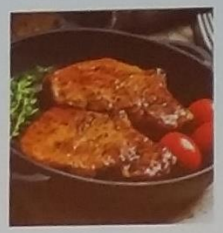


Prevenzione HEV

Preventing HEV infection

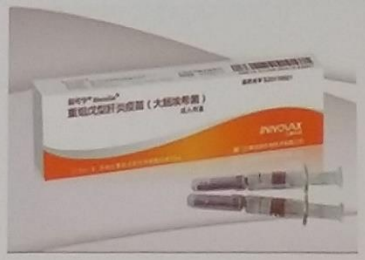
- Cook thoroughly meat at risk (>70°C at least 2 min)

  Johne, Appl Environ Microbiol. 2016

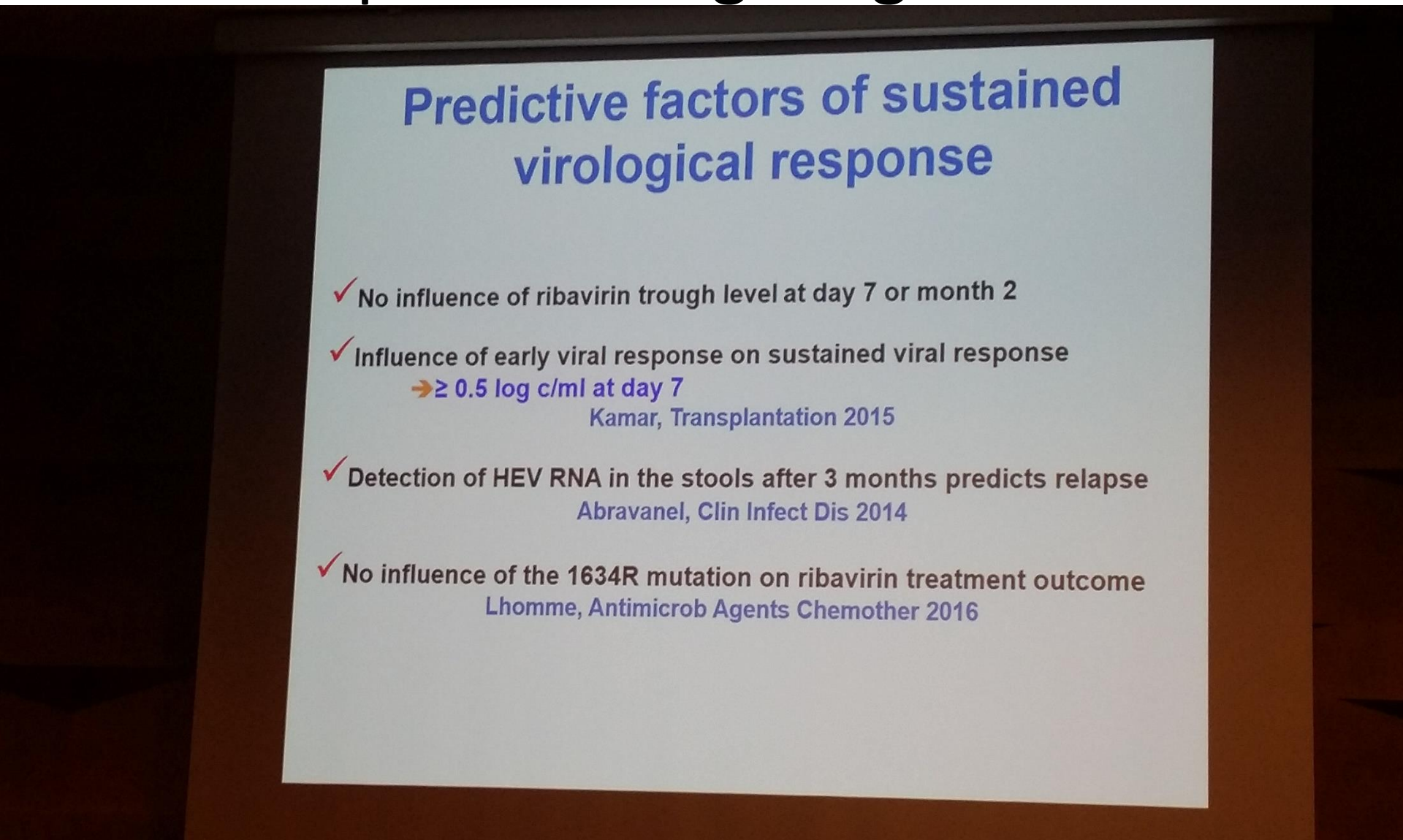


- Vaccine available in China

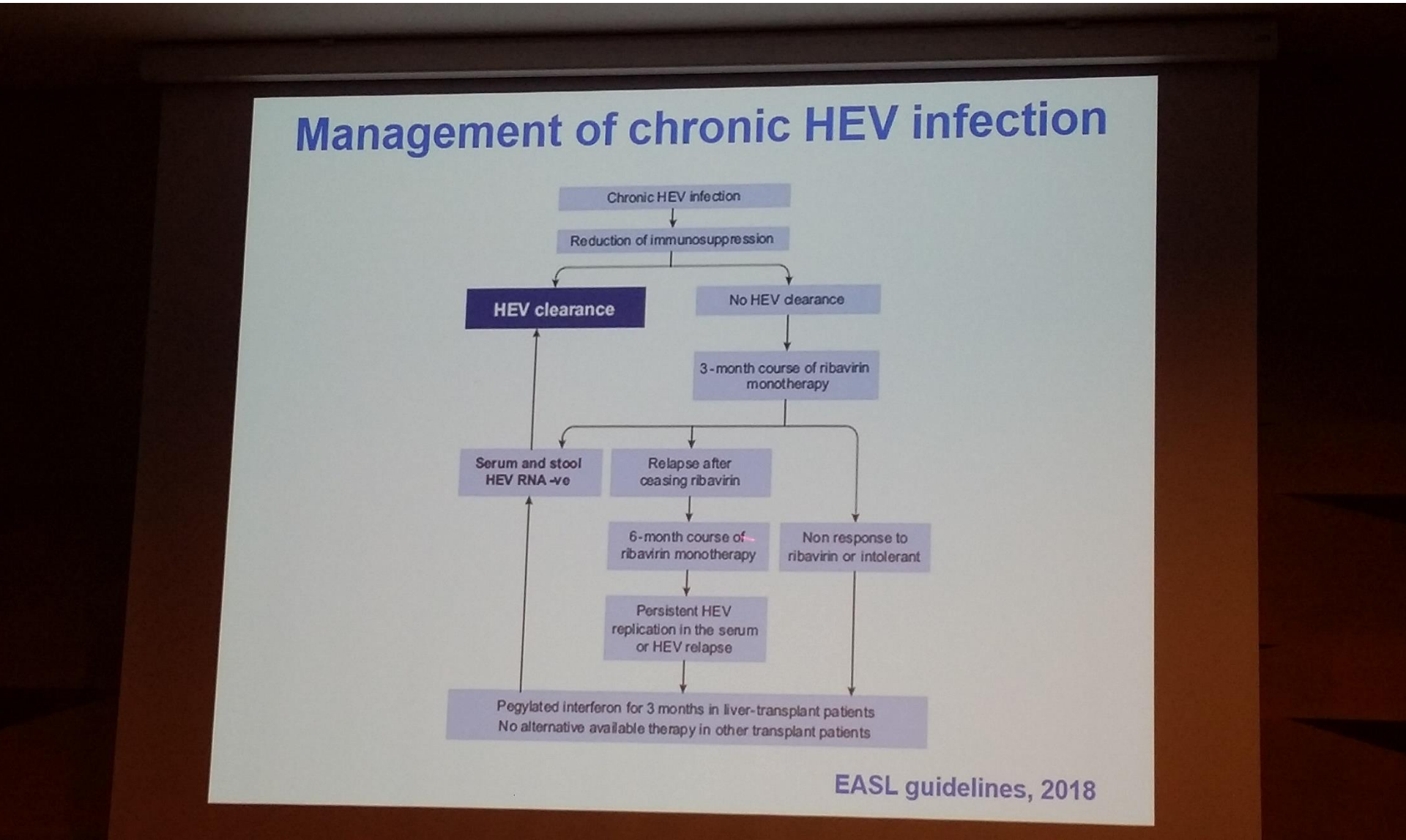
  Zhang, New Engl J Med 2015



Ribavirina o Sofosbuvir: fattori preditivi di guarigione

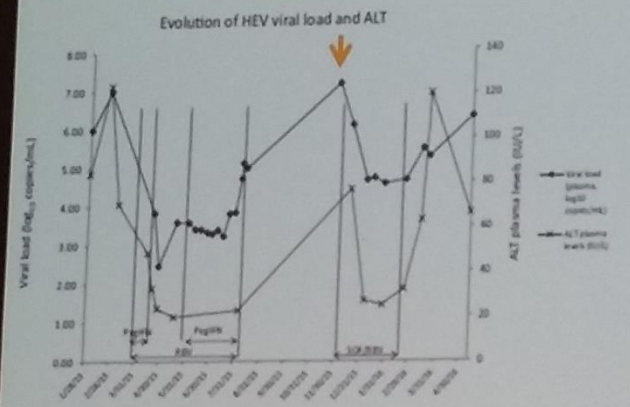


HEV: management

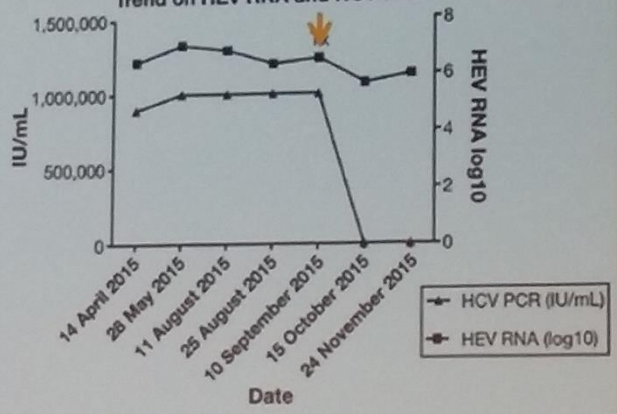


Sofosbuvir in HEV

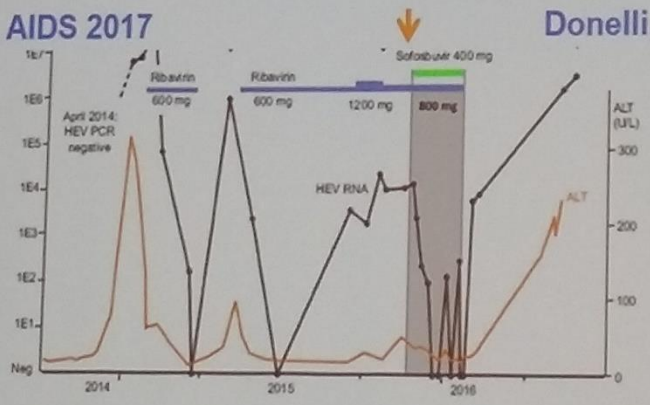
Sofosbuvir shows antiviral activity but is not fully efficient



Todesco, AIDS 2017

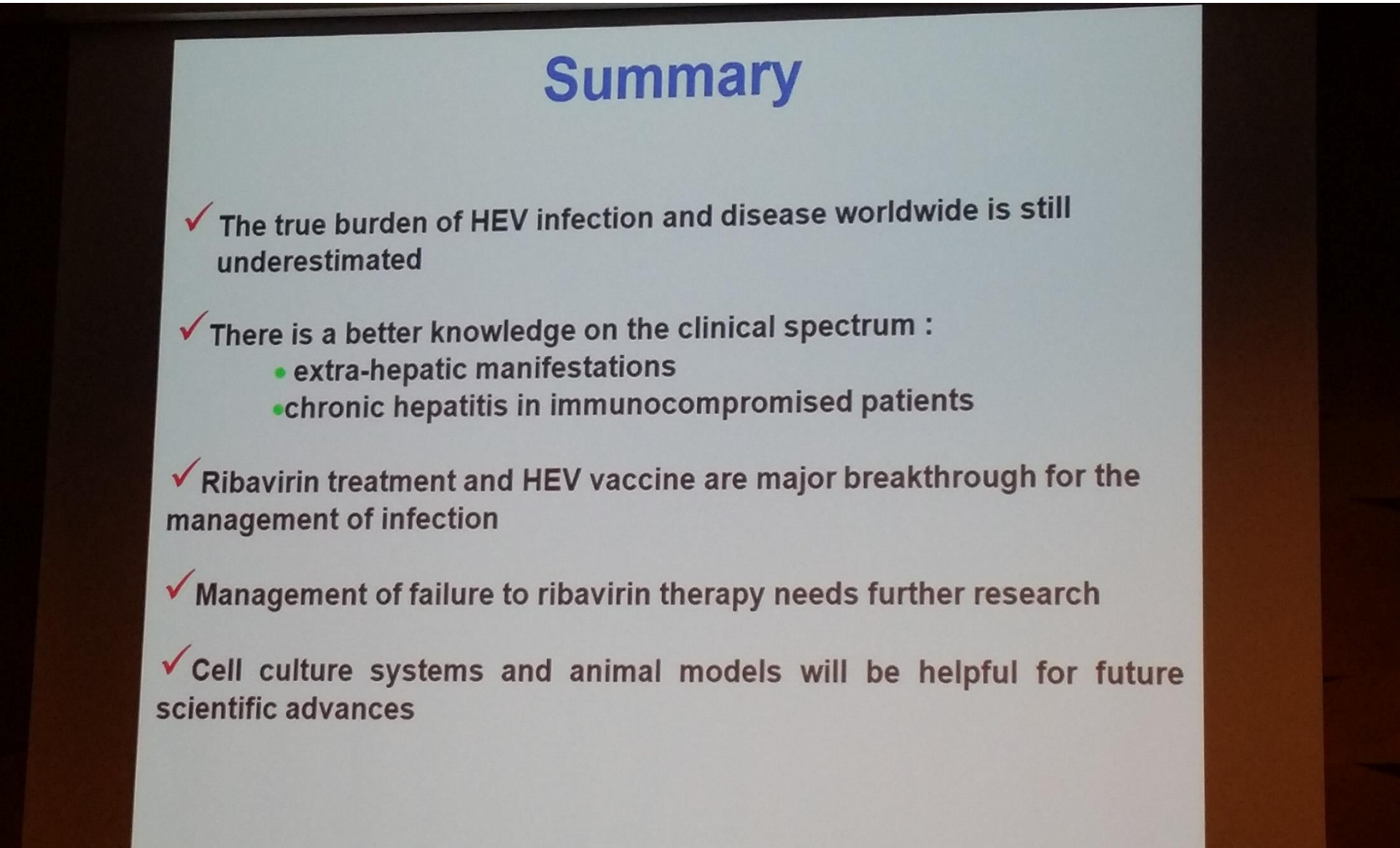


Donelli, Gastroenterology 2017

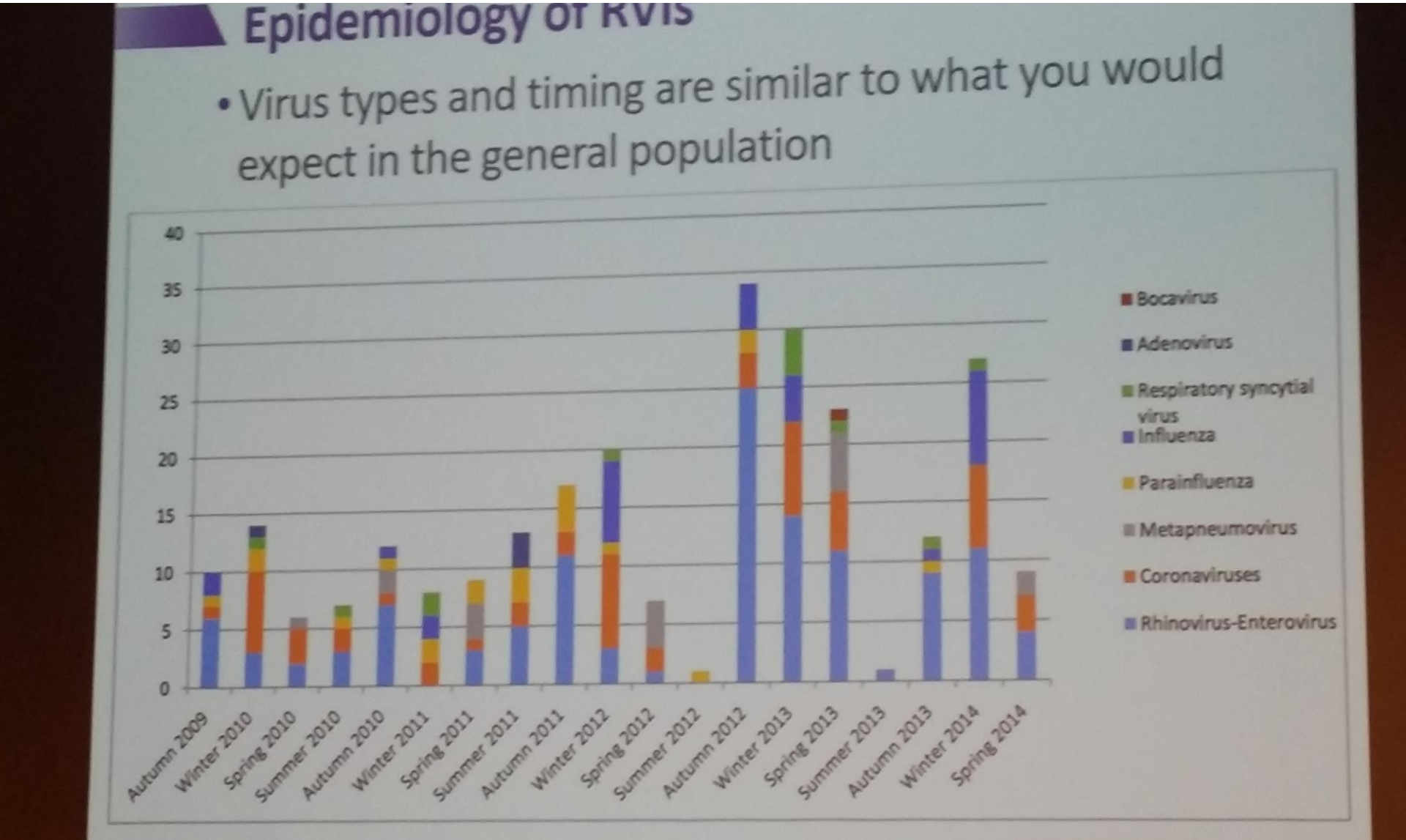


Van der Valk, J Hepatol 2017

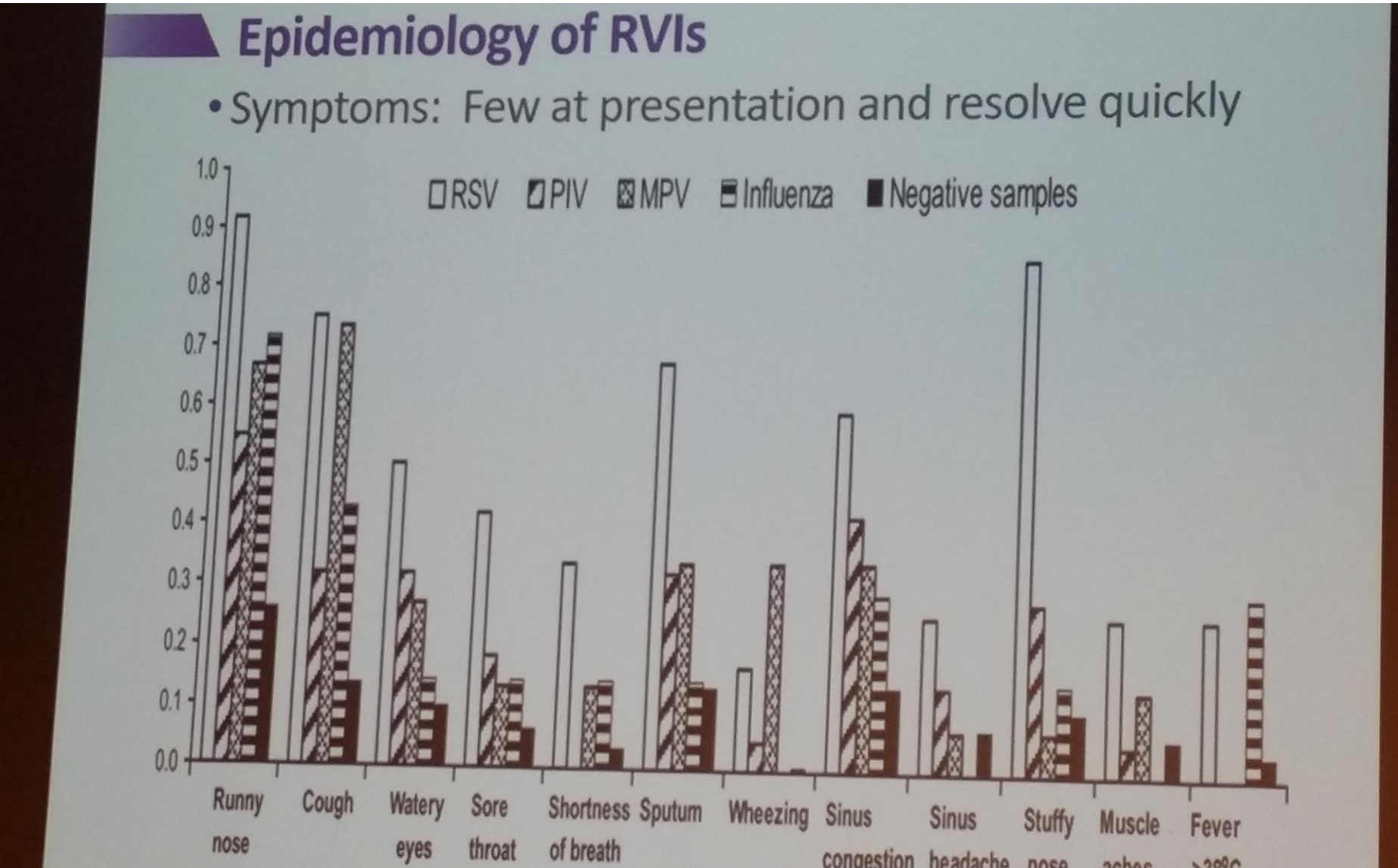
HEV: sommario



Virus sinciziale respiratorio

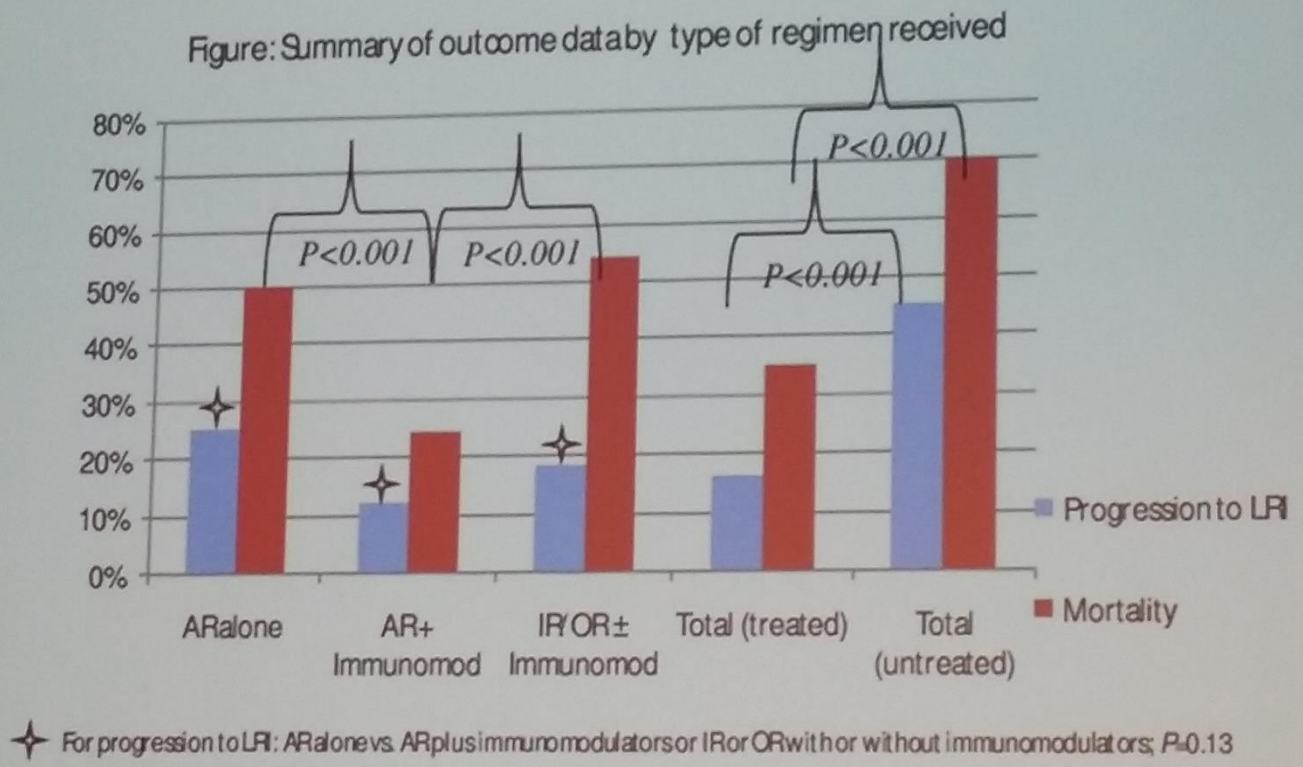


RVIs: virus sinciziale respiratorio



RSV : terapia con immunomod

RSV in Hematopoietic Stem Cell Transplantation



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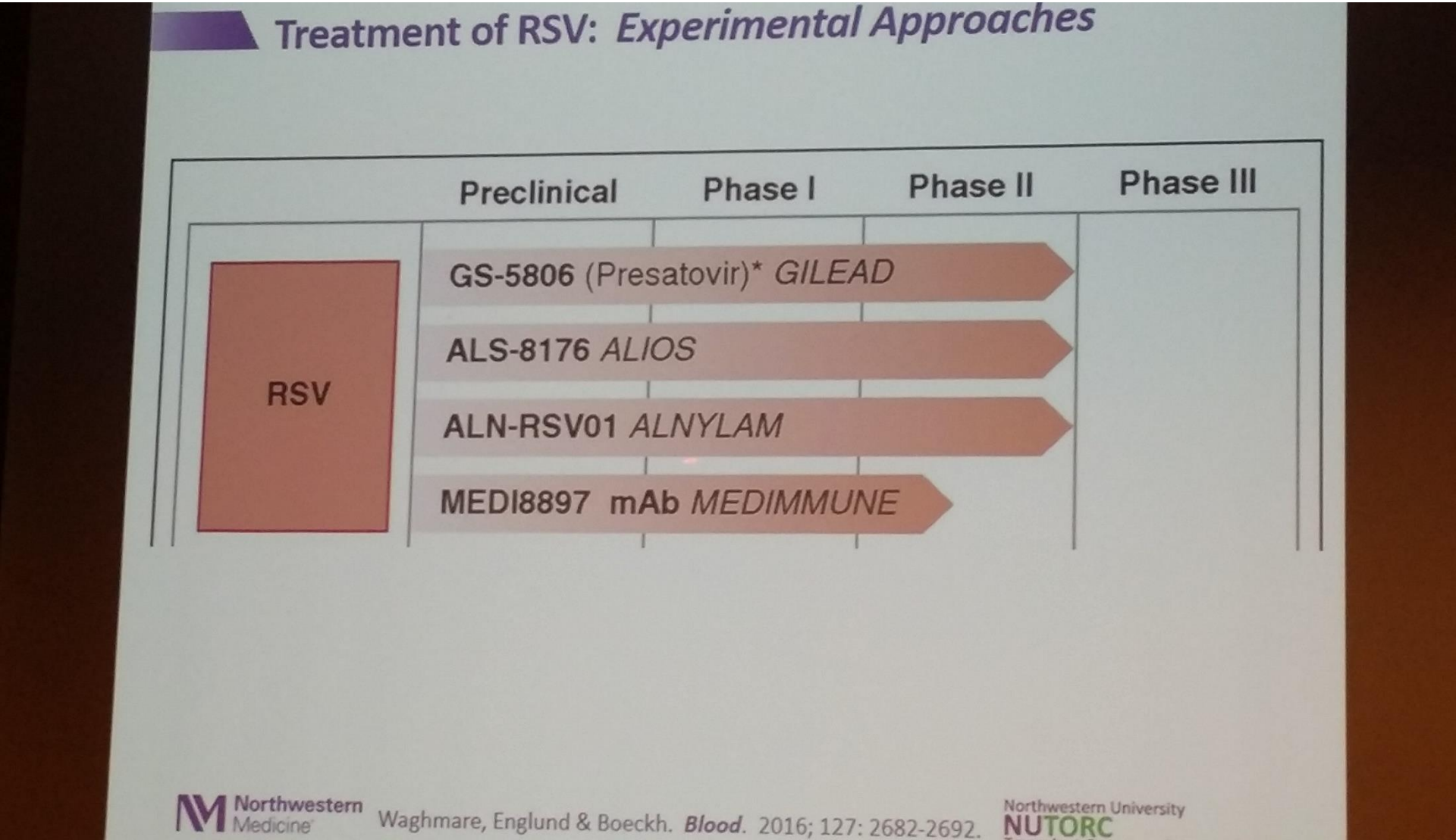
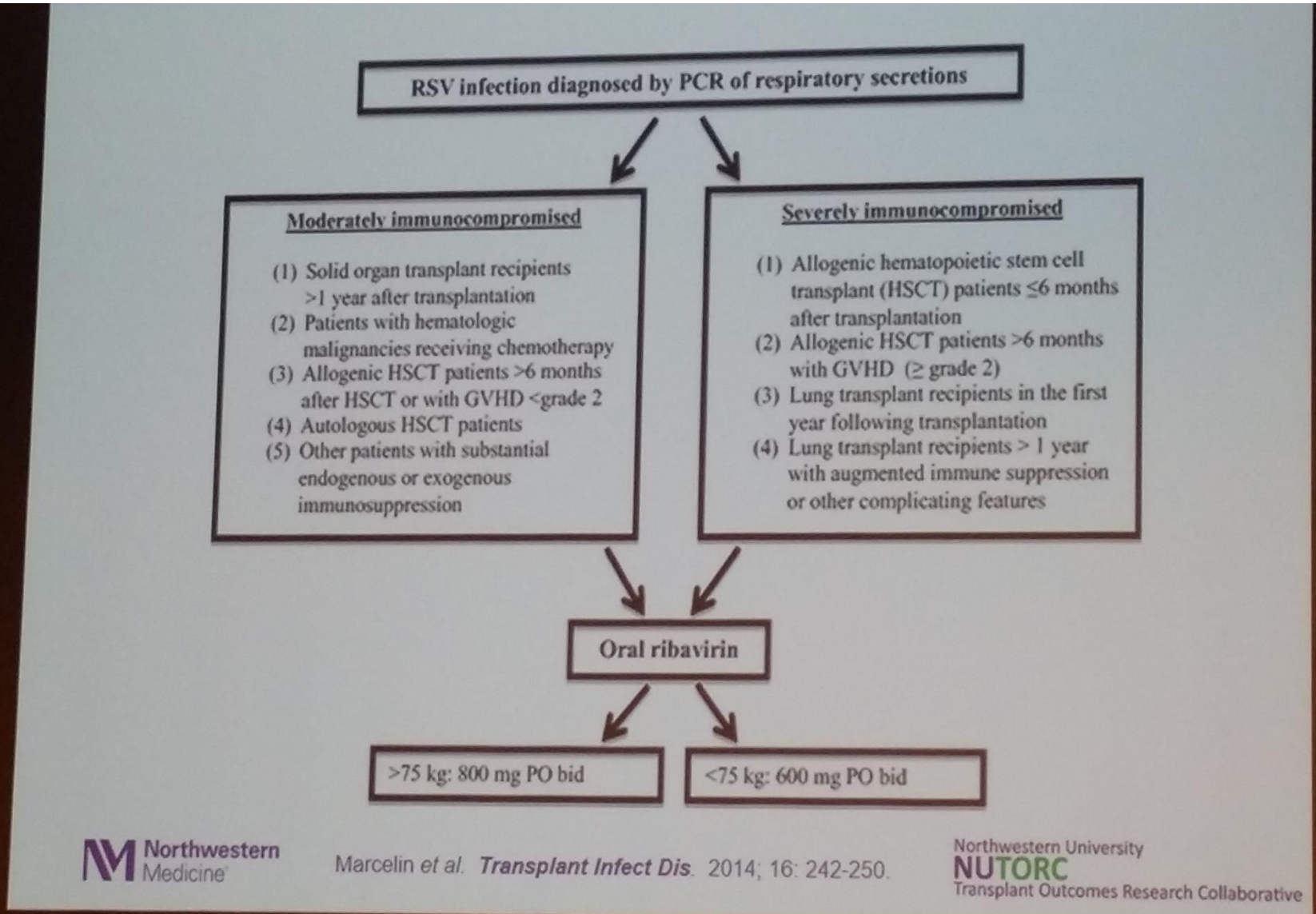
Shah & Chemaly. *Blood*. 2011; 117: 2755-2763.

Northwestern University NUTORC Transplant Outcomes Research Collaborative

RSV: altre terapie sperimentali



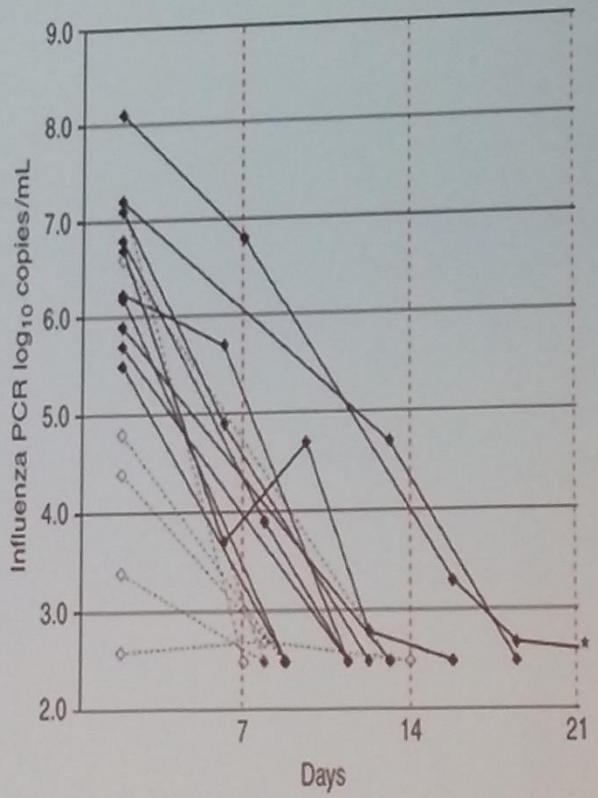
Virus Sinciziale respiratorio - RSV



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.

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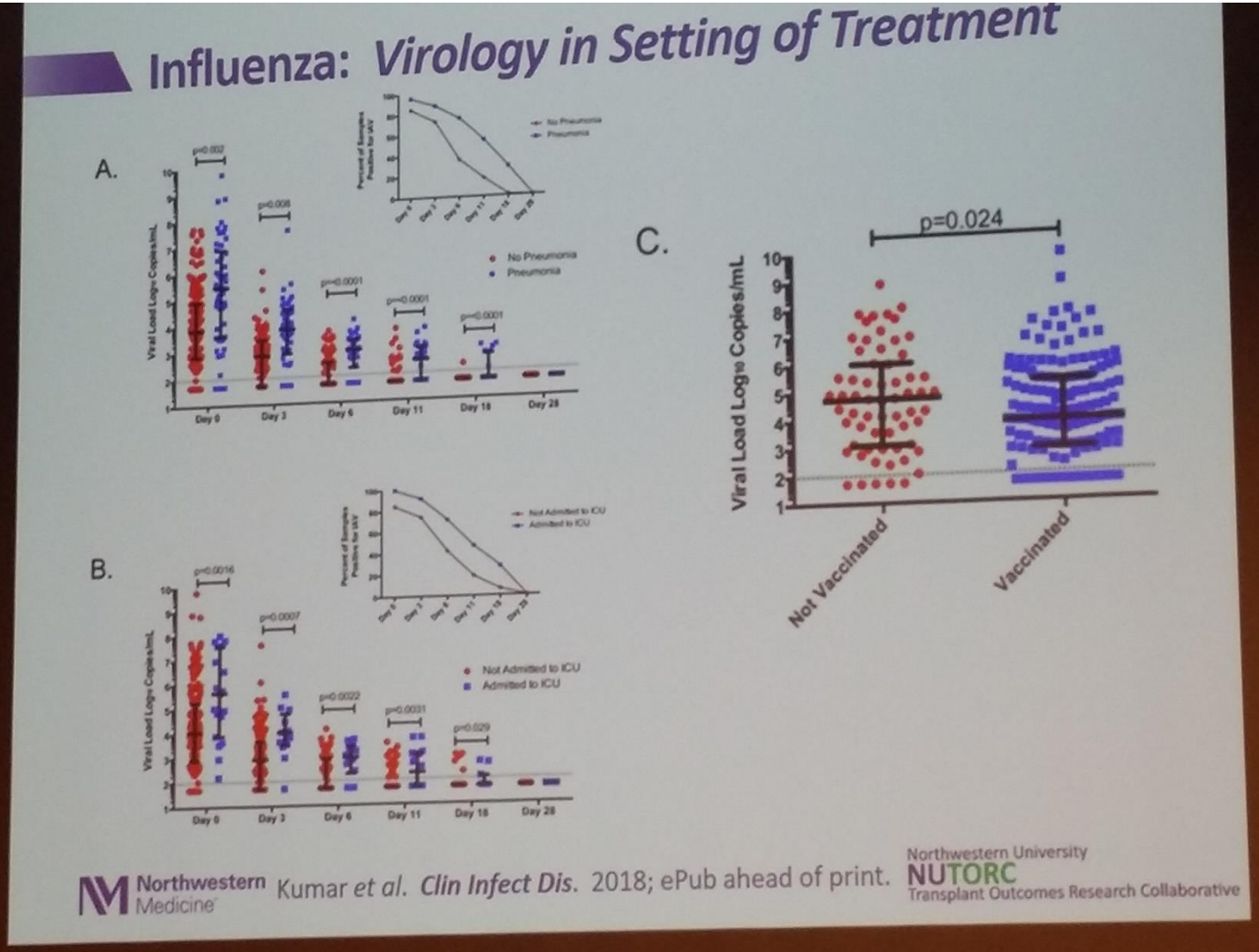
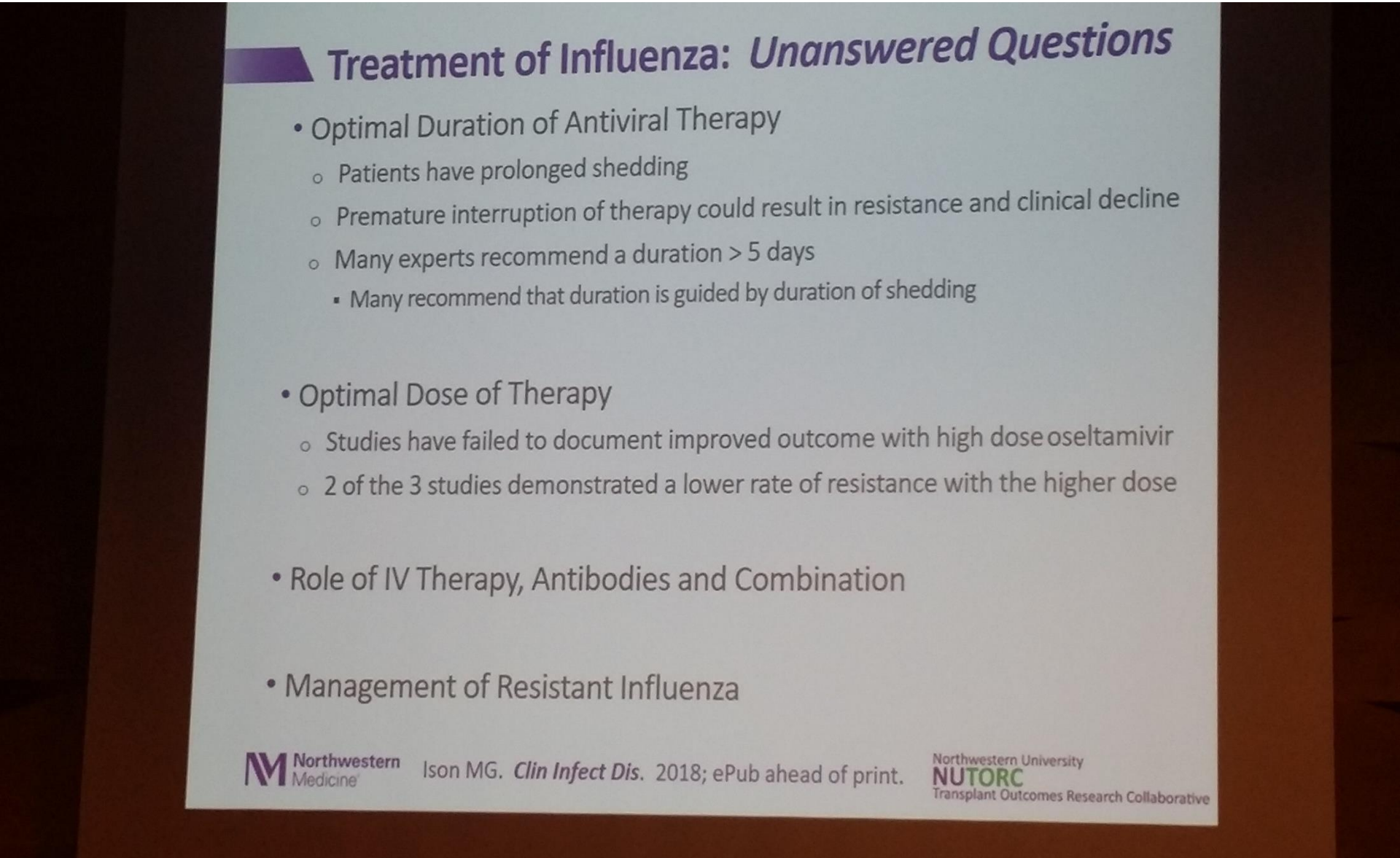
Northwestern University
NUTORC
Transplant Outcomes Research Collaborative

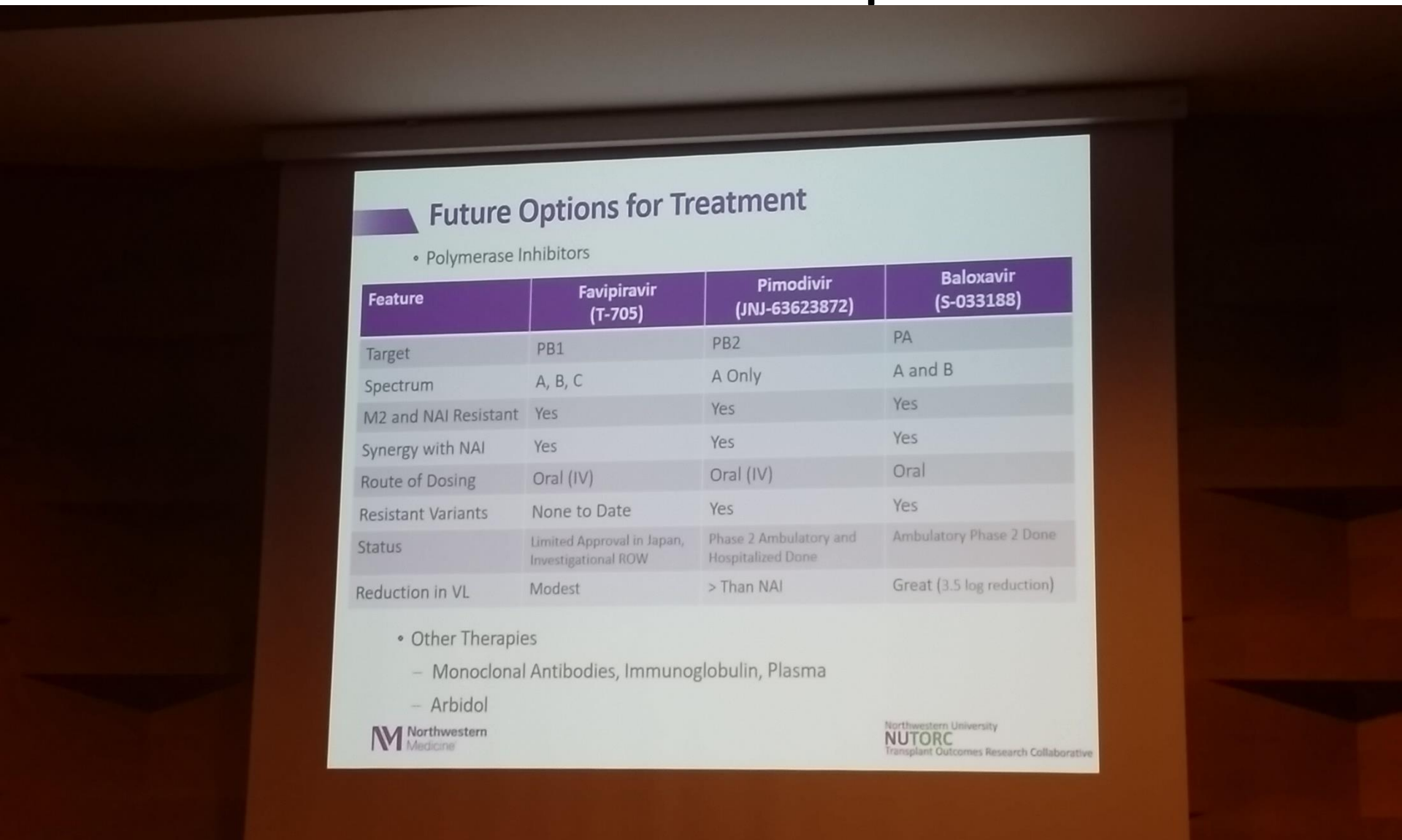
Trattamento virus influenzale



Influenza:durata terapia

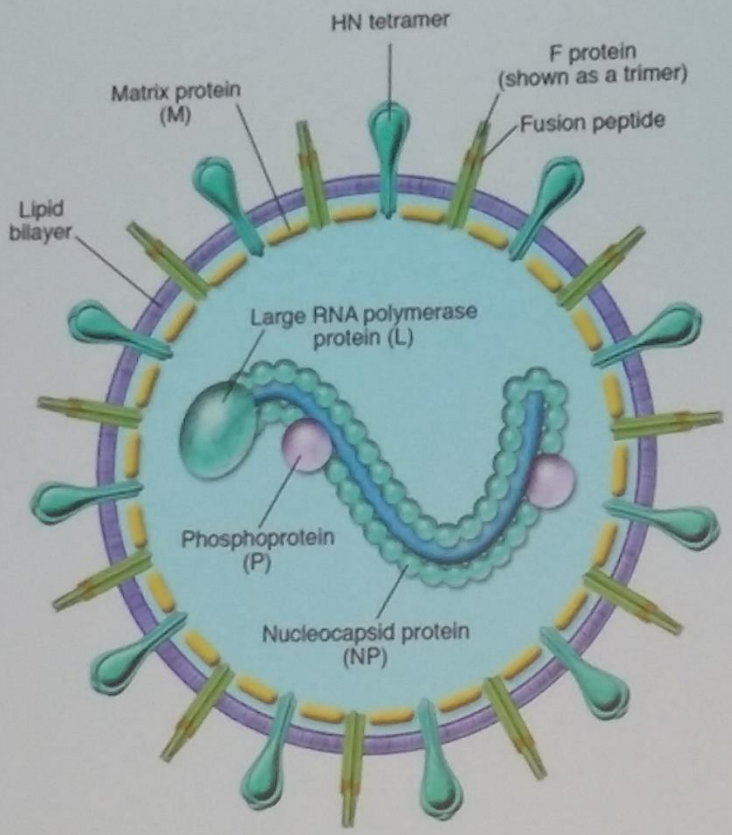


Opzioni terapeutiche future per il virus influenzale nei trapiantati



PIV: polyoma virus

PIV in Transplantation



HPV

Human Polyomavirus Infections in Immunocompromised Hosts

Hans H Hirsch

Transplantation & Clinical Virology
Department Biomedicine (Haus Petersplatz)

Infectious Diseases & Hospital Epidemiology
University Hospital Basel
Basel
Switzerland

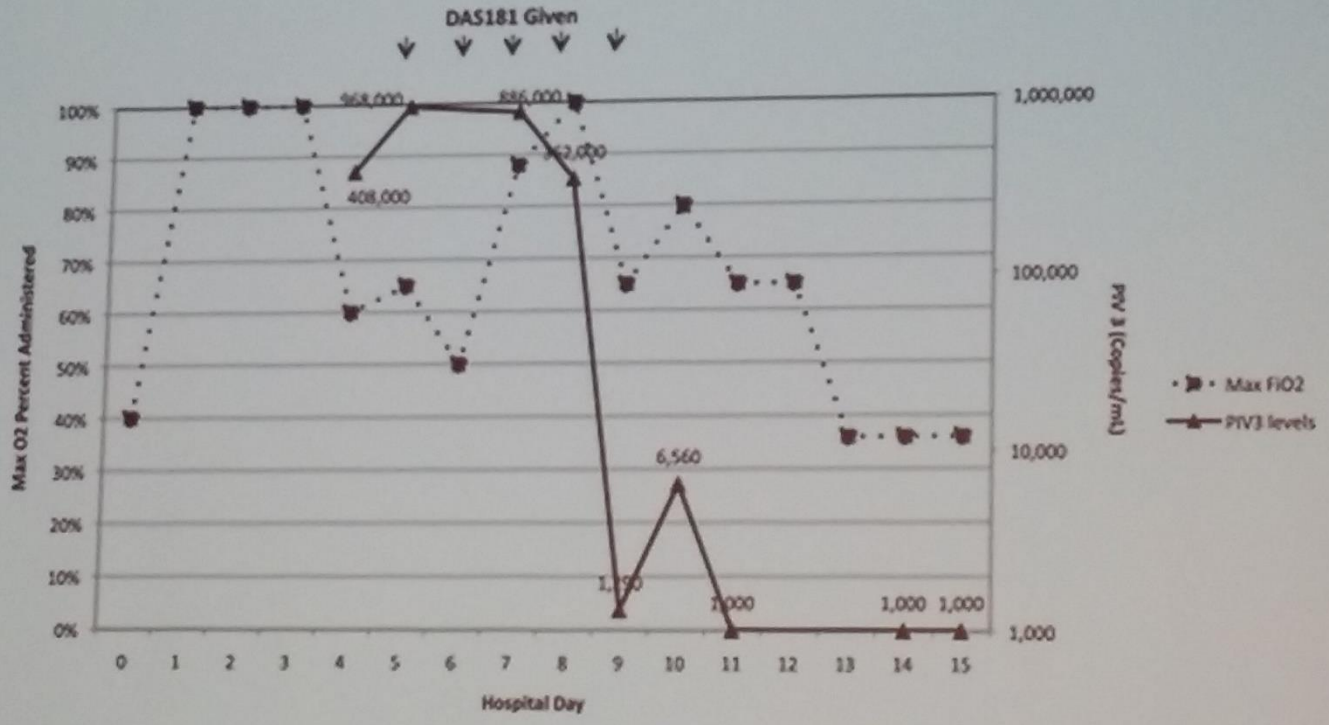
Departement
Biomedizin
Basel

University Hospital
Basel

Trattamento PIV

PIV: *New Treatment Options*

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



Drozd *et al.* ***Transplant Infect Dis.*** 2013; 15: e28-e32.

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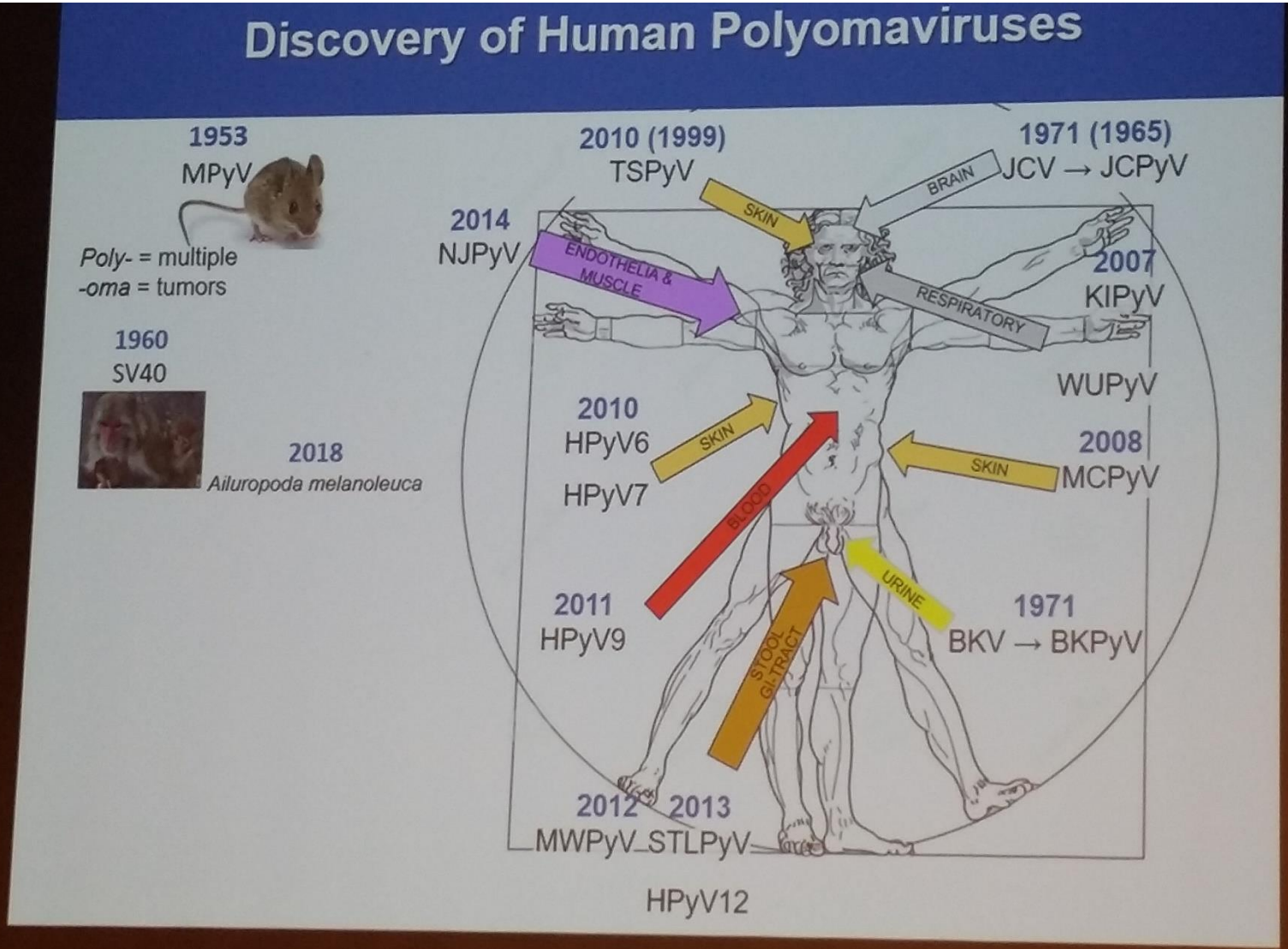
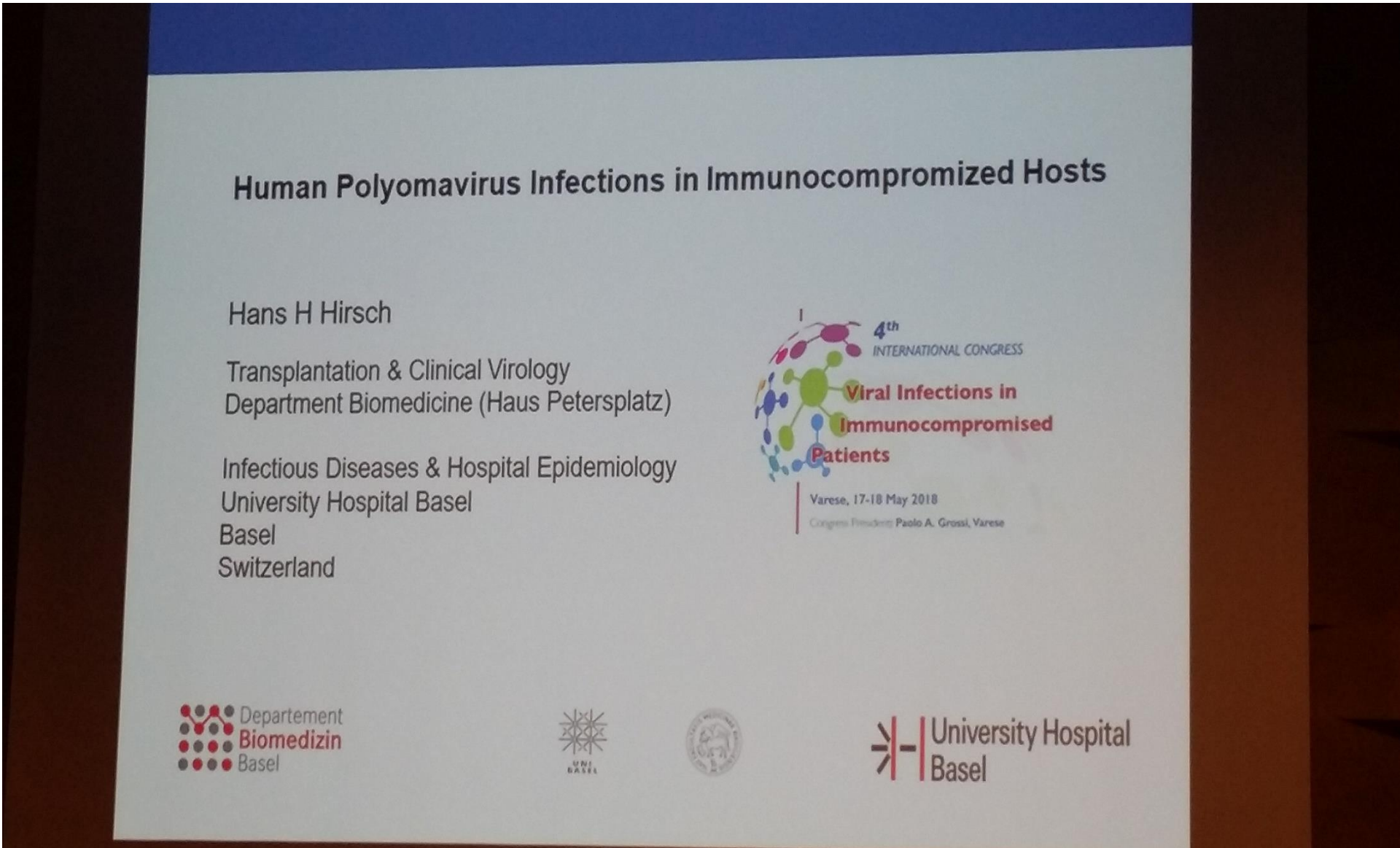
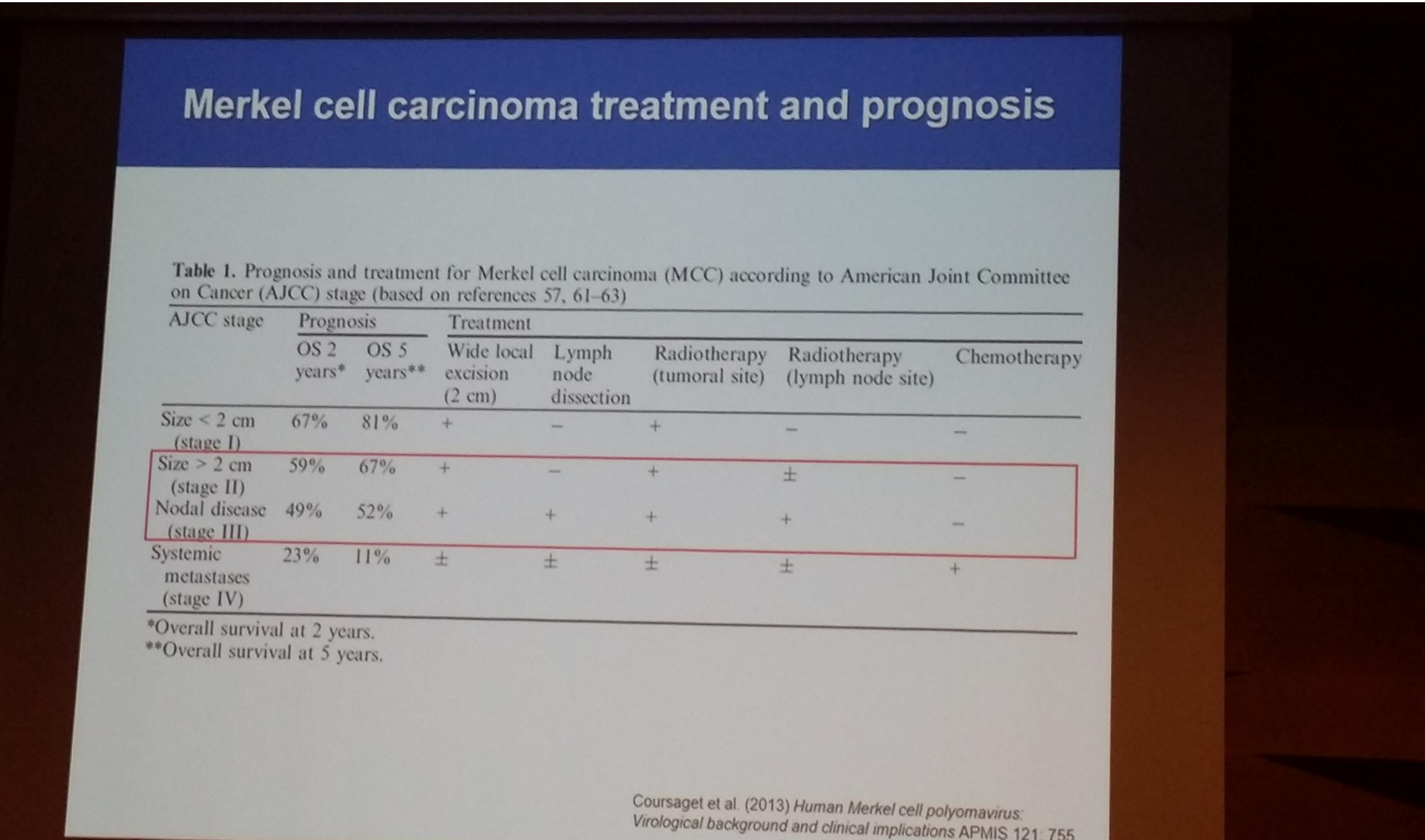
HPV : localizzazioni



Polyioma virus



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%	±	±	±	±	+

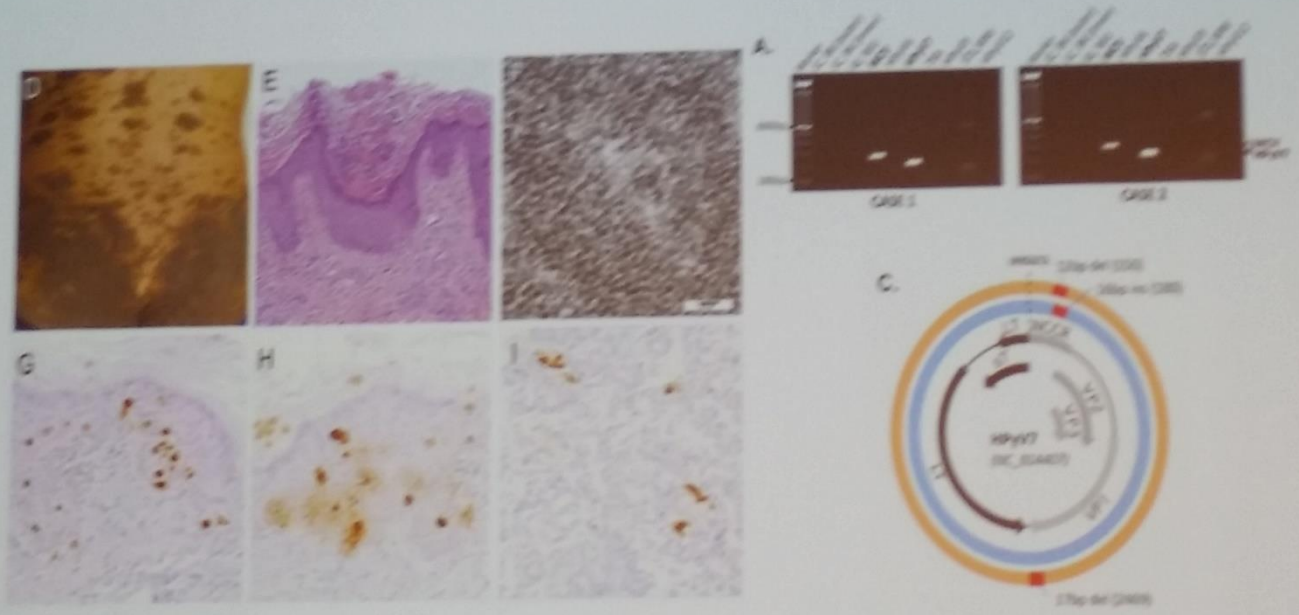
*Overall survival at 2 years.
**Overall survival at 5 years.

Coursaget et al. (2013) *Human Merkel cell polyomavirus: Virological background and clinical implications* APMIS 121: 755

HPyV.7

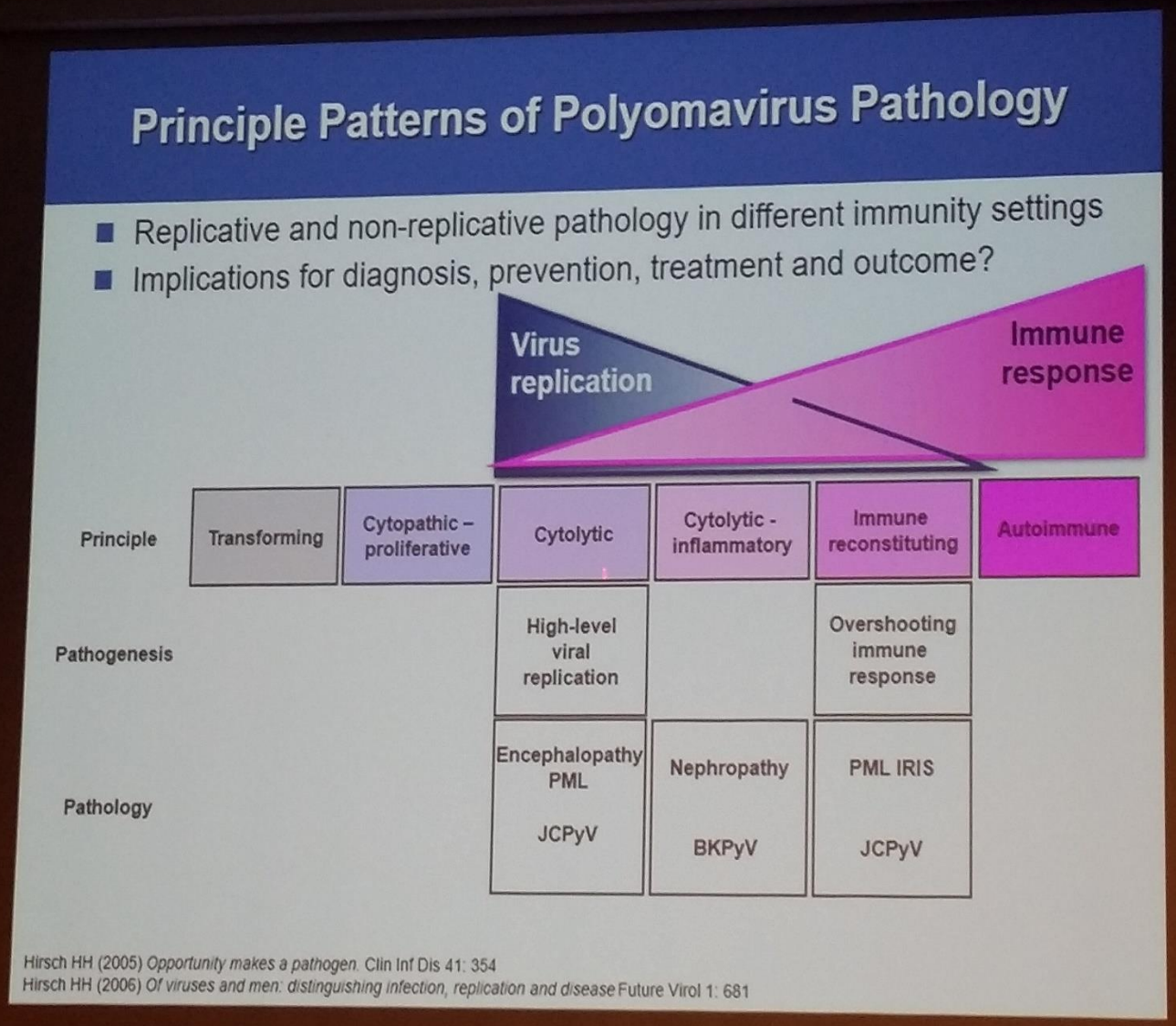
HPyV-7

- 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



Ho, Jedrych, Chang, Moore et al. (2014) *Human Polyomavirus 7-Associated Pruritic Rash and Viremia in Transplant Recipients* J Infect Dis

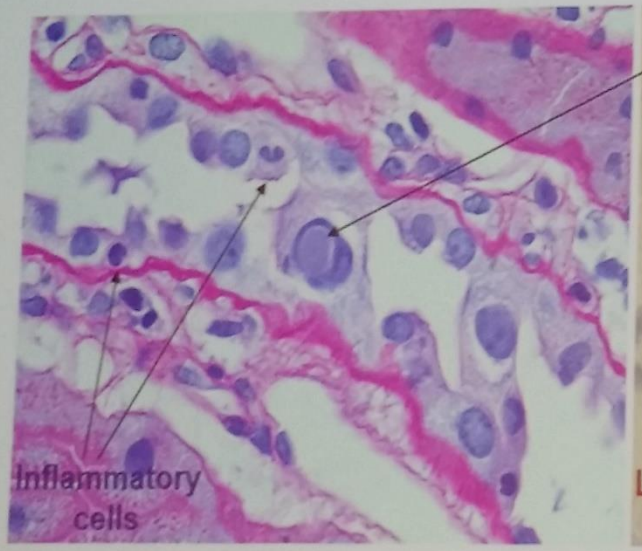
Polyomavirus-patologia

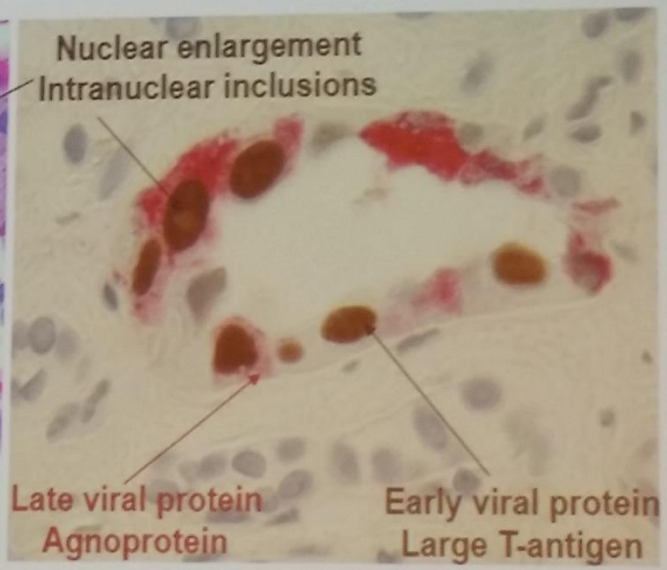


Polyiomavirus

What is BK Polyomavirus-associated Nephropathy ?

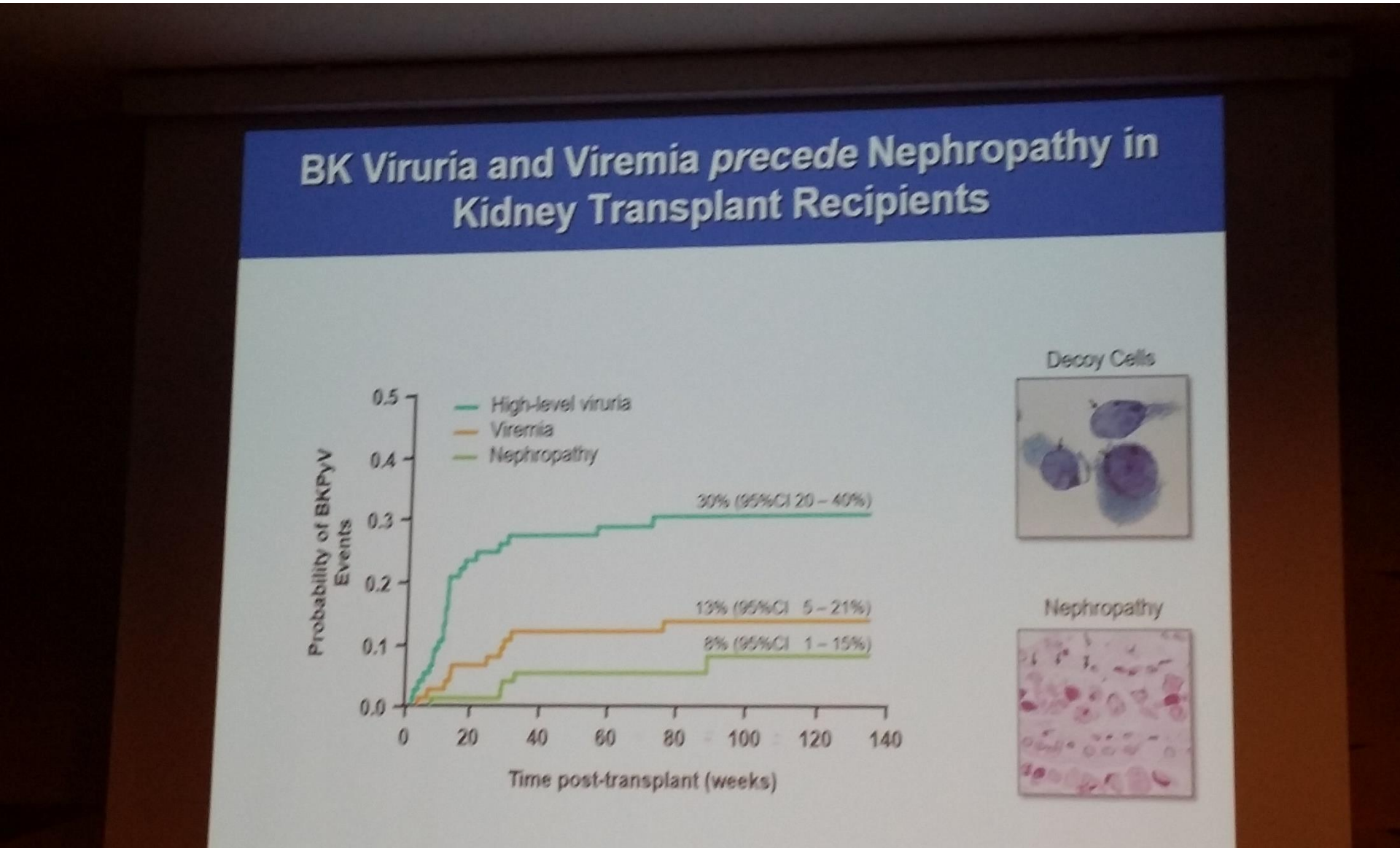
- Proven disease occurring in 5% of kidney transplants (range 1% - 15%)
  - Cytopathically altered renal tubular epithelial cells, cell lysis (necrosis), denudation
  - Secondary inflammation
  - Functional deficits in ~90%, progressive deterioration, graft loss in ~50%





Hirsch HH, Randhawa P (2013) *AST IDCOP Guidelines: BK Polyomavirus* Am J Transpl 13 (s4): 178
Hirsch *et al.* (2014) *European Perspective on Human Polyomaviruses in Solid Organ Transplantation.* Clin Inf Microbiol 20 (s7): 74

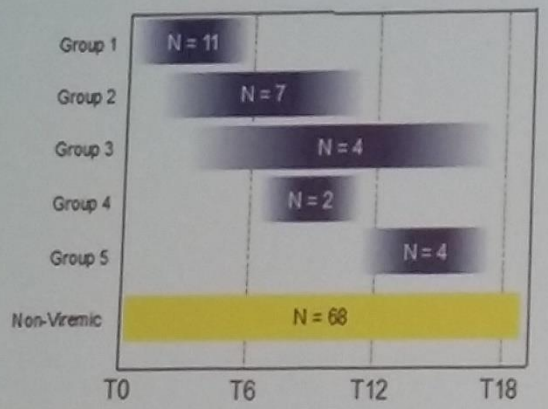
BK Polyiomavirus in trapiantati di rene

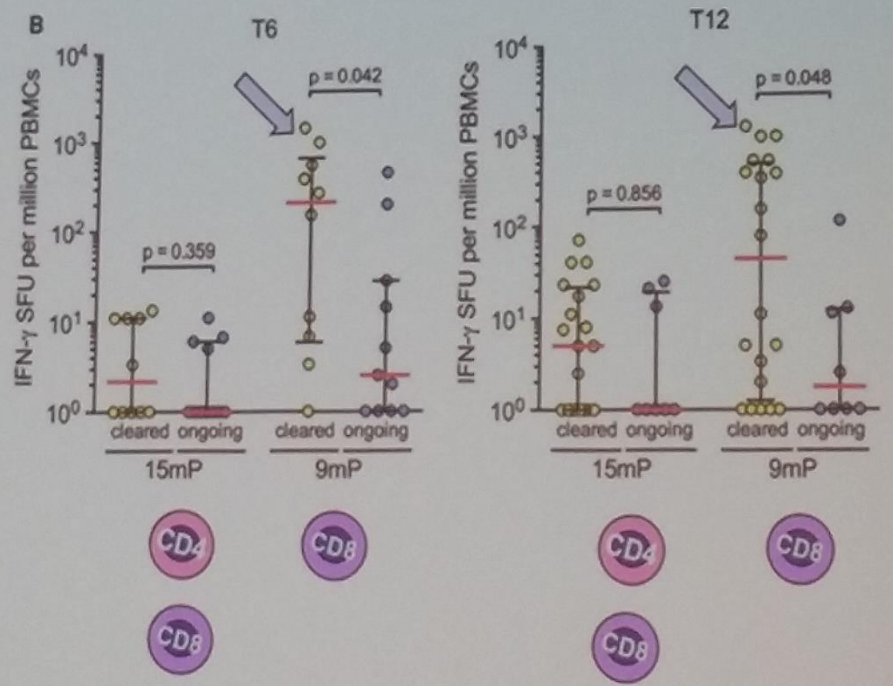


BKPyV

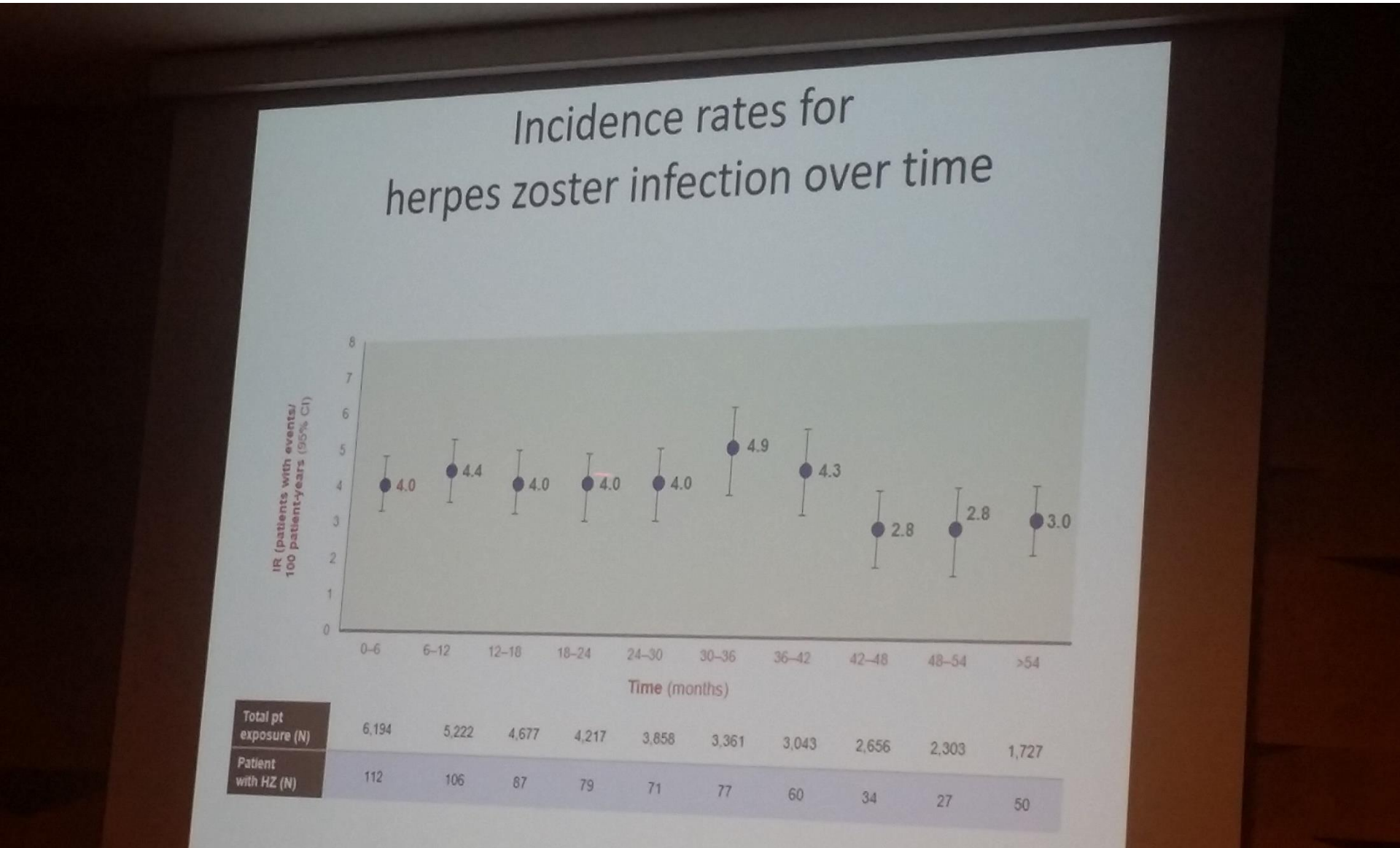
BKPyV T-cell Responses and Viremia Clearance

- 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
IR (patients with events/ 100 patient-years (95% CI)
0
1
2
3
4
5
6
7
8
4.0
4.4
4.0
4.0
4.0
4.9
4.3
2.8
2.8
3.0
0–6
6–12
12–18
18–24
24–30
30–36
36–42
42–48
48–54
>54
Time (months)
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

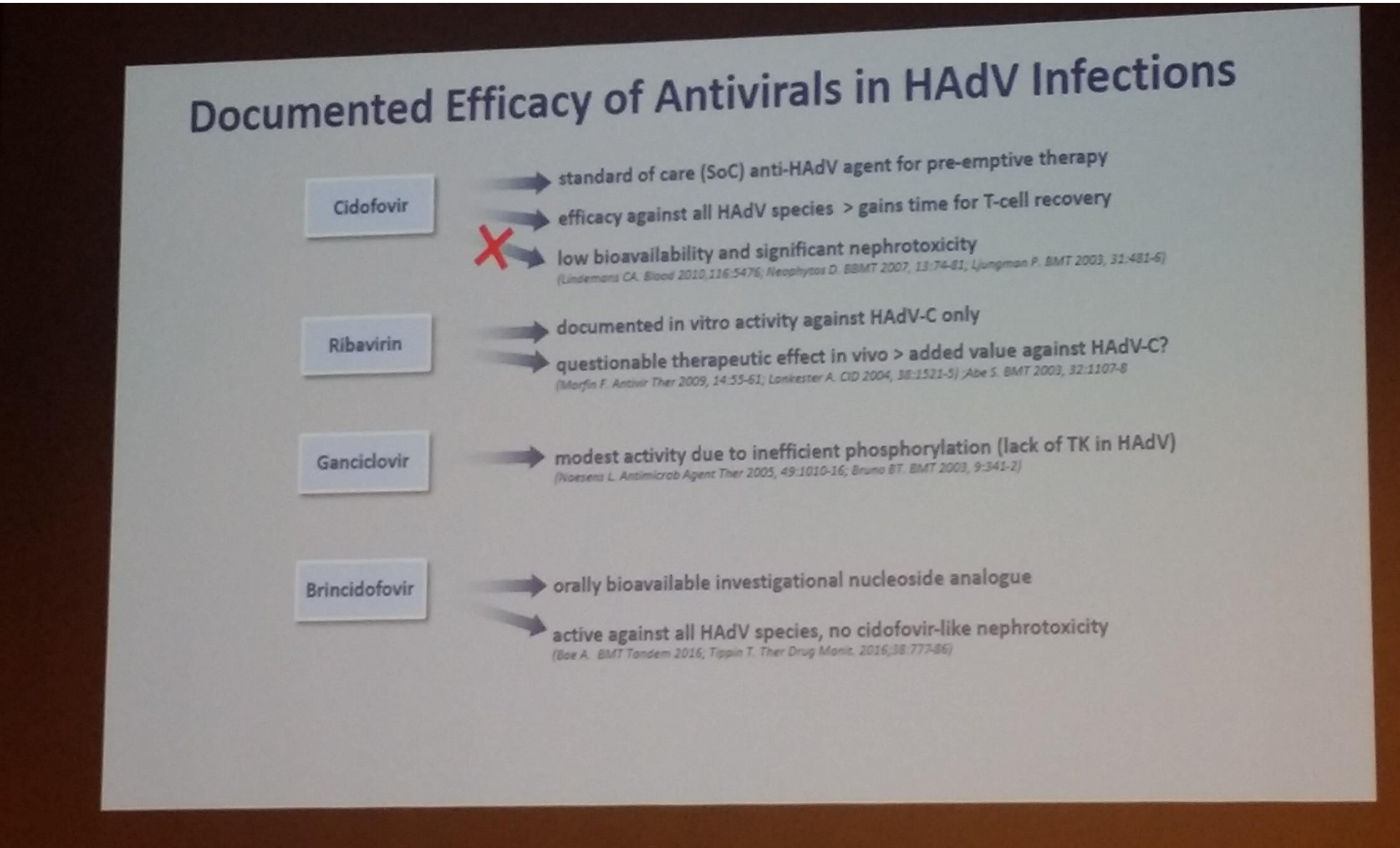
Adenovirus

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

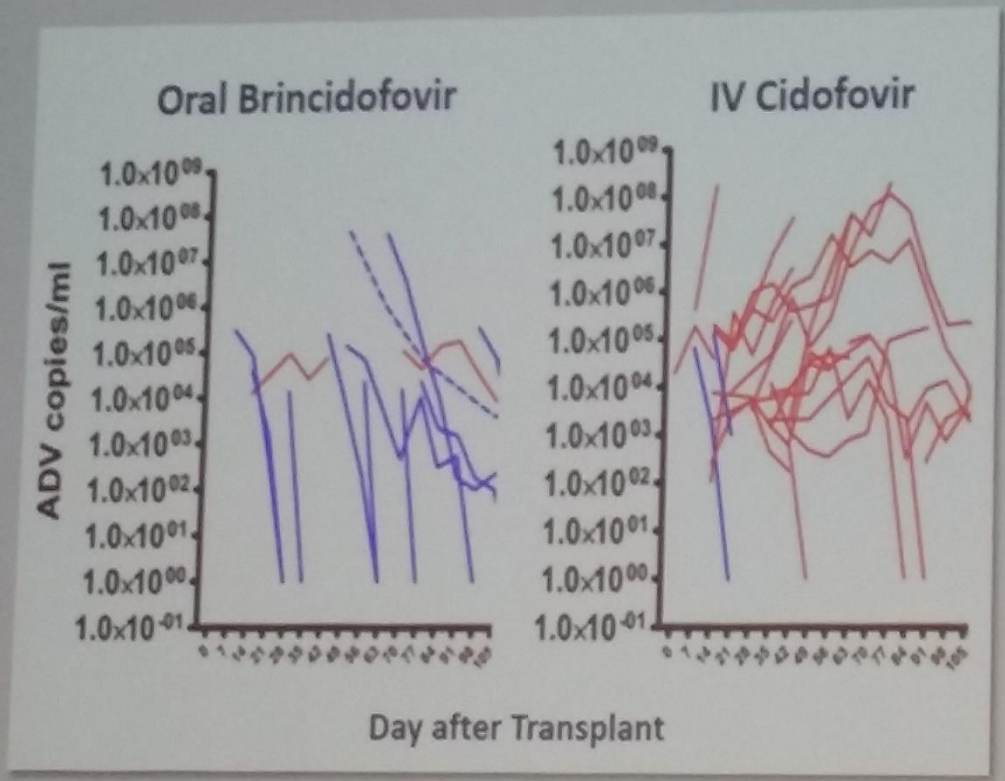
Adenovirus :terapia



Brincidofovir vs Cidofovir

Brincidofovir vs cidofovir in pediatric HCST recipients

Hiwarkar P et al. Blood 2017 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

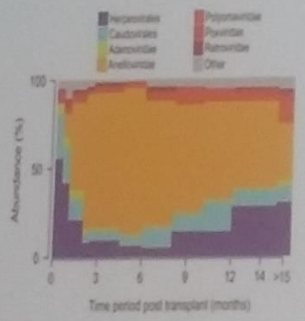
Viremie in trapiantati di cuore e polmoni

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%

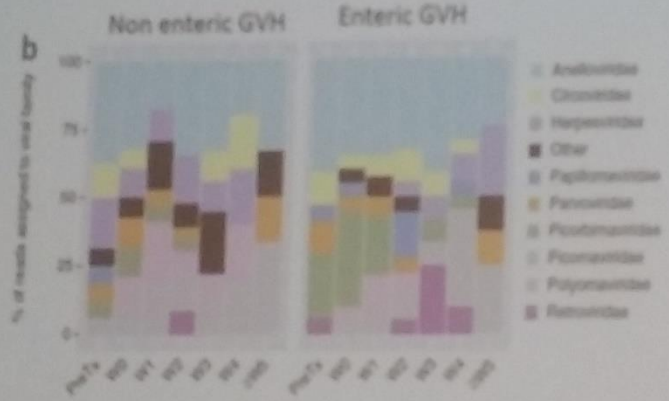
I De Vlaminck. Cell. 2013 Nov 21;155(5):1178-87.

HSCT trapiantato: 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