Infectious and Tropical Diseases Unit
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University of Insubria, Varese, Italy

Sistema Socio Sanitario
Regione Lombardia
ASST Sette Laghi

Kidney transplantation in HIV-infected patients

Paolo Grossi

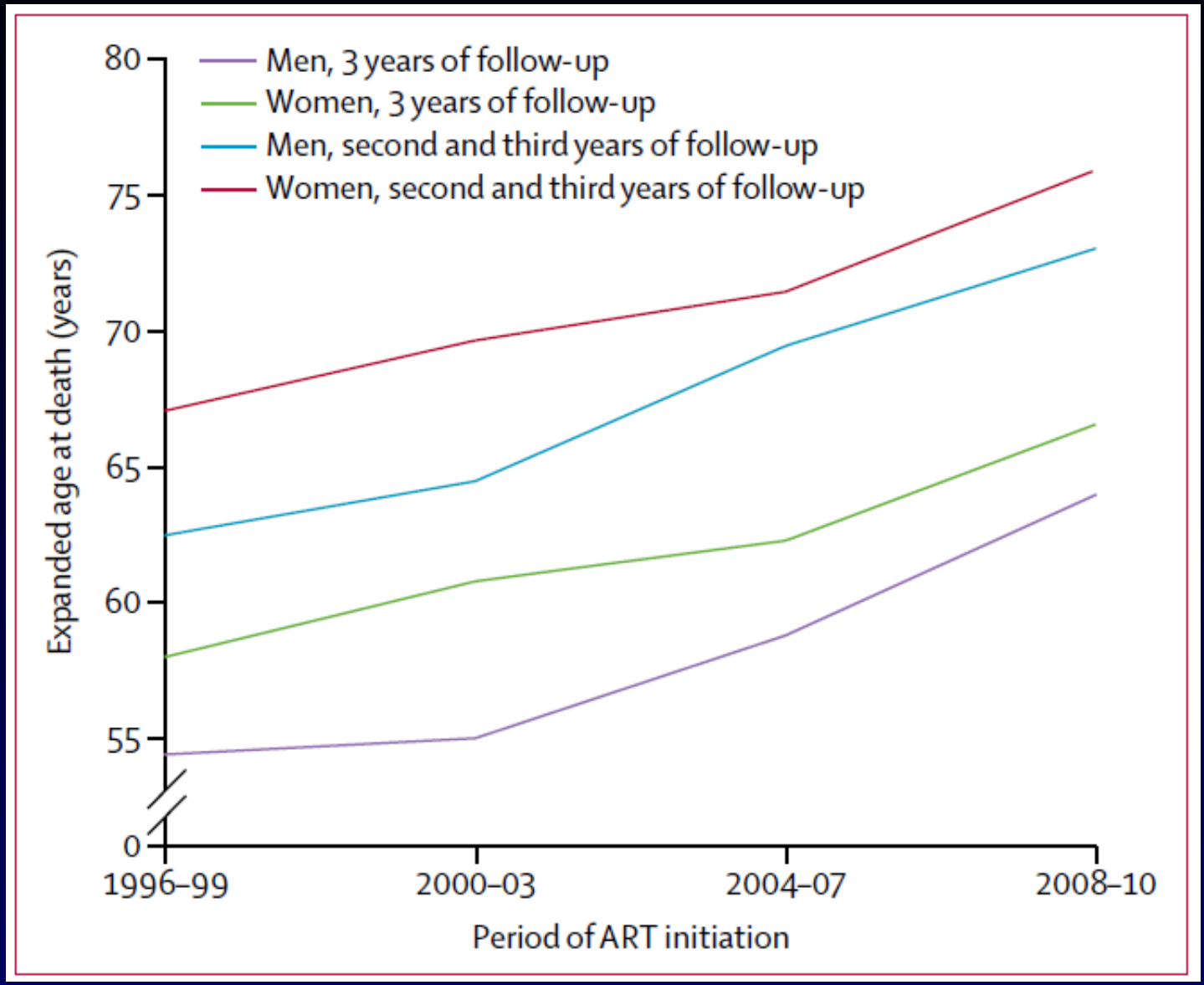
6th International Congress Infections & Transplantation
Varese, 18-20 Maggio 2017

Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013

- Improvements in the care of people living with HIV since the introduction of ART 20 years ago have led to improved survival and increased life expectancy in those starting ART.
- These improvements probably reflect the availability of superior antiretroviral agents, more options for the management of patients developing resistance, fewer drug interactions, better management of opportunistic infections and chronic diseases, and introduction of screening and prevention programmes.
- Prognostic models and estimates of life expectancy should be updated to account for these improvements.

The Antiretroviral Therapy Cohort Collaboration - Lancet HIV Published Online May 10, 2017

Expected age at death of men and women living with HIV starting cART aged 20 years, by period of initiation



The Antiretroviral Therapy Cohort Collaboration - Lancet HIV Published Online May 10, 2017

Life expectancy in HIV-infected patients

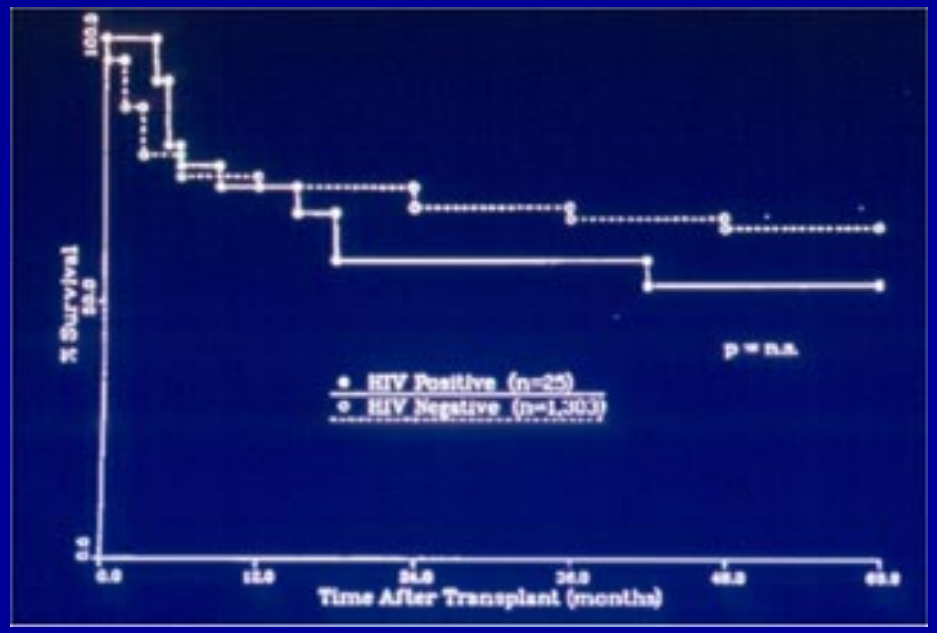
- Effective cART has dramatically changed the survival of people living with HIV infection.
- Many HIV-positive patients now have life expectancies similar to those of the general population; however, certain chronic diseases are more prevalent and, when present, these conditions appear to progress more rapidly.
- Coinfection with hepatitis C virus (HCV) can result in liver failure, which is a major cause of death among people with HIV.
- Kidney disease is also common, with HIV-associated nephropathy being a leading cause of renal failure.

Causes of CKD in Patients With HIV

- HIVAN (HIV Associated Nephropathy)
  - Term describes all HIV related glomerular diseases
  - CKD in patients with HIV
  - Biopsy proven FSGS
- Immune Mediated Renal Disease
- Hepatitis C Associated Cryoglobulemia
- ARV-Associated Renal Dysfunction

Transplantation in HIV+ Patients pre-HAART era

- 15 LTX recipients from 1981-1988 were HIV positive
- 6 infected before transplantation, 9 infected peri-operatively
- Cyclosporine based - 68% rejection, 65% given OKT3
- 2.75 year mean follow-up, 7/15 patients alive



12.75 year mean follow-up: 2/15 patients alive (both on anti-HIV therapy post-LTX)

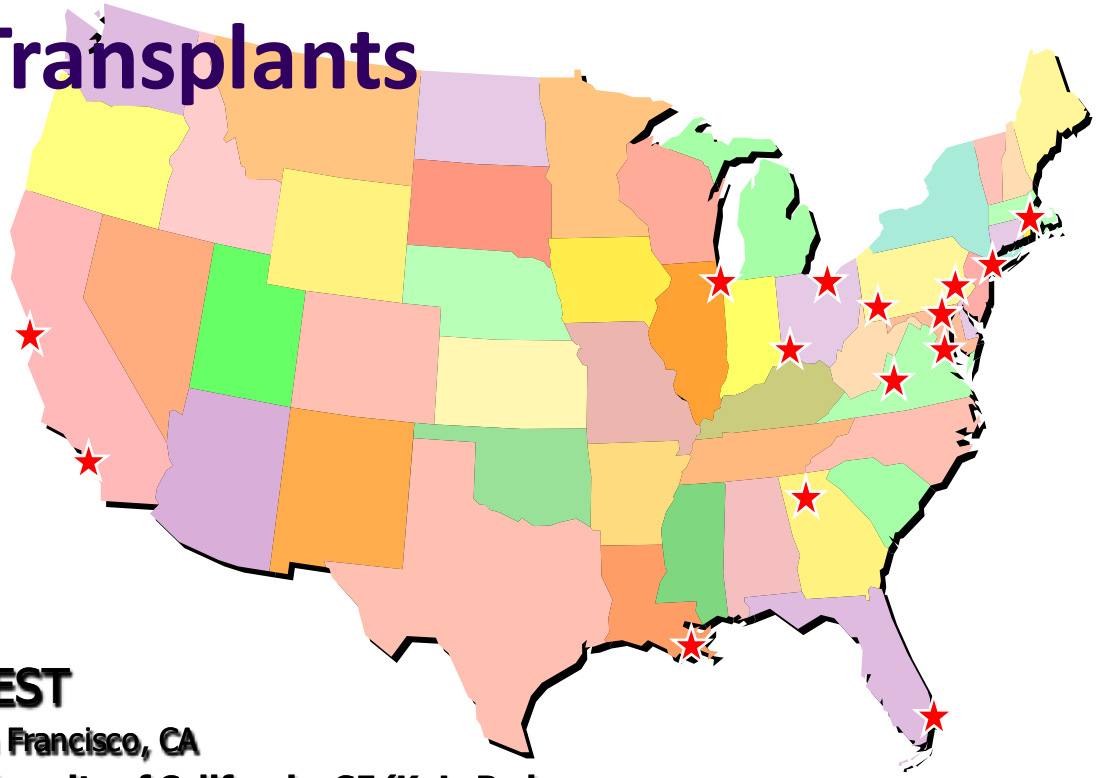
Tzakis A., et al: Transplantation 1990;49:354

Liver Transplantation in a Hemophilia Patient With Acquired Immunodeficiency Syndrome

- Liver transplantation was performed in a 38-year old man with moderate hemophilia A and AIDS in September 1997.
- Although AIDS has been an absolute contraindication to transplantation, the better outcome of our patient than past recipients suggests transplantation may be safe in AIDS patients receiving highly active antretroviral therapy.
- Given the potential clinical scenarios, eg, past opportunistic infections, persistently detectable HIV viral load, antiretroviral therapy intolerance due to liver dysfunction, and an unknown durability of immunologic recovery, it is critical to begin prospective clinical trials to determine the safety and efficacy of transplantation in AIDS and end-stage liver disease.

Ragni MV., et al. Blood 1999;93:1113

NIH TRIAL 150 Kidney and 125 Liver Transplants



NORTHEAST

Baltimore, MD

Johns Hopkins (K,L)

University of Maryland (K)

Boston, MA

Beth Israel Deaconess Medical Center (K, L)

New York, NY

Mt. Sinai School of Medicine (K, L, Peds K)

Columbia University (L, Peds L)

Philadelphia, PA

Drexel University (L)

University of Pennsylvania (K, L)

Pittsburgh, PA

University of Pittsburgh (K, L)

Washington, D.C.

Washington Hospital Center (K)

Georgetown Medical Center (K, L)

WEST

San Francisco, CA

University of California, SF (K, L, Peds K, Peds L)

Los Angeles, CA

Cedars-Sinai (L)

MID-WEST

Chicago, IL
University of Chicago (K, L, Peds K, Peds L)
Rush University (K, L)
Northwestern (K, L)

Cincinnati, OH
University of Cincinnati (K, L)

Cleveland, OH
Cleveland Clinic (K, L)

SOUTHEAST

Atlanta. GA
Emory University (K)

Charlottesville, VA
University of Virginia (K,L)

Miami, FL
University of Miami (K)

New Orleans, LA
Tulane (K, L, Peds K, Peds L)

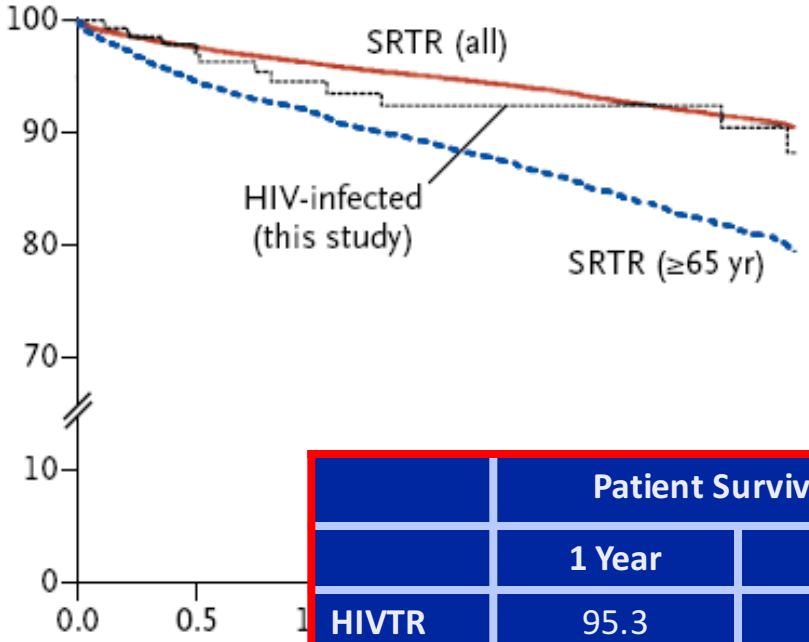
US Multicenter NIH Trial HIV TR
What have we learned?

- 275 transplant recipients
  - 125 LT
  - 150 KT
- >300 potential kidney and liver recipients active on waiting lists at end of UO1

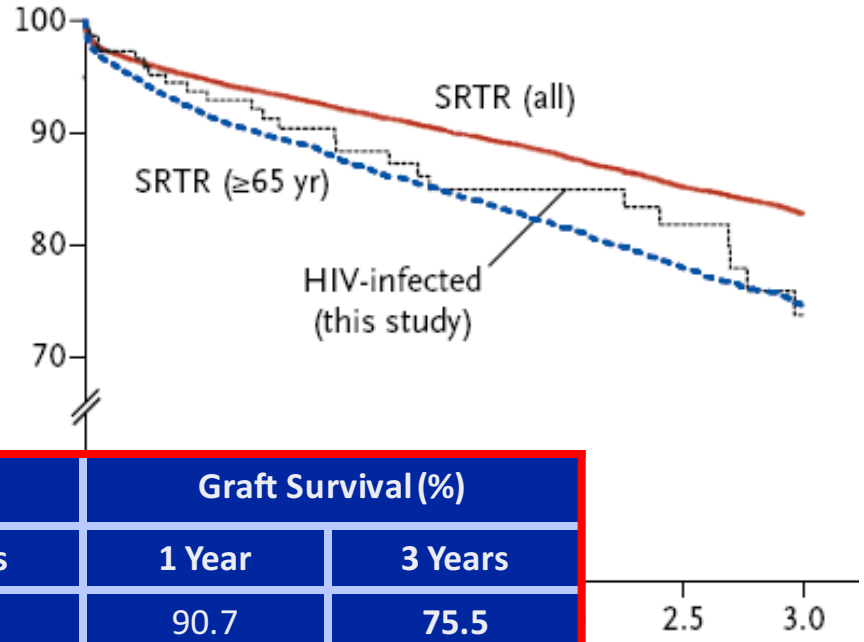
- <u>Selection Criteria</u>
- Standard transplant criteria
- CD4 ≥200 for KT, ≥100 for LT candidates
- Undetectable HIV RNA or expected control post-transplant for candidates unable to tolerate ARVs
- Treated OIs except visceral KS, PML, chronic cryptosporidiosis

Kidney Transplant Outcomes

Patient Survival



Graft Survival

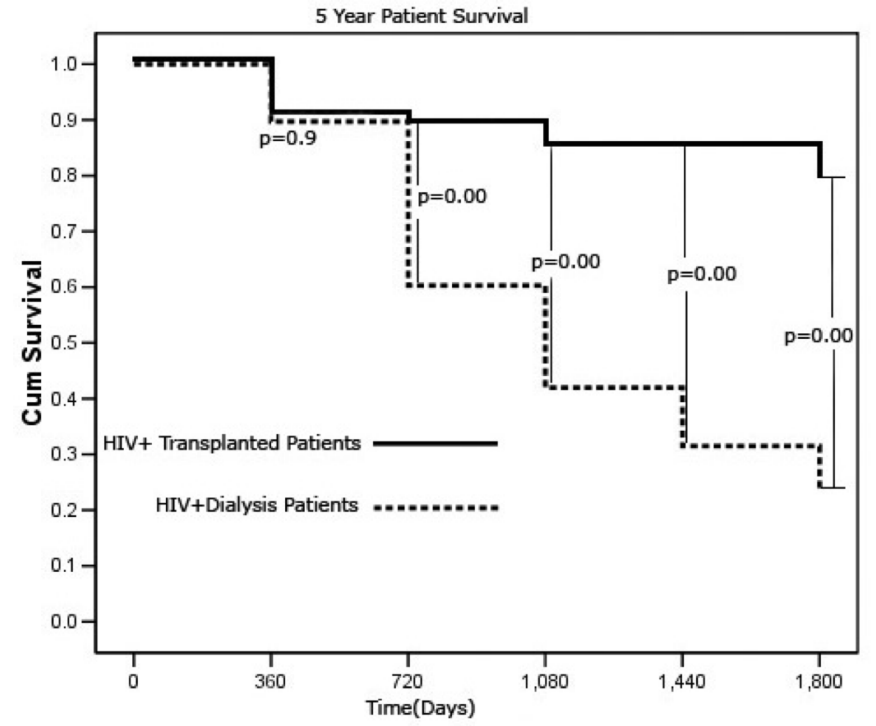


	Patient Survival (%)		Graft Survival (%)	
	1 Year	3 Years	1 Year	3 Years
HIVTR	95.3 (90.4, 97.7)	**90.6** (83.8, 94.7)	90.7 (84.7, 94.4)	**75.5 (66.8, 82.2)**
SRTR				
≥65 yr	91.8 (91.1, 92.4)	79.5 (78.0, 80.9)	88.3 (87.5, 89.1)	74.4 (72.9, 75.9)

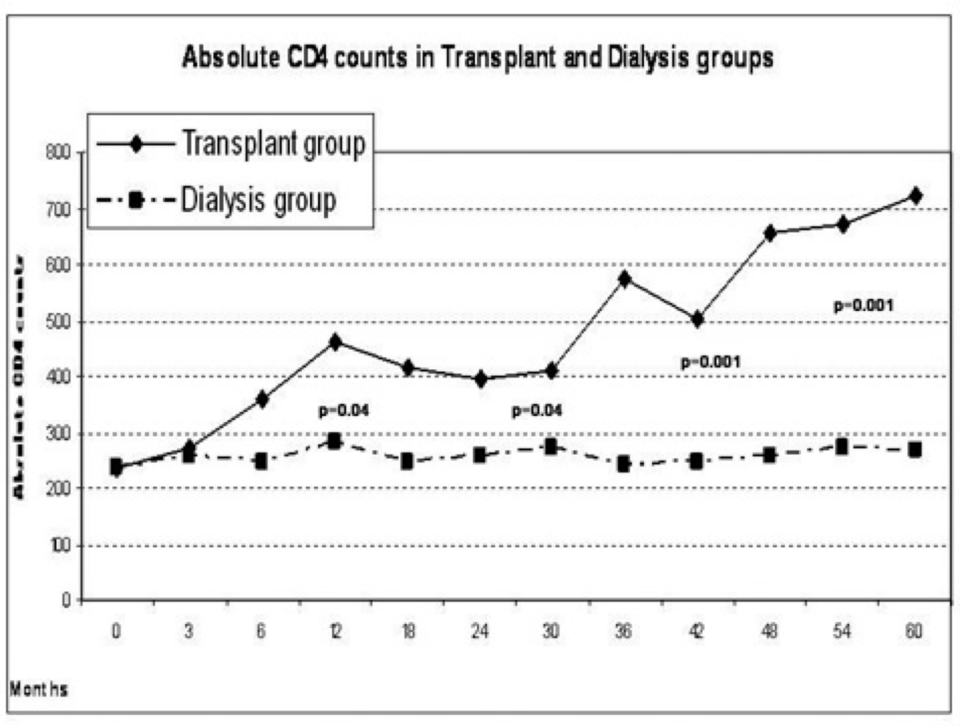
Stock et al. NEJM 363:2004-14; 2010

Clinical Outcome:
Dyalisis versus Transplantation in HIV positive patients

5 year patient survival



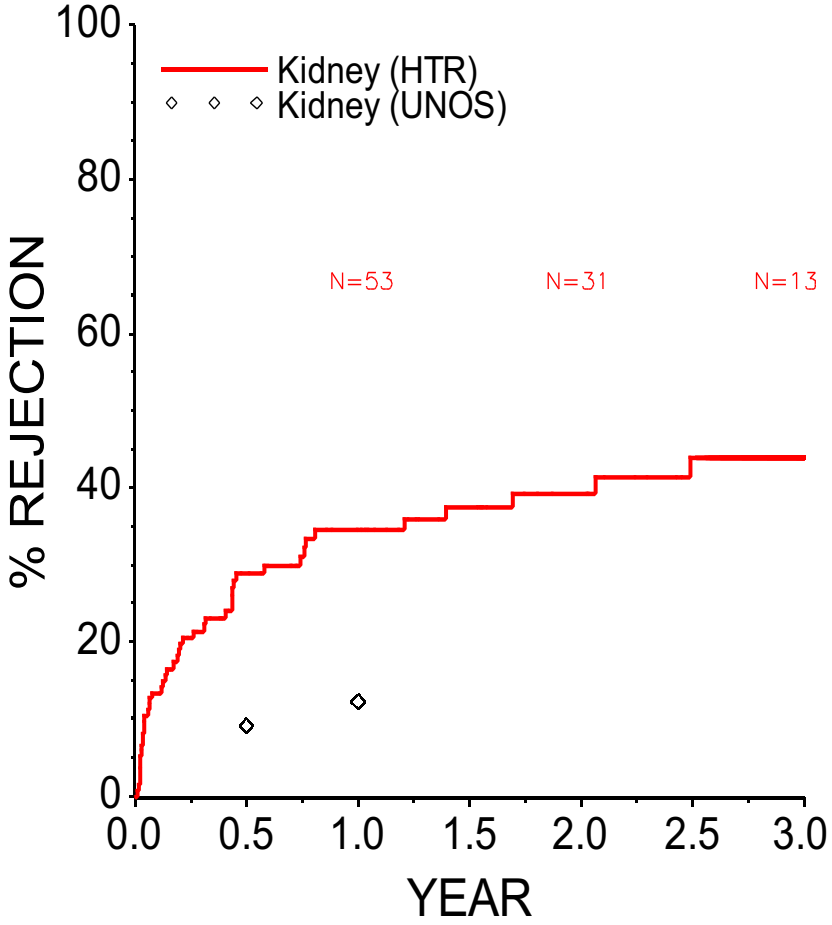
Absolute CD4 count



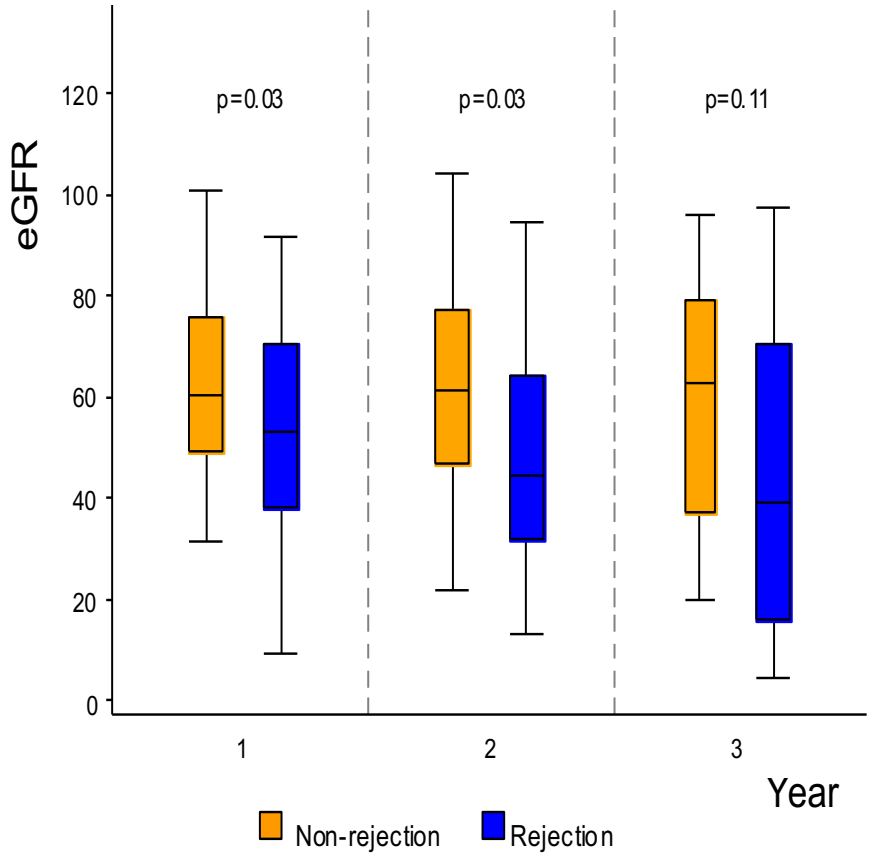
Mysore S, Kumar A, Shahid M et al. In HIV+ Patients with End Stage Renal Disease (ESRD) **Kidney Transplantation Significantly Prolongs Long-Term Patient Survival Compared to Chronic Dialysis Treatment**. Presented at American Transplant Congress, 1 June 2008 (Plenary Session: Joint Plenary Session)

Acute Rejection: An Unexpected Complication

Time to First Rejection



eGFR by Rejection Status



Stock et al. NEJM 363:2004-14; 2010

Possible Reasons for High Rates of Acute Rejection in HIV-infected Patients

- Overly cautious use of IMS in early post-LT period
- Difficulties in achieving adequate immunosuppression due to drug-drug interactions
- Reflects dysregulated immune responses in HIV-infected patients

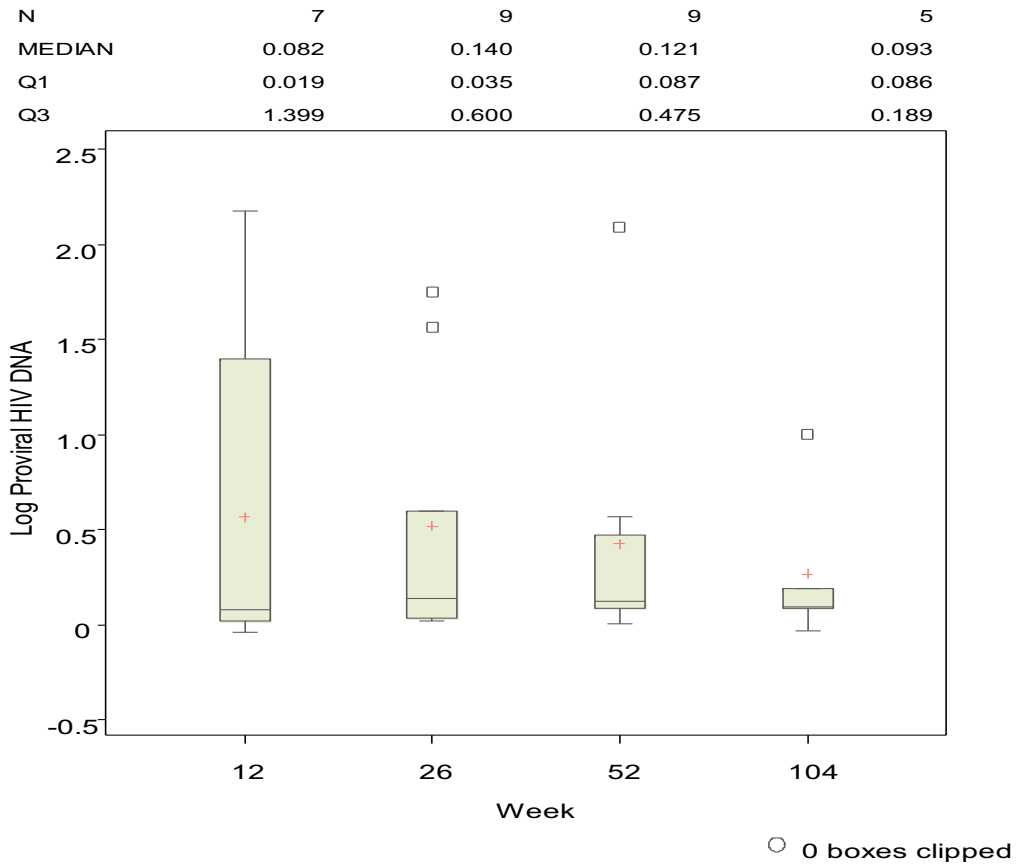
Future Strategies to Impact High Rejection Rates

- 2-3 fold higher incidence of rejection rate (independent of cART regimen)
- Ideal kidney transplant population to test the efficacy of new immunosuppressive agents
- CCR5 blockade (maraviroc) a logical choice
  - entry port for the HIV virion into the lymphocyte
  - maravoric is available for anti-HIV therapy
  - transplant literature suggestive of efficacy in blocking the alloimmune response

Reduction of HIV Persistence Following Transplantation in HIV-Infected Kidney Transplant Recipients

P. G. Stock, B. Barin, H. Hatano, R. L. Rogers, M. E. Roland, T.-H. Lee, M. Busch, S. G. Deeks

American Journal of Transplantation (Impact Factor: 6.19). 03/2014; DOI: 10.1111/ajt.12699



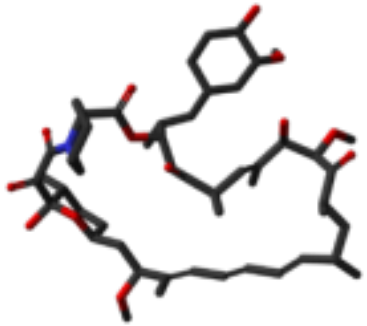
Sizable reductions in HIV DNA levels in HIV infected kidney transplant recipients exposed to sirolimus

Sirolimus - Potential Effects on HIV

- Reduces CCR5 expression on T cells (Heredia 2003; Gilliam. 2007; Mulampaka 2011)
- Inhibits STAT-mediated signaling and T cell homeostatic proliferation (Li 2011)
- Enhances the formation of CD8+ T cell memory (Araki 2009)
- Enhances T regulatory cell number and function (Baan 2005; Coenen 2005, Hippen 2011)
- Decreases PD-1 expression on T cells

Sirolimus - Potential Effects on HIV

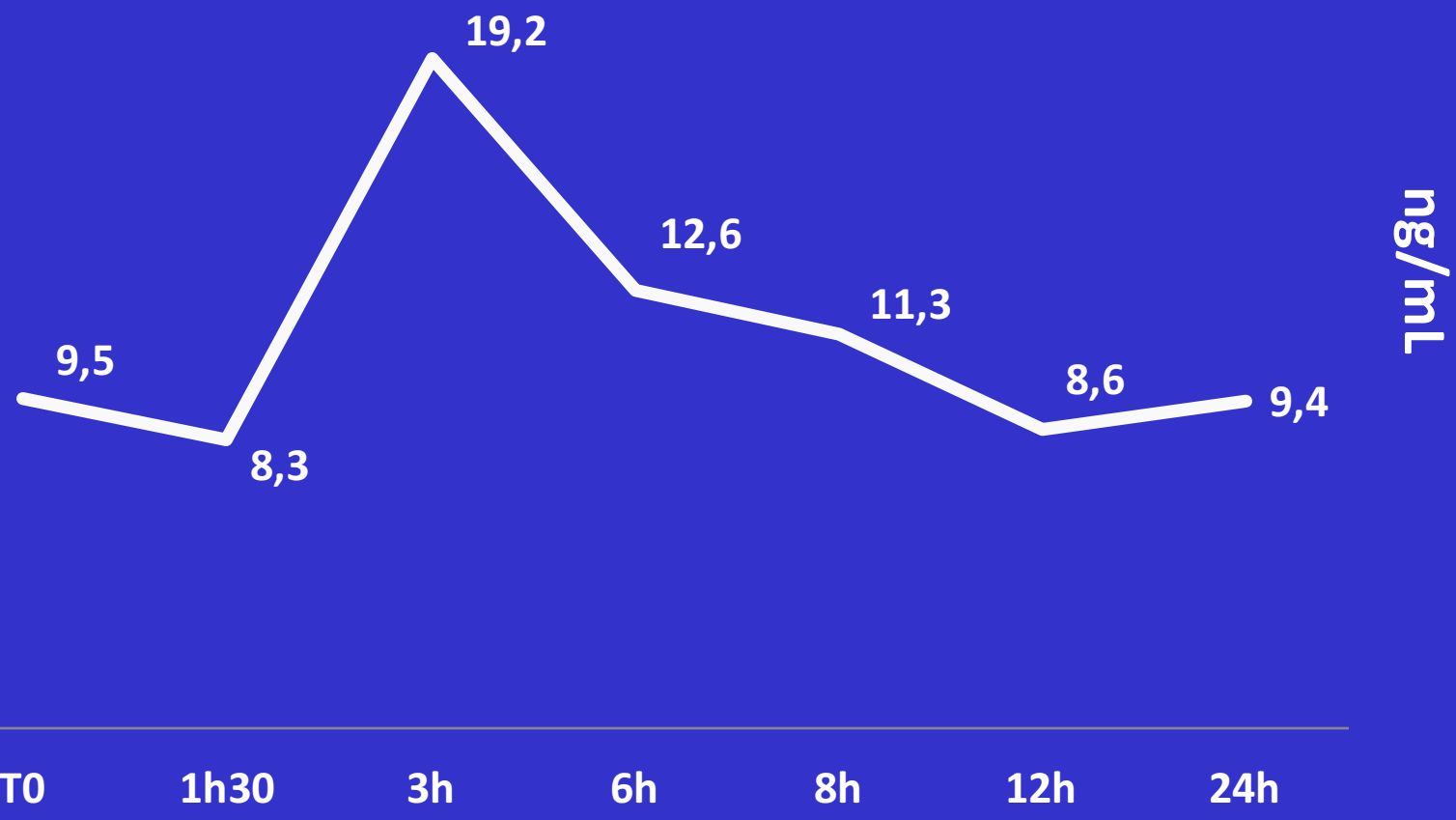
- Sirolimus has beneficial effects on CMV, HCV and HIV replication *in vivo* or *in vitro*
- Can reduce burden of HHV8 and HPV-related illnesses
- Associated with lower HIV-1 DNA levels in HIV-1-infected patients following renal transplantation
- May lead to transcriptional profile similar to HIV-1 elite controllers



Do drug interactions dictate outcomes? YES

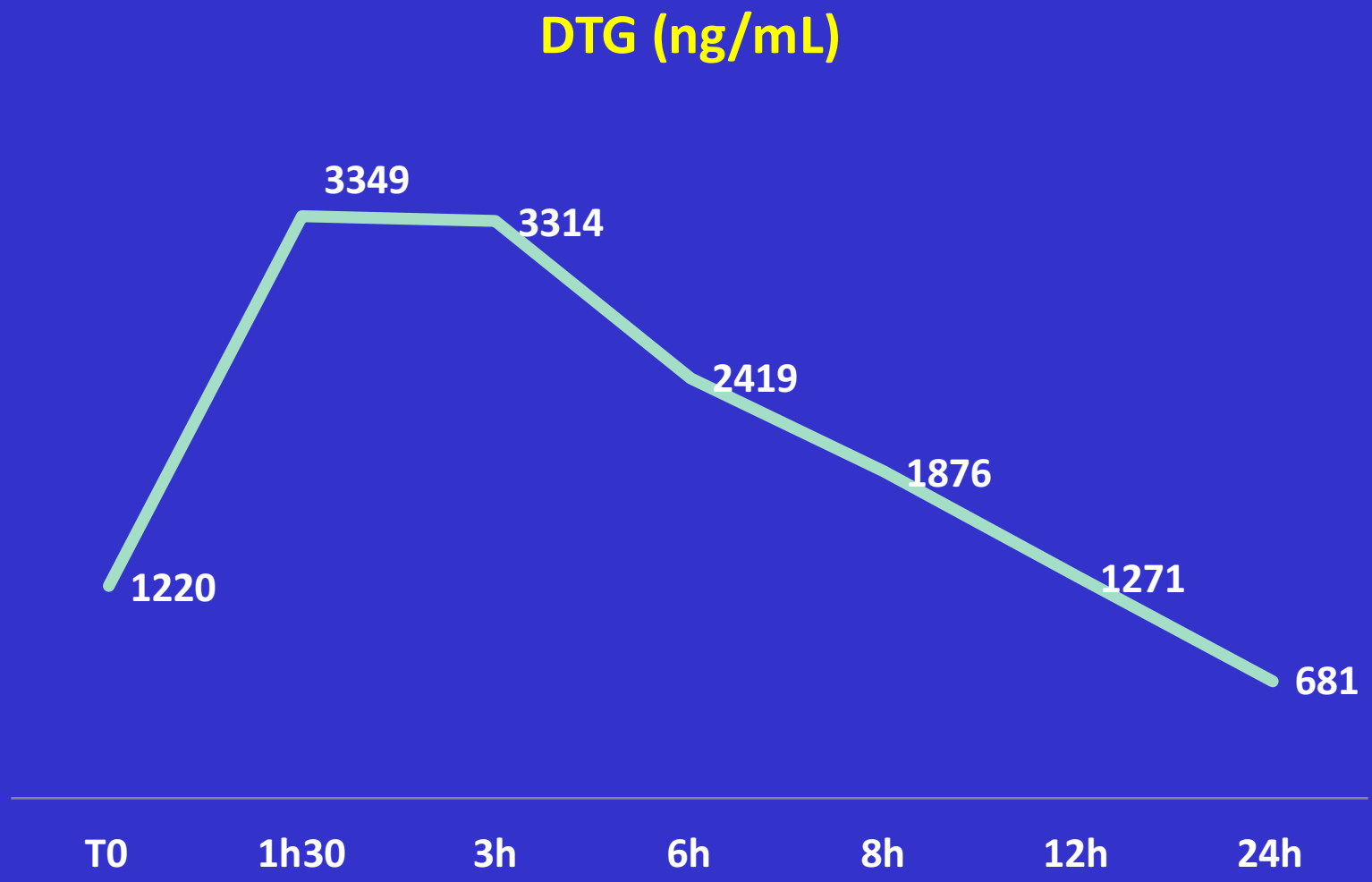
- PIs & NNRTIs have significant drug interactions with ISs => increased incidence of rejection/toxicity
- TAC may have better outcomes than CsA; appropriate CsA dosing/regimen unclear
- Integrase inhibitors – fewer IS interactions, less rejection, may improve lipid profiles
- Maraviroc – fewer IS interactions; CCR5 blockade may improve transplant outcomes

Kinetics of Tacrolimus in an HIV-infected Kidney Transplant Recipient on Dolutegravir



Grossi P. unpublished

Kinetics of Dolutegravir in an HIV-infected Kidney Transplant Recipient on Tacrolimus



Grossi P. unpublished

MODULARIO
Salute - 3

MOD. 5 - U.G.

COPIA

Ministero della Salute

CONSIGLIO SUPERIORE DI SANITA'
SESSIONE XLIV
SEZIONE II
Seduta del 31 Maggio 2002
IL CONSIGLIO SUPERIORE DI SANITA'
SEZIONE II

Vista la relazione del Dipartimento della Tutela della Salute Umana, della Sanità Pubblica Veterinaria e dei Rapporti Internazionali – Direzione Generale della Prevenzione, avente per oggetto: Sottoposizione al parere del Consiglio Superiore di Sanità del protocollo "Trapianto epatico in soggetto HIV positivo" e di uno schema di protocollo nel trapianto di organi, tessuti o cellule la cui tipologia o le cui applicazioni non siano di consolidata attività clinico – assistenziali, proposti dal Centro Nazionale Trapianti.

Vista la Legge del 1/4/99, n. 91 "Disposizioni in materia di prelievi e di trapianti di organi e di tessuti";

vista la Legge 28 marzo 2001, n. 145 "Ratifica ed esecuzione della Convenzione del Consiglio d'Europa per la protezione dei diritti dell'uomo e della dignità dell'essere umano riguardo all'applicazione della biologia e della medicina: Convenzione sui diritti dell'uomo e sulla biomedicina, fatta a Oviedo il 4 aprile 1997, nonché del Protocollo addizionale del 12 gennaio 1998, n. 168, sul divieto di clonazione di esseri umani", e in particolare il capitolo VI relativo al "*Prelievo di organi e tessuti da donatori viventi a scopo di trapianto*";

Criteria for transplantation in HIV-infected individuals

	Kidney transplant	Liver transplant	Heart transplant	Lung transplant	Kidney-pancreas transplant
Meet center specific inclusion criteria	X	X	X	X	X
CD4 count > 100 cells/uL, <200 cells/uL (without history of OI)	NR	X	NR	NR	NR
CD4 count > 200 cells/uL during 3 months before transplantation	X	X[1]	X	X	X
Undetectable HIV viral load while receiving antiretroviral therapy	X	X	X	X	X
Detectable HIV viral load due to intolerance of HAART, HIV can be suppressed post-tx	NR	X	NR	NR	NR
Documented compliance with a stable antiretroviral regimen	X	X	X	X	X
Absence of active opportunistic infection and malignancy[2]	X	X	X	X	X
Absence of chronic wasting or severe malnutrition	X	X[3]	X	X	X
History of hepatitis B or C with lack of evidence of advanced fibrosis or cirrhosis	X	NA	[4]	[4]	X
Acceptance of life-long *Pneumocystis* prophylaxis	X	X	X	X	X
Donor free of hepatitis C	X[5]	X[5]	X	X	X
Appropriate follow-up with providers experienced in the management of HIV	X	X	X	X	X
Ready access to immunosuppressive medication therapeutic drug monitoring	X	X	X	X	X

NA = not applicable; NR = not recommended.

[1]With a history of AIDS defining illness such as opportunistic infection or malignancy.

[2]Patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, and visceral Kaposi's sarcoma were excluded from the study.

[3]BMI > 21.

[4]Absence of data, although patients with controlled hepatitis B may be considered. Extreme caution for hepatitis C infected patients.

[5]HCV infected donors may be considered for HCV infected recipients on an individual basis.

Blumberg EA, Rogers CC. AJT. 2013;13: 169–178

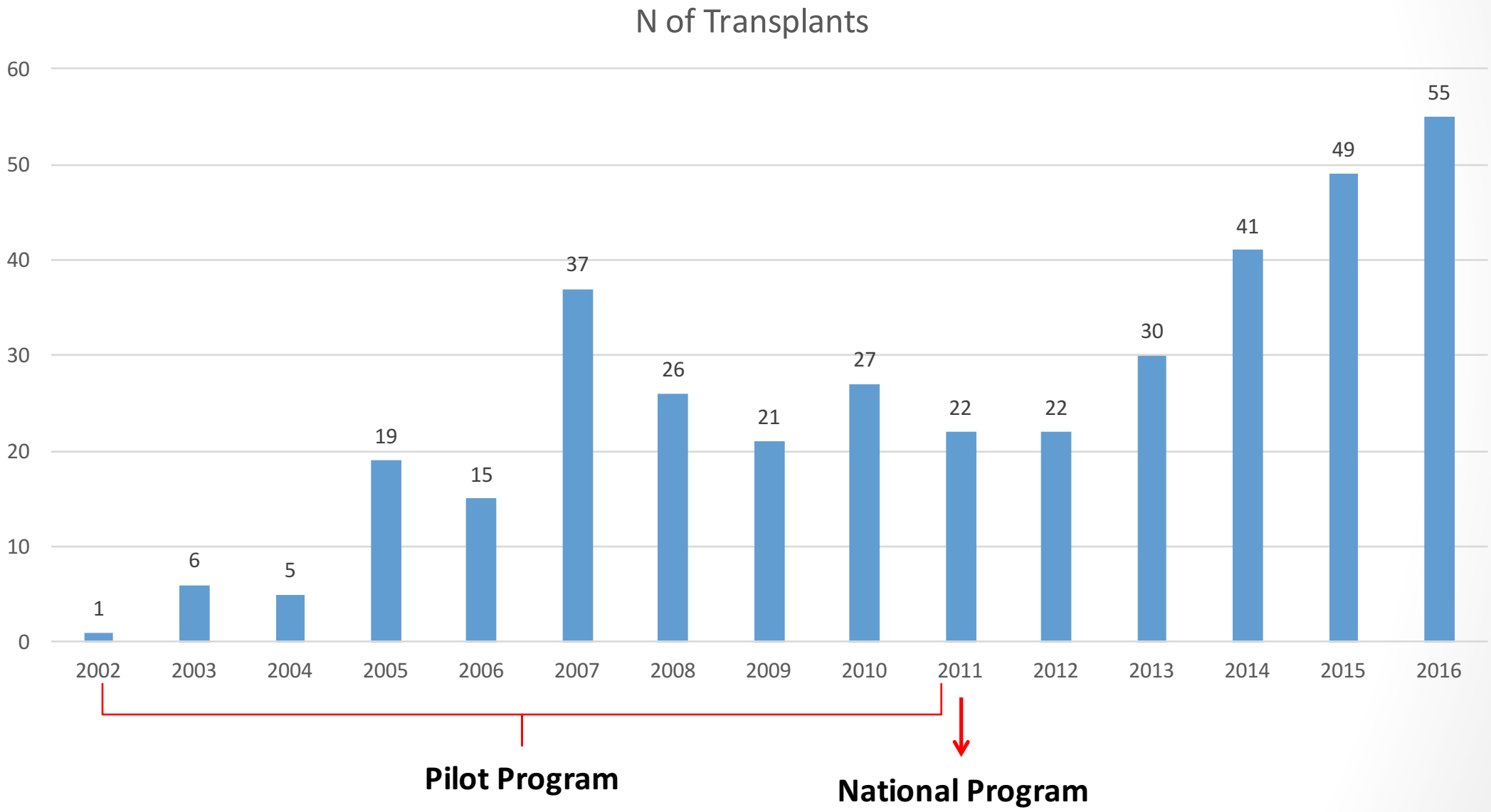
Conferenza permanente per i rapporti tra lo stato le regioni e le province autonome di Trento e Bolzano INTESA 20 aprile 2011

«Progetto Trapianti di organi solidi in pazienti HIV+». (Rep. Atti n. 79/CSR del 20 aprile 2011). (11A06078) (G.U. Serie Generale n. 113 del 17 maggio 2011)

V. Attivazione locale del Programma

- **Tutti i centri di trapianto che presentano i requisiti previsti e che desiderano intraprendere tale attivita', devono ottenere l'autorizzazione dal proprio assessorato, previo parere dei direttori generali delle aziende coinvolte e del Centro Nazionale Trapianti che svolge funzione di coordinatore del programma e si occupa della sorveglianza, della registrazione e dell'analisi centralizzata delle informazioni generate dal programma nelle sue varie fasi.**

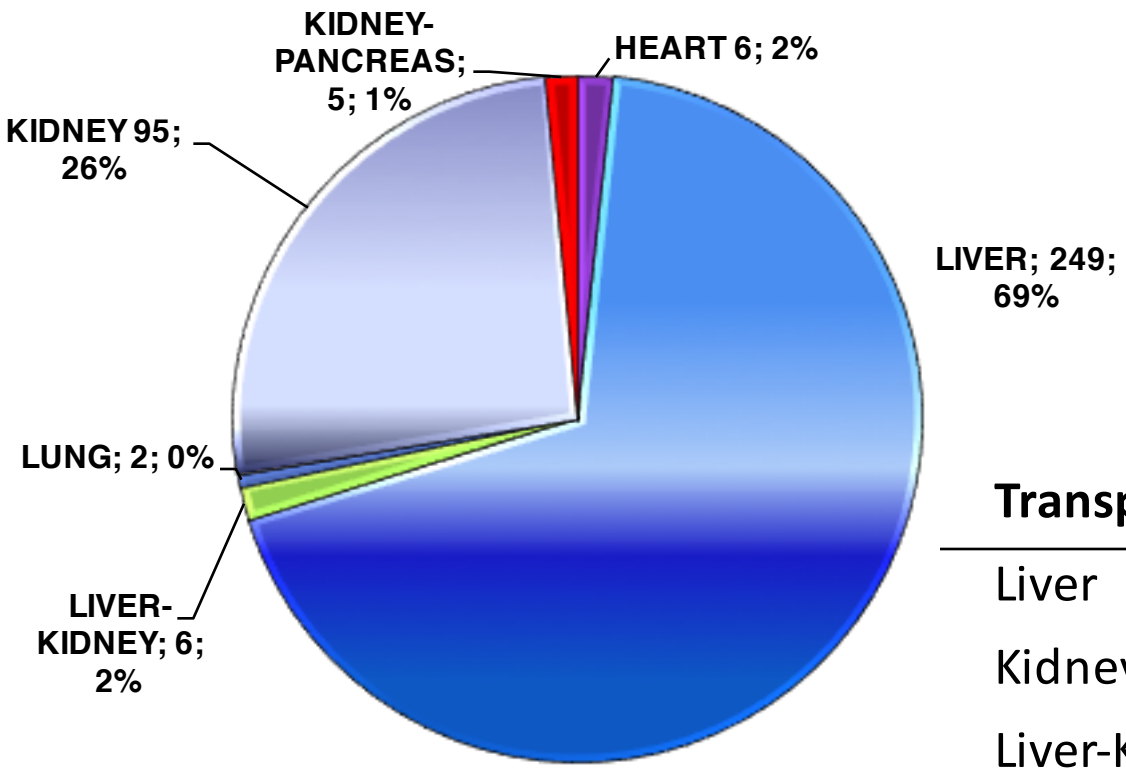
Solid Organ Transplant in HIV-Infected Individuals Italy 2002-2016



Centro Nazionale Trapianti

Solid Organ Transplant Activity in Italy

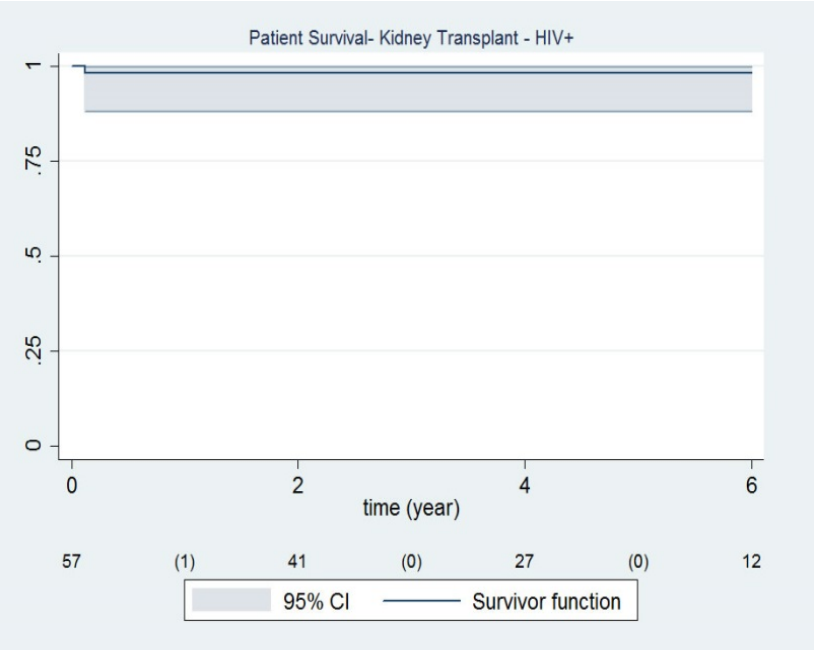
363 transplants from 09.2002 to 31.12.2016

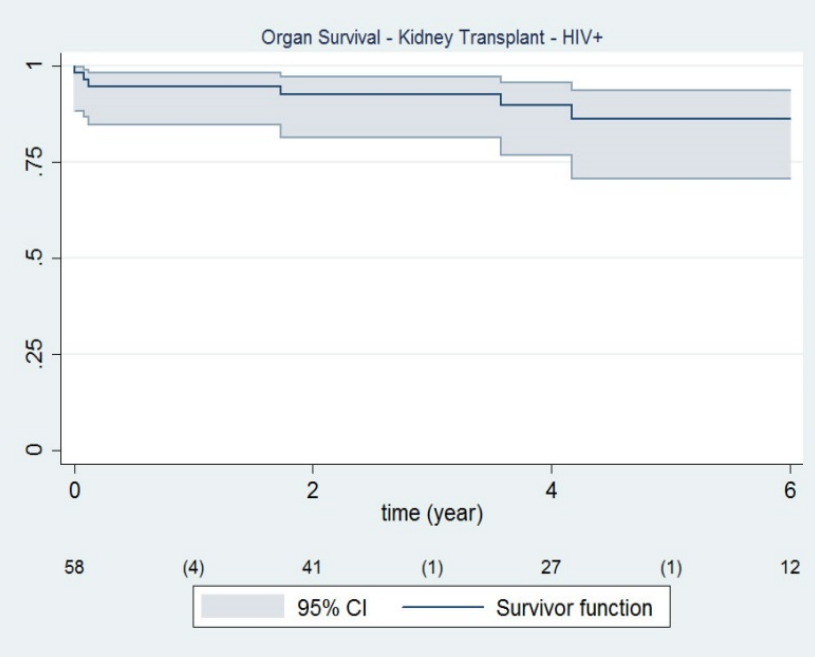


Transplanted Organ	Number
Liver	249
Kidney	95
Liver-Kidney	6
Pancreas-Kidney	5
Pancreas	1
Heart	6
Lung	2

Centro Nazionale Trapianti

Trapianto di Rene in soggetti HIV+ : Outcome





5 year patient and graft survival are similar to the HIV-negative recipients*.

**Dati Sistema Informativo Trapianti al 31 dicembre 2015*

Centro Nazionale Trapianti

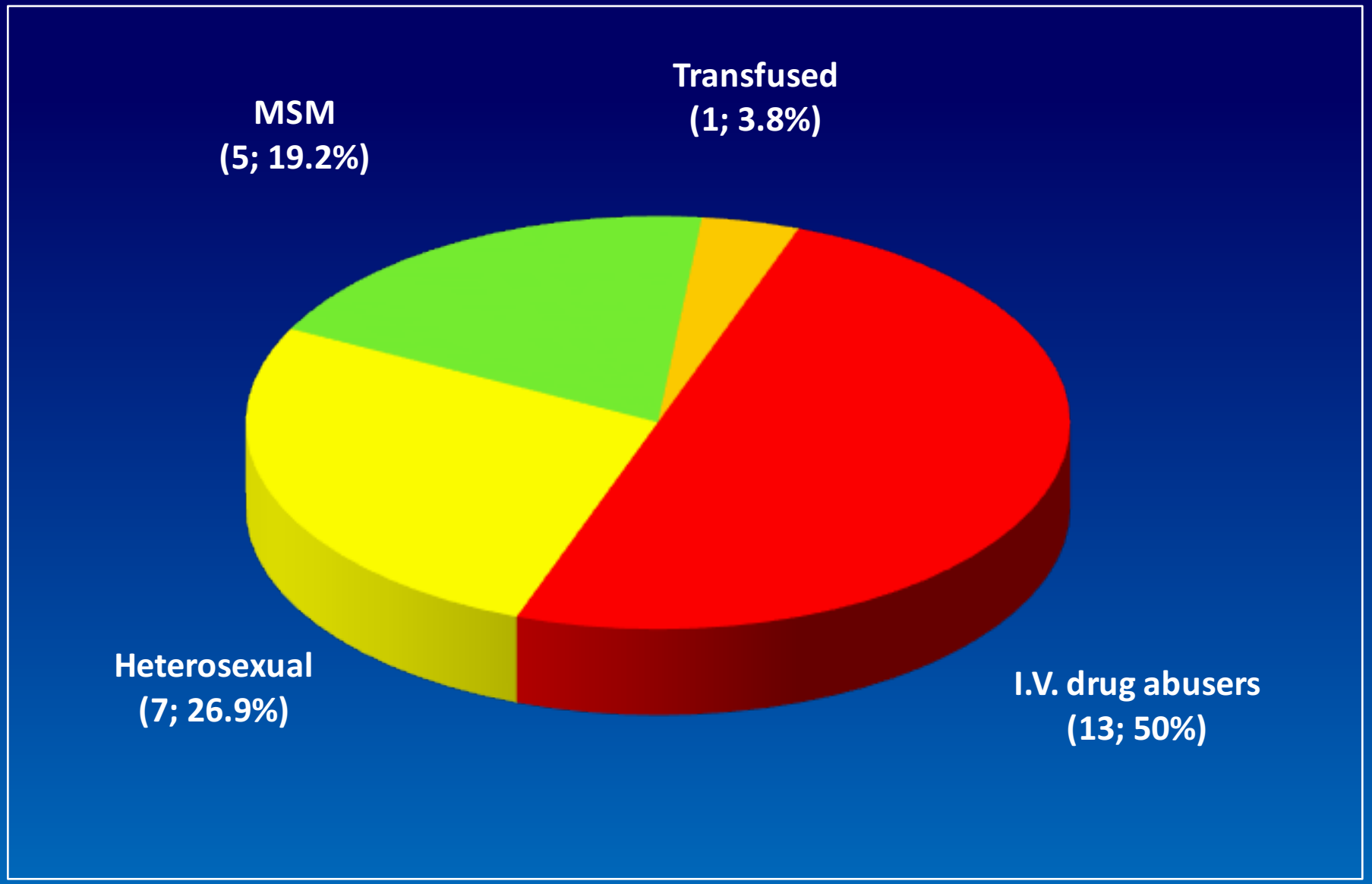
Centro Nazionale Trapianti

KIDNEY TRANSPLANT IN HIV – VARESE EXPERIENCE

N° KT *(November 2006-April 2017)*	26 (1 from living related donor)
GENDER	Male= 20 (76.9 %) Female= 6 (23.1 %) (1 redo in another center)
AGE (median)	48 (34-63) yrs
TIME ON THE WAITING LIST (median days)	112 (1-1227)
Median CD4 count at the time of Tx	439 (210-668)
Undetectable HIV-RNA at Tx	26/26 (100%)

17 patients received the graft from increased risk donors (7 i.v. drug users, 7 with high risk sexual behaviour, 2 homeless & 1 with hemodilution); 6 from HCV infected donors, 2 from standard donor and 1 from living donor

Risk factors for HIV infection in 26 KT recipients



cART regiment post-KT

Class of drugs in cART regiment	N (%)	Switch
NRTI + NNRTI	10	1 -> PI + Fusion Inhibitor ->PI +INI 2-> NRTI+INI
NRTI + INI	8	
NRTI + PI	2	
CCR-5 Antagonist + NtRTI + INI	2	
CCR-5 Antagonist + NRTI + PI	1	1 -> NRTI + PI
NtRTI + PI	1	
NRTI + PI + NtRTI + INI	1	
PI + INI	1	

Results

Follow-up (median months)	58.8 (0.13-126.8)
Patient survival at 1 year 3 years 5 years	96.0% 91.4% 85.7%
Graft survival at 1 year 3 years 5 years	96.0% 86.9% 81.1%
Primary graft non function Delayed graft function	1/26 1/26
Causes of death	Gastric Cancer (1) Cardiac (2) Post-surgery complications(1)

Post-transplant opportunistic infections in HIV-infected liver and kidney recipients

	Liver recipients			Kidney recipients	
Country (reference)	**Spain [53]**	**France [75]**	**USA [74]**	**Spain [46]**	**USA [9,74]**
No. of patients	84	105	125	20	150
Follow-up (months)	24	36	32	40	28
No. of cases with at least one opportunistic infection	9 (11%)	5 (5%)	6 (5%)	ND	7 (5%)
Opportunistic infections					
Tuberculosis	2	1	0	0	0
PCP	1	0	1	0	1
Oesophageal candidiasis	2	2	3	0	2
Other invasive fungal infections	3[a]	0	0	1	0
CMV disease	2	1	0	1	0
Other opportunistic infections	0	1[b]	1[c]	2[d]	1[e]
Neoplasm					
Kaposi sarcoma	0	ND	1	0	3
Non-Hodgkin lymphoma	0	ND	0	1	0

ND, no data; PCP, *Pneumocystis jiroveci* pneumonia; CMV, cytomegalovirus.
[a]Two mucormycosis and one aspergillosis.
[b]Non-tuberculous mycobacteria.
[c]Bronchial candidiasis.
[d]Other viruses.
[e]Chronic cryptosporidiosis.

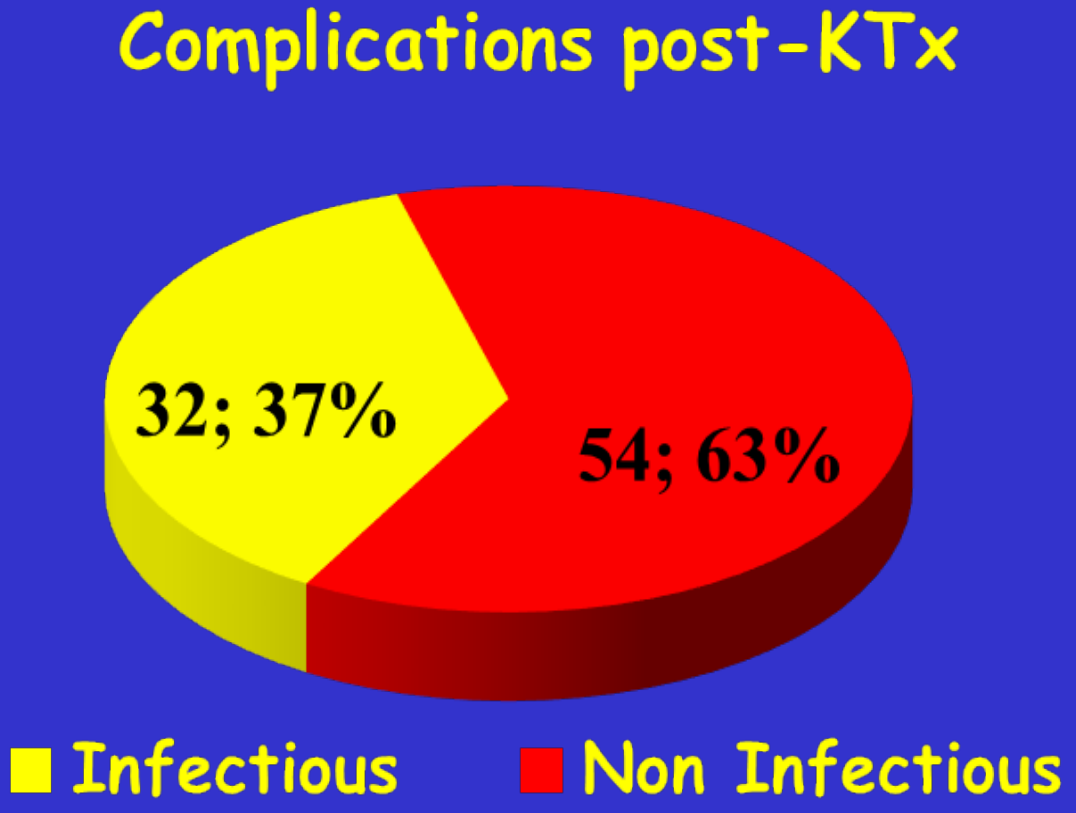
Mirò JM, et al. CMI, 2014;20 (Suppl. 7), 119–130

Results

N. of days (median) after KTx before restarting cART	17.5 (6-46)
N. of patients with HIV-RNA detectable before restarting cART	5/25
HIV-RNA Viral Load	2,300 (ZA) 23,000 (MG) 94,000 (BA) 245,000 (ND) 828,000 (HB)
Timing (Days) of HIV-RNA detectability while on stop treatment	7 (ZA) 20 (ND) 28 (HB, BA)

Results

20/22 (90.9%) patients developed 86 potentially life-threatening complications or required hospital admission during the follow-up

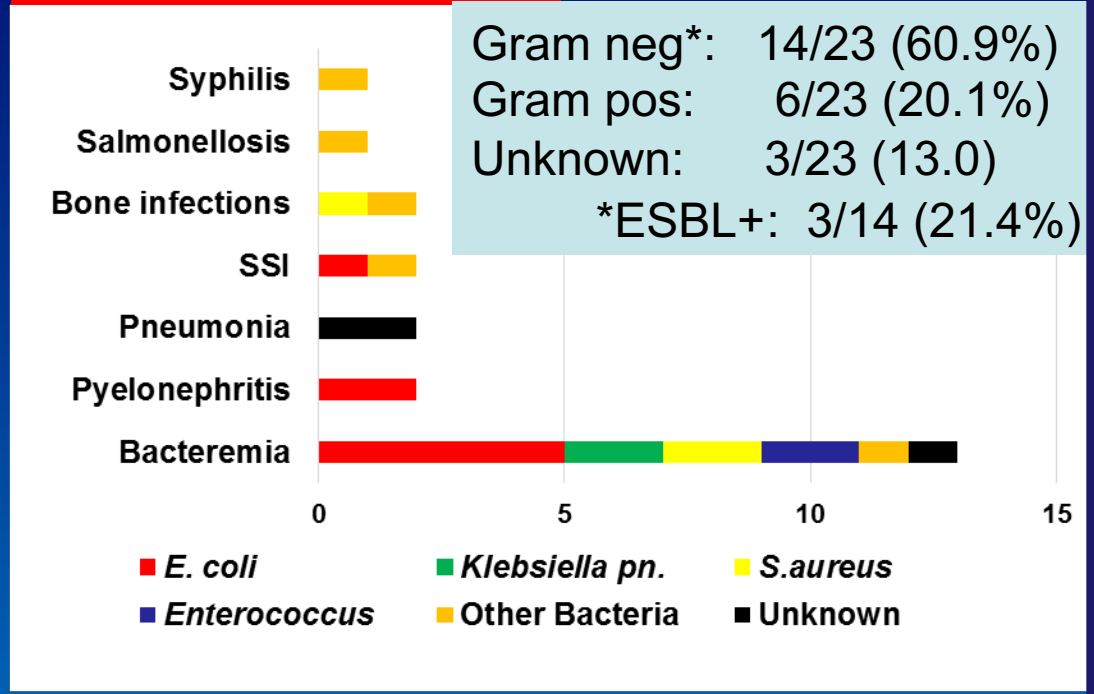


Etiology and Localization of Infectious Complications

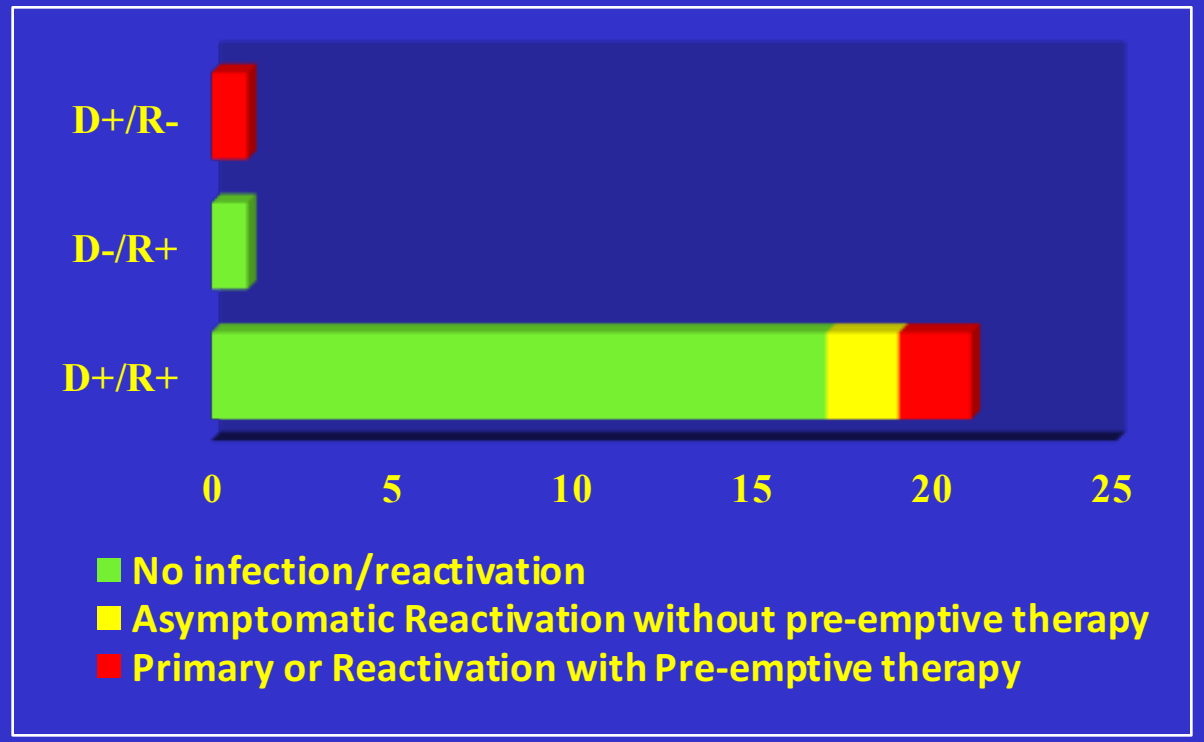
13/22 (59%) patients developed infectious complications at a median of 448 (4-2341) days after KT.
All episodes were successfully treated

Bacterial infections 23/32 (71,9%)

Gram neg*: 14/23 (60.9%)
Gram pos: 6/23 (20.1%)
Unknown: 3/23 (13.0)
*ESBL+: 3/14 (21.4%)



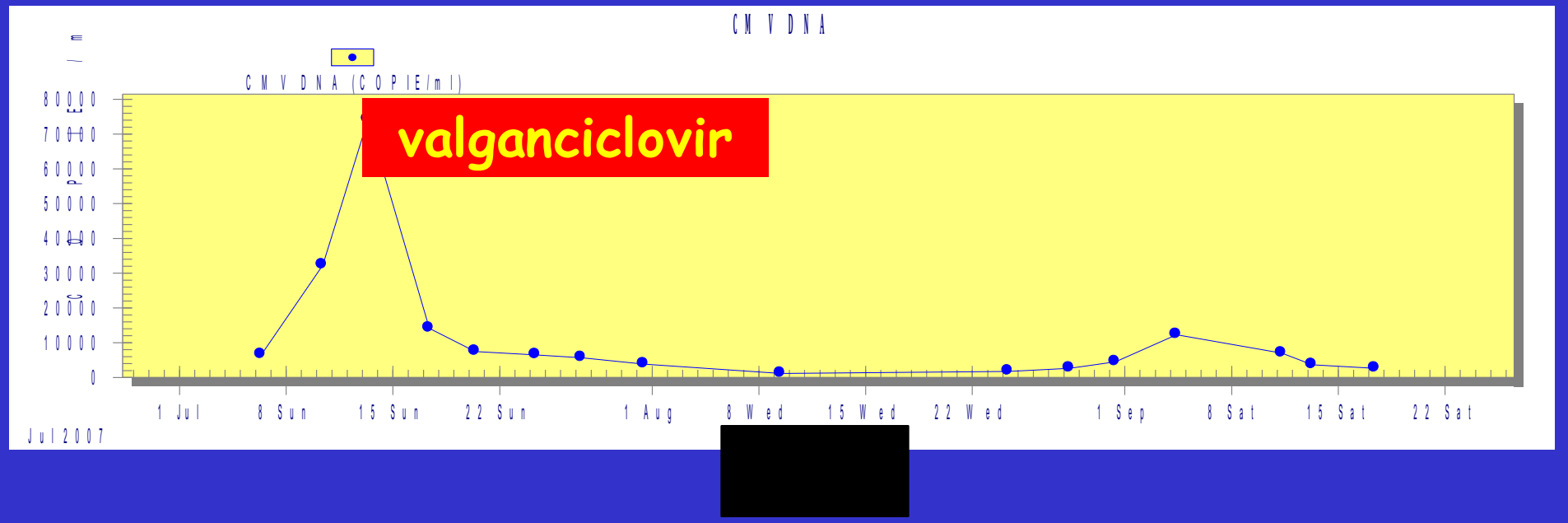
CMV infections according to donor/recipient serology in 22 HIV infected KT recipients



Primary CMV infection was observed in a D+/R- recipient which was successfully treated with valganciclovir for 31 days

- **CMV reactivation** was observed in 4/21 (19.4%) pre-KT CMV+ recipients
- Only 2 of these (9,5% of all CMV+ recipients) were treated preemptively for 12 and 19 days, respectively.
- All patients were asympomatic and all cleared the infection without further relapses

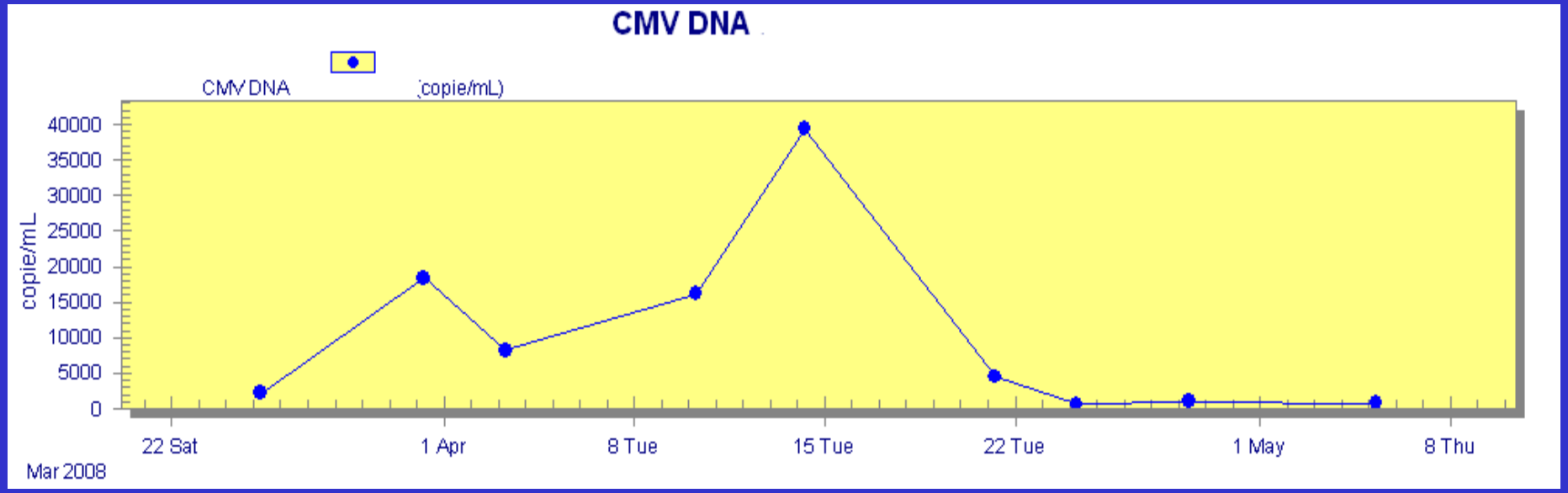
HCMV DNAemia in a HIV+ Kidney transplant recipient (D+/R-)



Tx date 8.4.2007

HCMV DNAemia in a HIV+ Kidney transplant recipient treated with thymoglobulin for steroid resistant rejection (BANFF 1B)

Thymoglobulin 1.5 mg/kg
13-22 march, 2008



When to treat with the new DAA in the setting of non liver Organ Transplantation ?

- Before listing
- While on the waiting list
- After transplant

Annals of Internal Medicine

ORIGINAL RESEARCH

Treatment With Ledipasvir–Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection

A Randomized Trial

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Table 2. Response During and After Treatment

Variable	Ledipasvir-Sofosbuvir		Total (*n* = 114)
	12 wk (*n* = 57)	24 wk (*n* = 57)	
HCV RNA level less than the LLOQ during treatment, *n/N (%)*			
Baseline	0/57 (0)	0/57 (0)	0/114 (0)
Week 1	9/57 (16)	7/57 (12)	16/114 (14)
Week 2	31/57 (54)	33/57 (58)	64/114 (56)
Week 4	50/57 (88)	52/57 (91)	102/114 (89)
Week 8	56/56 (100)*	57/57 (100)	113/113 (100)
Week 12	56/56 (100)*	57/57 (100)	113/113 (100)
Week 16	NA	57/57 (100)	57/57 (100)
Week 20	NA	57/57 (100)	57/57 (100)
Week 24	NA	57/57 (100)	57/57 (100)
HCV RNA level less than the LLOQ after end of treatment, *n/N (% [95% CI])*			
SVR4	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
SVR12	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
Overall virologic failure (relapse), *n/N (%)*	0/0 (0)	0/0 (0)	0/0 (0)

HCV = hepatitis C virus; LLOQ = lower limit of quantification; NA = not available; SVR4 = sustained virologic response at 4 wk; SVR12 = sustained virologic response at 12 wk.

* Excluding 1 patient in the 12-wk group who discontinued study treatment early at week 4 because of a serious adverse event. This patient achieved SVR12.

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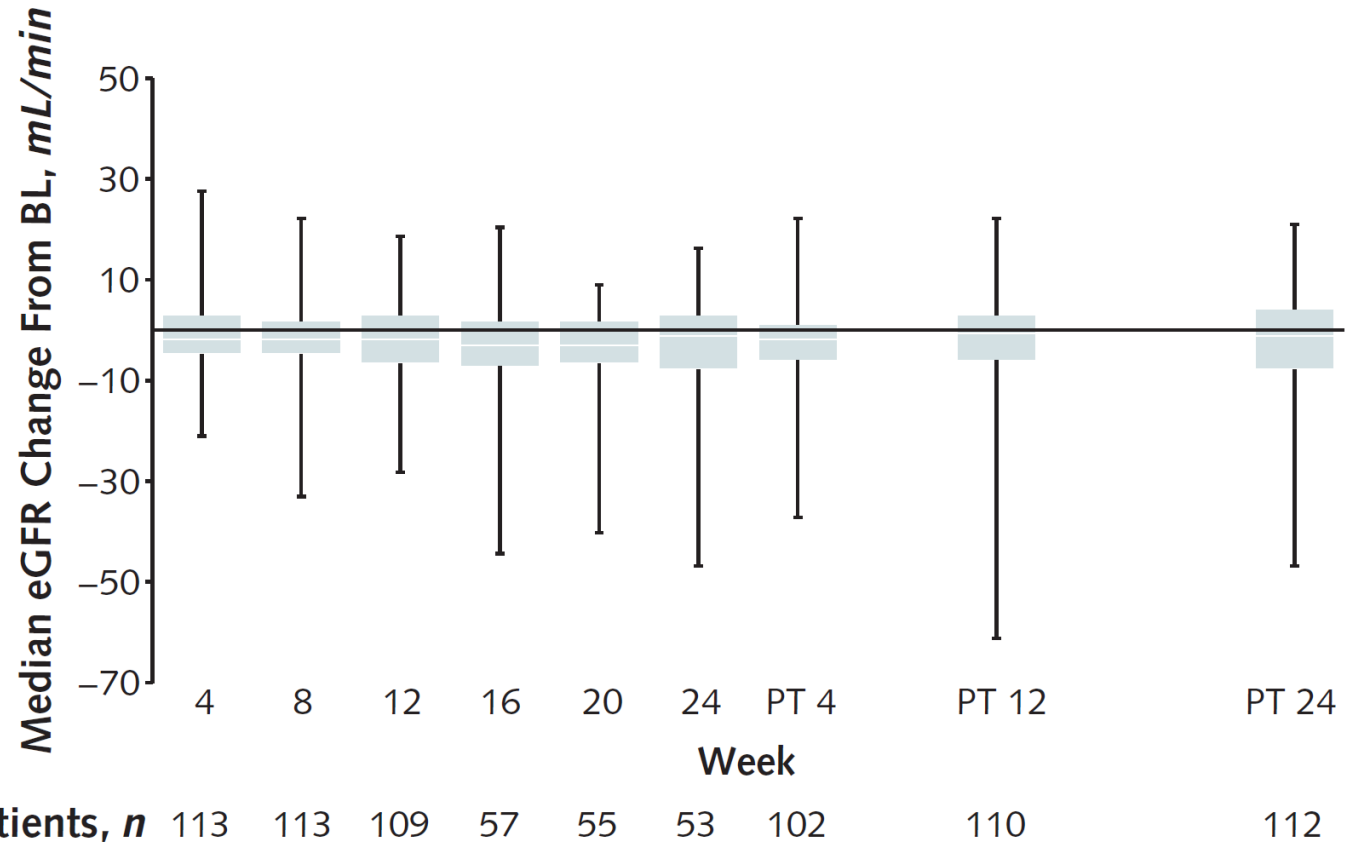
Figure 1. Median change in eGFR by Cockcroft–Gault equation.



The horizontal line is the median value, the box is interquartile range, and the whiskers show overall range. BL = baseline; eGFR = estimated glomerular filtration rate; PT = posttreatment.

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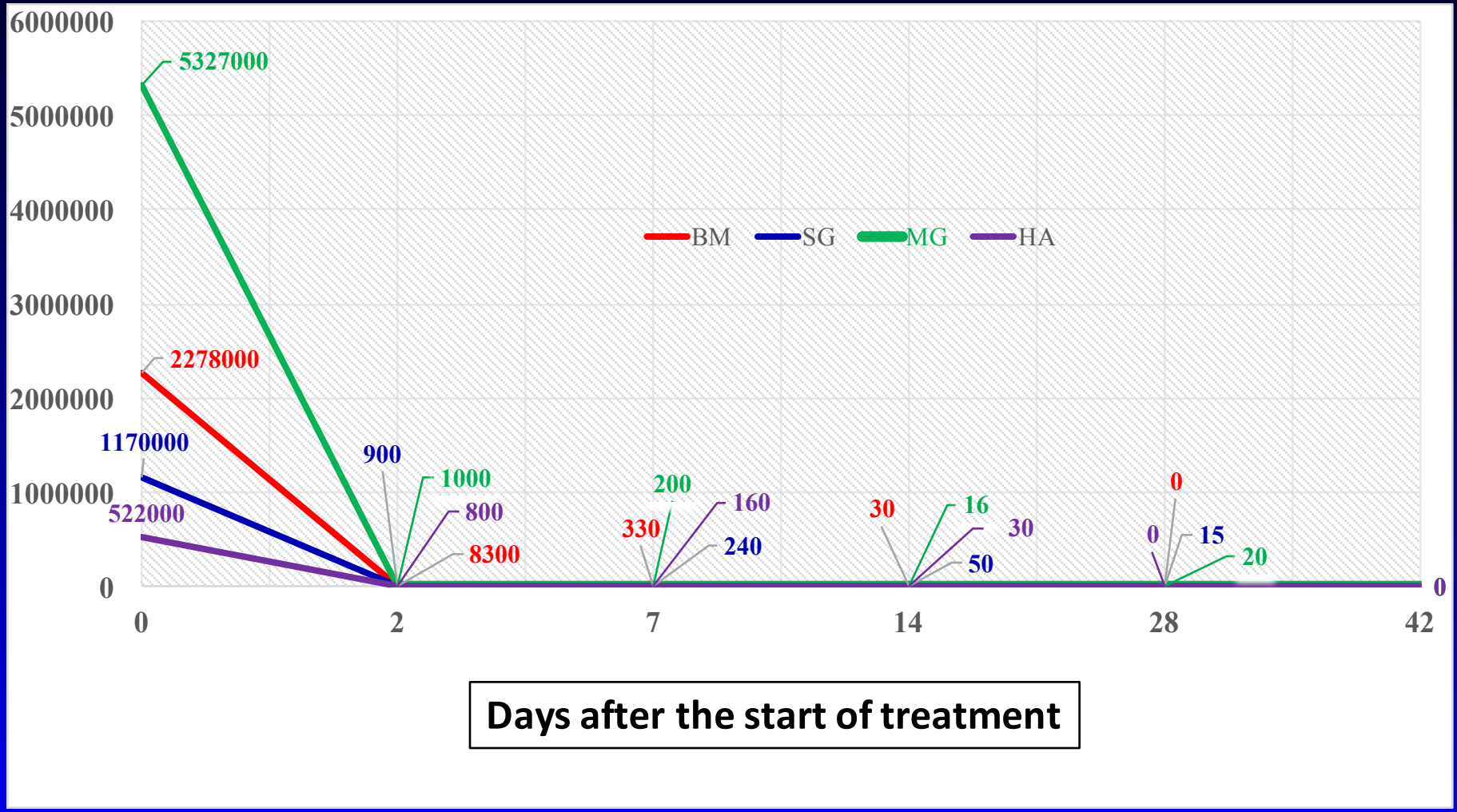
New HCV Treatment in Kidney Transplant Recipients
Varese experience

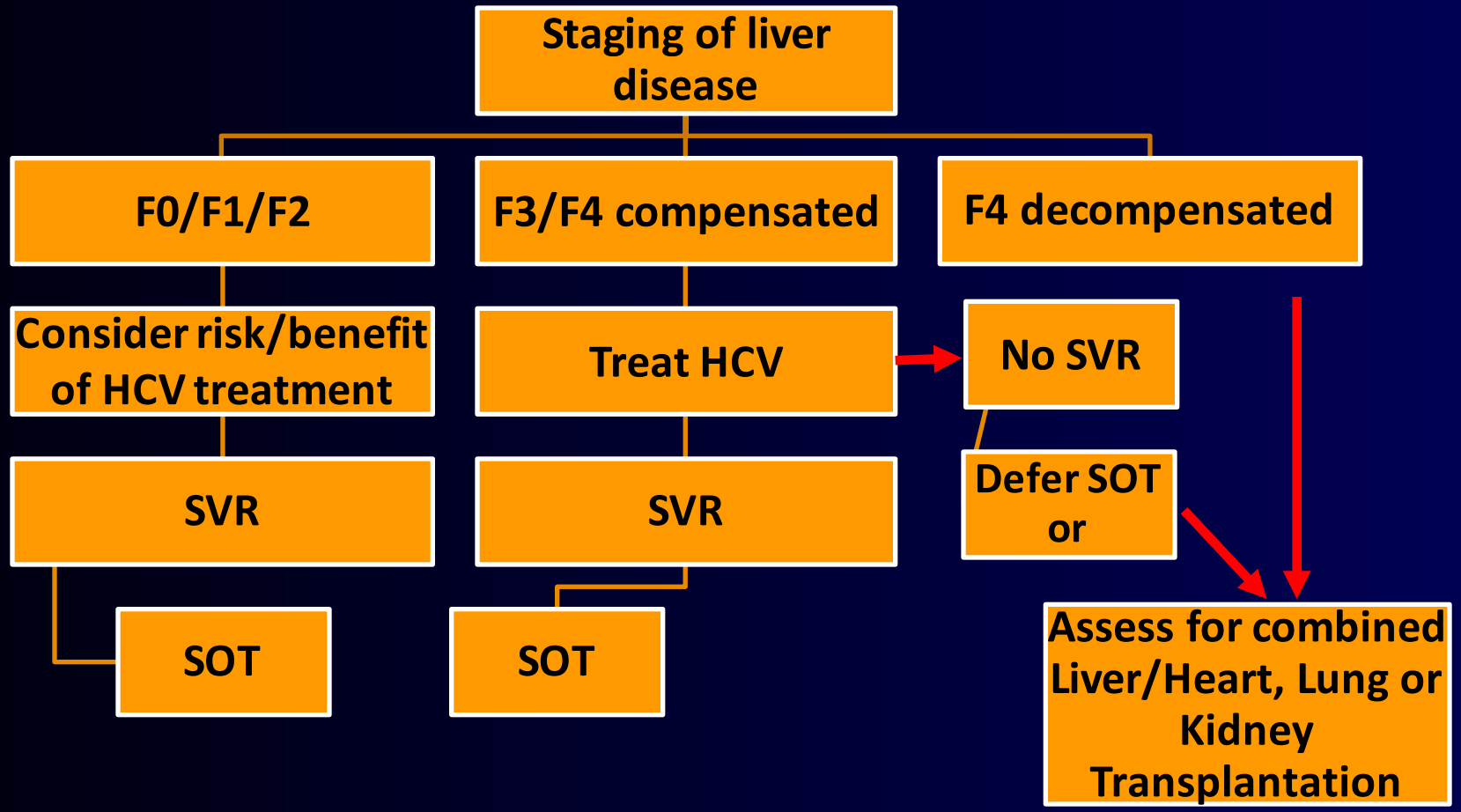
Pt	Sex/ Age	HCV-RNA UI/mL	HCV Genotype	Liver biopsy/ Fibroscan	Antiviral therapy	Treatment outcome	Side effects
B.M. HIV+	M, 55	2.78 x10^6	1a	Mild activity/ F3-F4	Sofosbuvir + Simeprevir (12 wk)	SVR	Fatigue
A.G.	M, 72	1.08 x10^6	1b	F2	Sofosbuvir+ Ledipasvir (12 wk)	SVR	None
F.A.	M, 50	1.43 x10^6	1b	F2	Sofosbuvir+ Ledipasvir (24 wk)	SVR	None
S.G.	M, 69	1.17 x10^6	1b	F2	Sofosbuvir+ Ledipasvir (12 wk)	SVR	None
S.M.F.	F, 72	4.71 x10^6	1a	F3	Sofosbuvir+ Ledipasvir (12wk)	SVR	None
H.A. HIV+	M, 47	1.67 x10^6	3	F2	Sofosbuvir+ Daclatasvir (24wk)	SVR	None
M.G. HIV+	M, 48	5.32 x10^6	1a	F2	Sofosbuvir+ Ledipasvir (12wk)	SVR	None

One patient treated with LED/SOF required everolimus dose reduction by 50%

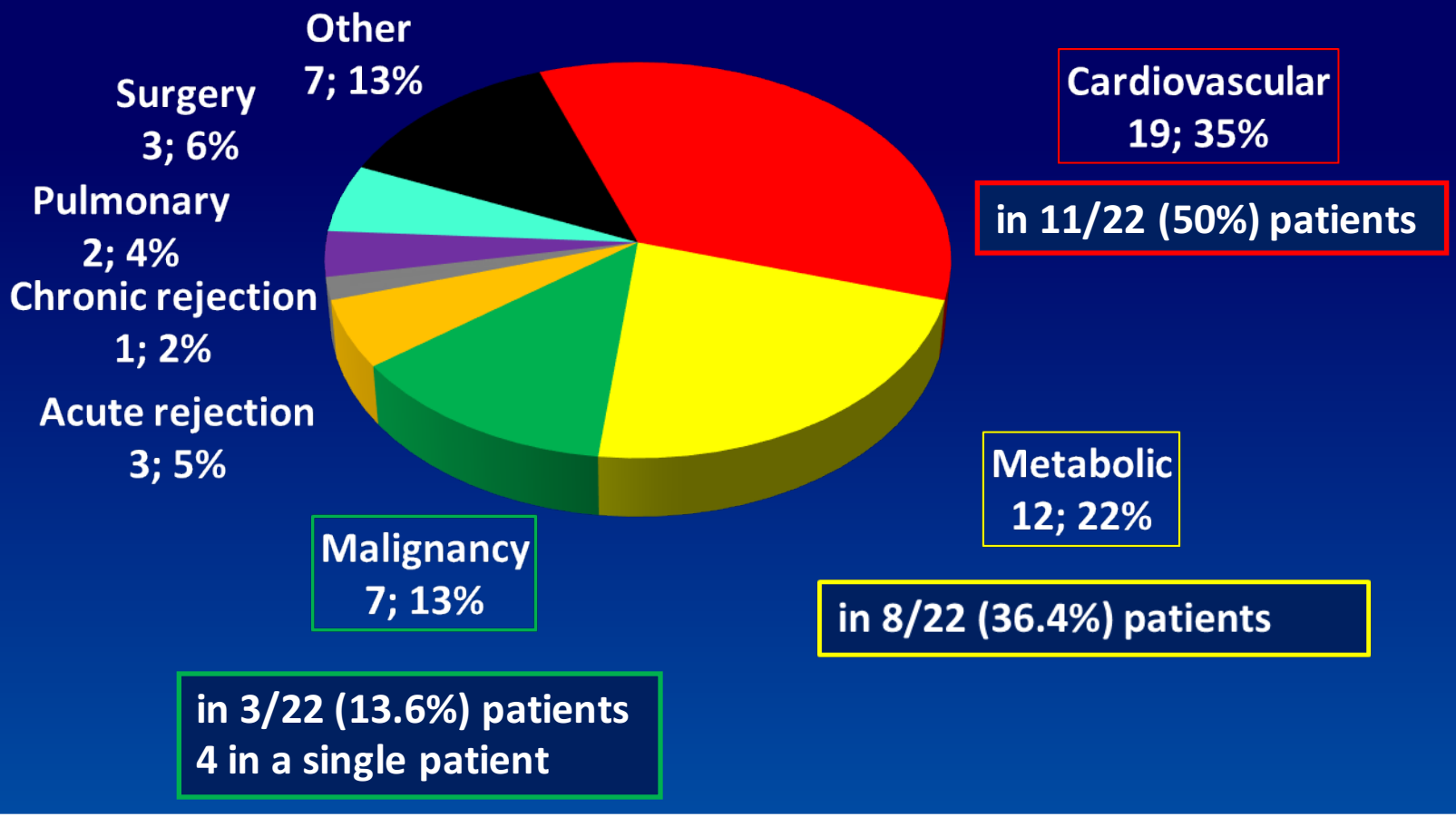
HCV-RNA after the START of Treatment with DAAs in Kidney Transplant Recipients



Proposed algorithm for treatment with the new DAAs of non hepatic organ transplant candidates



Non-Infectious Complications



- 15/22 (68.2%) patients developed non-infectious complications at a median of 730 (1-2744) days after KT
- Only 3 (13.6%) patients experienced an acute rejection episode (steroid resistant in 1 case followed by graft loss)

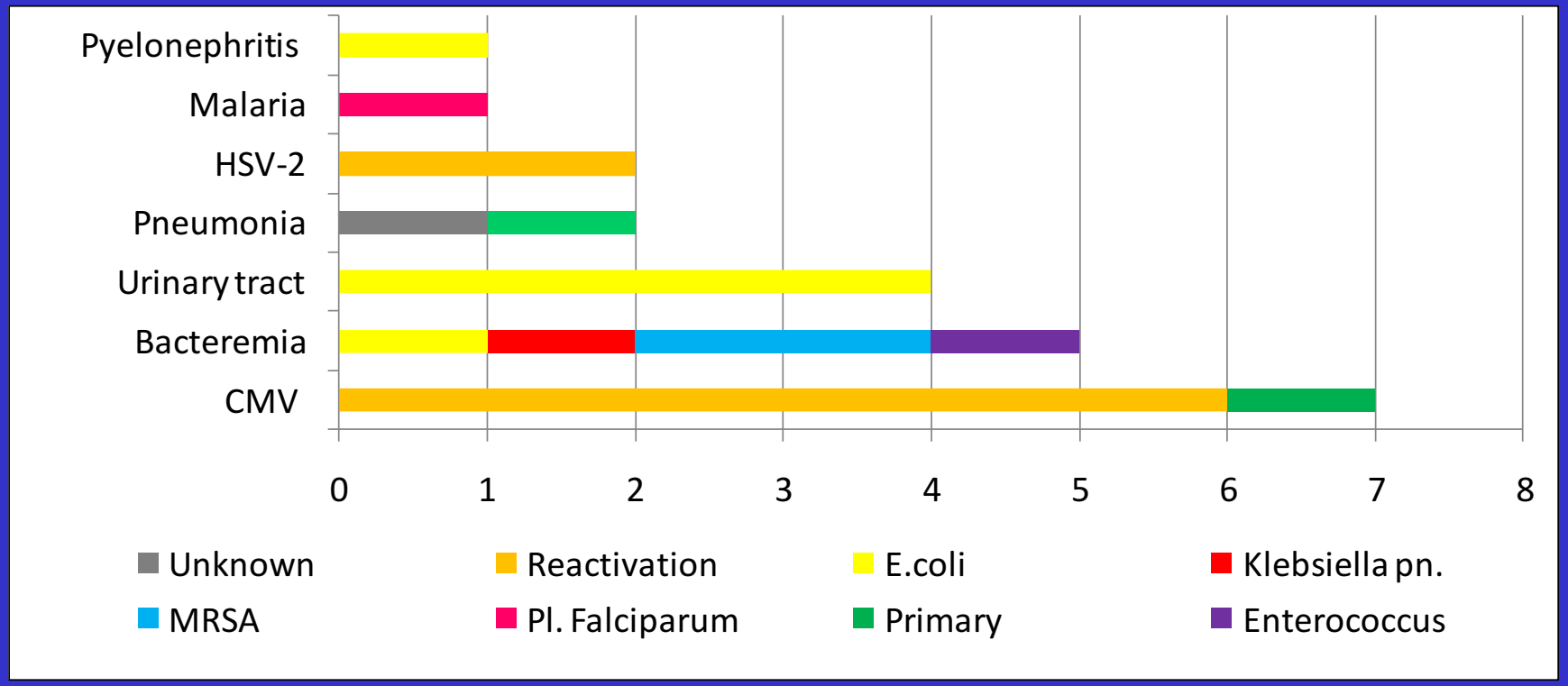
Key points

- Kidney transplantation in patients with HIV infection is a viable therapeutic option
- Ideal immunosuppressive regimen remains uncertain
- Higher rates of rejection are reported in clinical trials
- Immunosuppressive therapy does not seem to negatively impact the course of HIV infection
- Some immunosuppressive drugs may exert antiretroviral actions
- Special attention should be paid to the potential interaction between ART and immunosuppressive drugs
- A close collaboration between infectious disease specialists and transplant professionals is mandatory in order to optimize transplantation outcomes in these patients
- Transplantation from HIV+ donors to HIV+ is currently being researched

CONCLUSIONS

- Our experience, although in a limited number of patients, confirms excellent results of kidney transplantation in HIV-infected individuals
- However, most of the patients experienced potentially life-threatening complications or required hospital readmission.
- None of the patients developed AIDS defining opportunistic infections during the follow-up
- The rate of rejections in our series was very low
- Cardiovascular, metabolic and neoplastic complications were the most common.
- An intensive monitoring of drug-drug interactions and a multidisciplinary expert team is required for the optimal management of this challenging transplant population

Etiology and localization of complications after transplantation



9/13 patients developed infectious complications at a median of 34 (4-1224) days after transplantation

P.Grossi, Unpublished data