Kidney Transplantation in HIV-Infected Patients

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Improved Survival of HIV+ Dialysis Patients in the Era of HAART

Annual Death Rates of HIV+ and HIV− Dialysis Patients (per 1000 patient-years)

Year	HIV Infected	HIV Negative
1990	458.6	263.2
1991	407.7	256.6
1992	525.6	265.9
1993	487.8	266.7
1994	605.0	254.9
1995	490.55	251.5
1996	475.2	247.7
1997	291.6	237.3
1998	250.5	230.6
1999	240.2	236.4

HAART →

Ahuja et al. J Am Soc Nephrol 2002

Should HIV+ Patients with ESRD Be Considered for Transplantation?

1998 US Transplant Center Survey Response Rate: 149/248 (60%)	YES	NO	UNSURE
Is HIV testing required for prospective recipients?	100%		
Would a patient who refuses HIV testing be considered for transplantation?	12%	**84%**	4%
Would an HIV-infected ESRD pt be considered for cadaveric transplantation?	9%	**88%**	3%
Would an HIV-infected ESRD pt be considered for living donor transplantation?	5%	**91%**	4%

Spital et al. Transplantation 1998

Kidney Transplant Outcomes Were Poor in the Pre-HAART Era

Retrospective Cohort Study (1987-1997)

	USRDS CAD (N=63,178)	HIV+ CAD (N=32)
Graft survival		
One-year	85	81
Three-year	73	53*
Five-year	61	44*
Patient survival		
One-year	95	97
Three-year	88	83
Five-year	78	71*

[A]Percent survival calculated by life table analyses.
Data presented as mean ± standard deviation.
Graft survival includes death with functioning graft.
*$P < 0.05$ vs. USRDS population by Wilcoxon (Gehan) statistic.
CAD = cadaveric renal transplant recipients.

In multivariate analysis, HIV was independently associated with patient mortality and graft loss

Swanson et al. Transplant Infectious Diseases 2002

Significant Increase in HIV Kidney Transplant Recipients Since 2001

208 (0.26%) in 2001-6 vs. 43 (.06%) in 1995-2000 (p<0.001)
(US Renal Data System)

TABLE 3. Adjusted analysis of logistic regression factors associated with HIV+ kidney transplant recipients

Factor	aOR	95% CI	*P*
Transplanted after 2001	2.21	1.49–3.28	<0.001
African American recipient	2.96	2.26–3.88	<0.001
Male recipient	2.34	1.73–3.18	<0.001
Hepatitis C coinfection	4.21	2.96–5.98	<0.001
Greater than 4 yr on dialysis before transplant	1.98	1.43–2.75	<0.001
Induction therapy	0.39	0.29–0.53	<0.001
Donor age (per yr)	0.99	0.98–0.99	0.036
Tacrolimus use at discharge	0.66	0.49–0.89	0.007

aOR, adjusted odds ratio; CI, confidence interval.

HIV not associated with all-cause graft loss in analysis adjusting for multiple variables including HCV

Yoon et al. Transplantation 2011

Kidney transplants in HIV-positive recipients under HAART. A comprehensive review and meta-analysis of 12 series

Luis Landin[1], Jose C. Rodriguez-Perez[2], Miguel A. Garcia-Bello[2], Pedro C. Cavadas[1], Alessandro Thione[1], Peter Nthumba[3], Marino Blanes[4] and Javier Ibañez[1]

1-year survival was 0.93 (95% CI, 0.90-0.96) among 254 HIV kidney transplant recipients

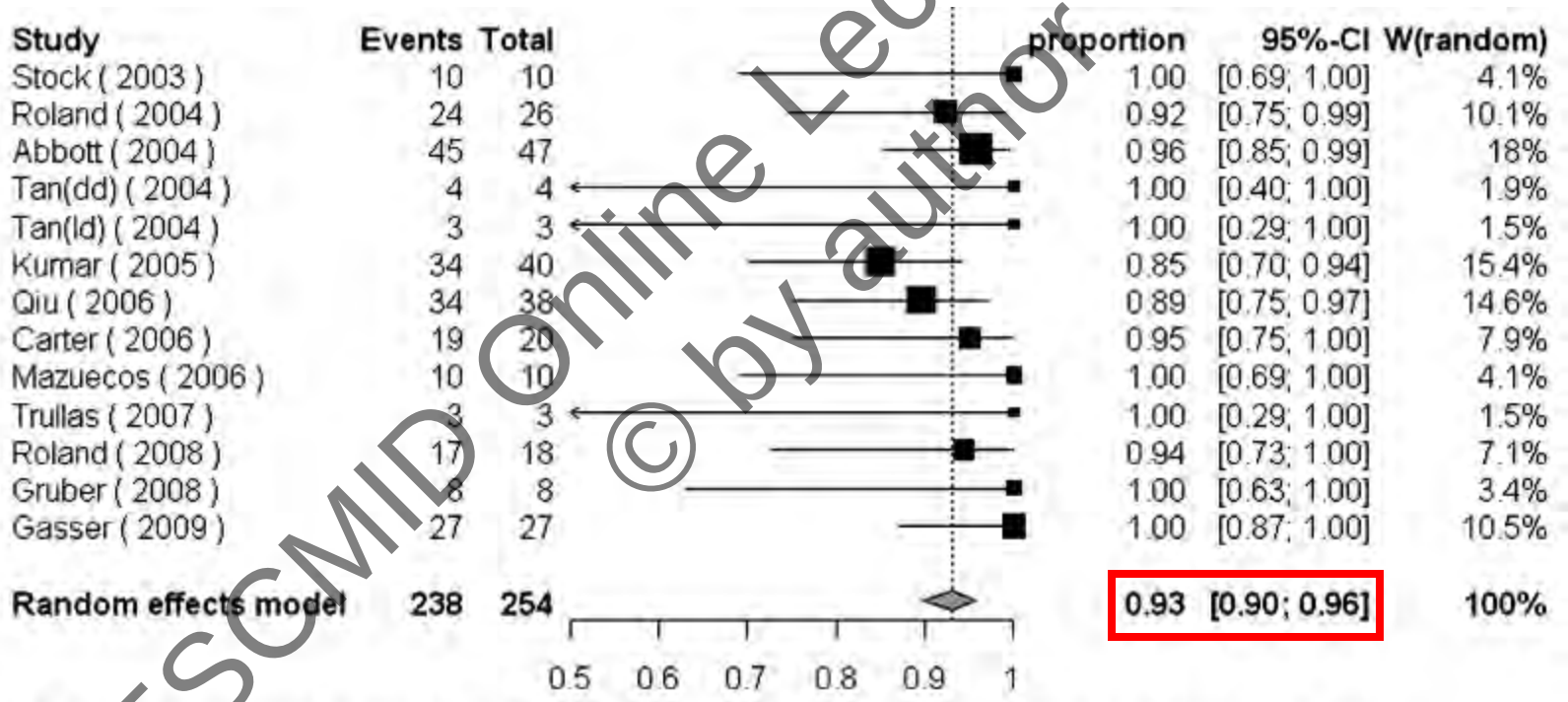


Fig. 1. Pooled estimated proportion of patients surviving the first year, analysed using a random effects model.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes of Kidney Transplantation in HIV-Infected Recipients

- 150 kidney recipients prospectively enrolled between 8/03 and 6/09 in the United States
- HIV-related eligibility criteria
  - CD4>200
  - HIV-1 RNA undetectable
  - Stable ARV regimen for 16 weeks
  - Treated opportunistic infections acceptable EXCEPT:
    - Progressive multifocal leukoencephalopathy
    - Chronic intestinal cryptosporidiosis
    - Primary CNS lymphoma
    - Visceral Kaposi's sarcoma

Stock et al. NEJM 2010

Baseline HIV-Related Characteristics of 150 Kidney Transplant Recipients

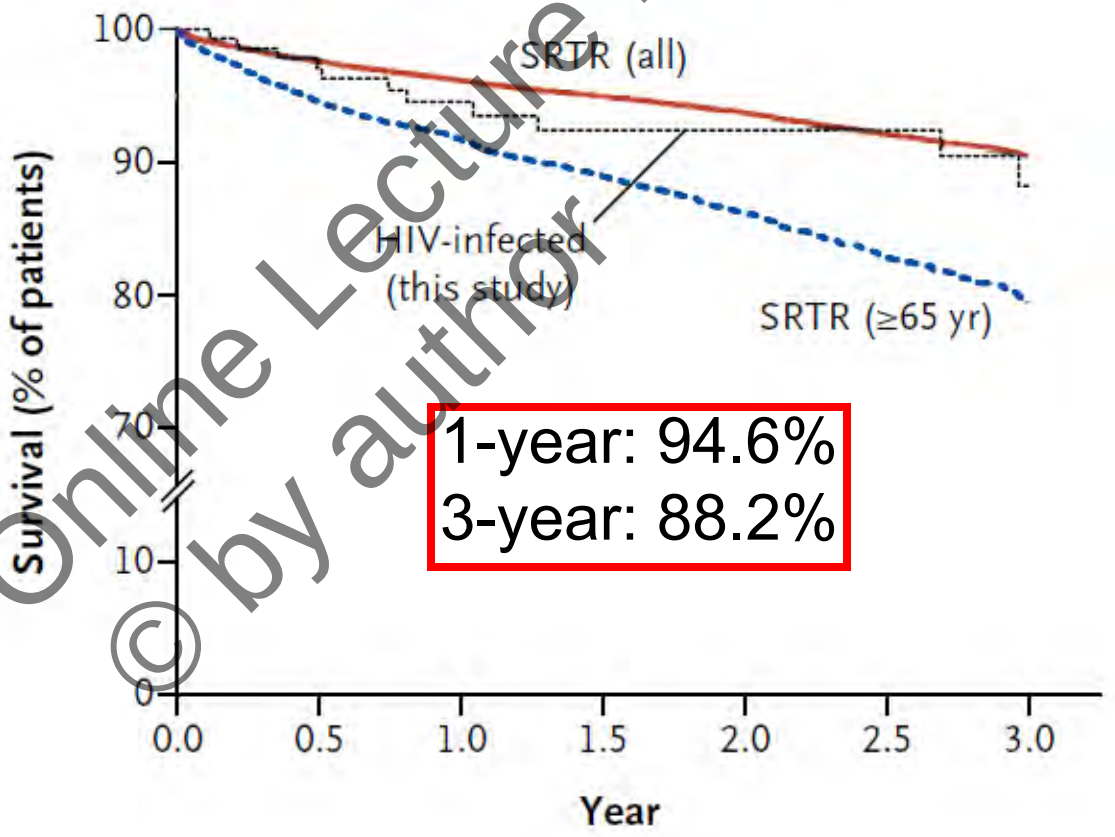
Survivors followed for median of 1.7 years

Prior opportunistic complication — no. (%)¶	36/150 (24)
CD4+ count — per mm³‖	
Median	524
Interquartile range	385–672
Viral hepatitis — no. (%)	
Hepatitis C RNA detectable	28/150 (19)
Hepatitis B surface antigen–positive	5/150 (3)
HAART regimen — no. (%)**	
Protease-inhibitor–based	63/150 (42)
NNRTI-based	59/150 (39)
Protease-inhibitor–based and NNRTI-based	15/150 (10)
Nucleoside analogues only	5/150 (3)
Raltegravir-based	6/150 (4)
None	2/150 (1)

Stock et al. NEJM 2010

Patient Survival Similar to Rates Observed in Scientific Registry of Transplant Recipients (SRTR)

Hazard of death was marginally higher in HCV+ recipients (p=0.09) and with ATG induction (p=0.06)

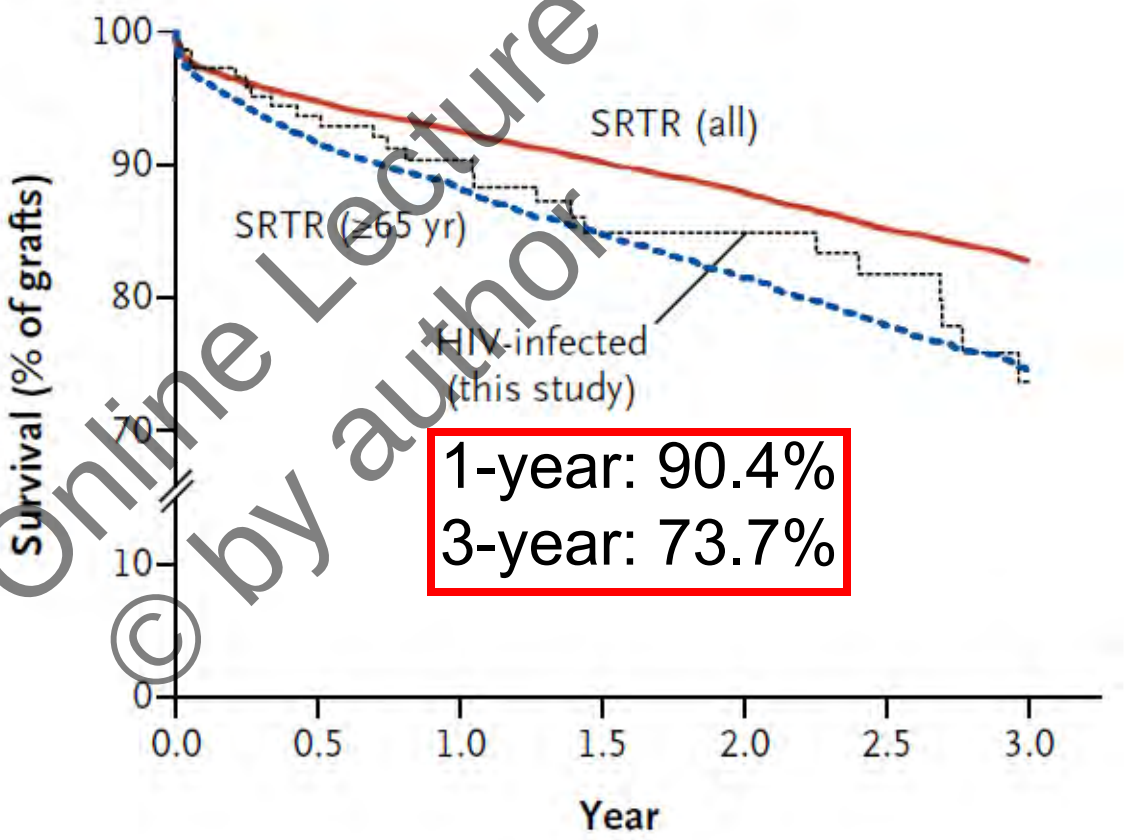


No. at Risk			
SRTR (all)	29,928	16,792	6508
HIV-infected (this study)	96	68	36
SRTR (≥65 yr)	4,226	2,215	836

Stock et al. NEJM 2010

Graft Survival Similar to Rates Observed in the Older Adults (≥65)

- Graft loss associated with treated rejection (HR 2.8, p=0.02) and ATG induction (HR 2.5, p=0.03)
- Graft from living donor was protective (HR 0.2, p=0.02)



No. at Risk			
SRTR (all)	29,064	16,114	6215
HIV-infected (this study)	93	64	31
SRTR (≥65 yr)	4,103	2,133	807

Stock et al. NEJM 2010

Patient and Graft Survival Compared to SRTR

Population	Patient Survival		Graft Survival	
	At 1 Year	At 3 Years	At 1 Year	At 3 Years
	percent (95 percent confidence interval)			
Study patients	94.6 (88.9–97.4)	88.2 (78.3–93.8)	90.4 (83.9–94.3)	73.7 (61.9–82.4)
SRTR patients				
Age ≥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)
Overall	96.2 (96.0–96.4)	90.6 (90.2–91.0)	92.5 (92.3–92.8)	82.8 (82.3–83.3)

- Causes of 11 deaths:
  - Cardiac (3)
  - Sepsis (2)
  - Pulmonary infection (2)
  - Renal-cell carcinoma (2)
  - Unknown (2)

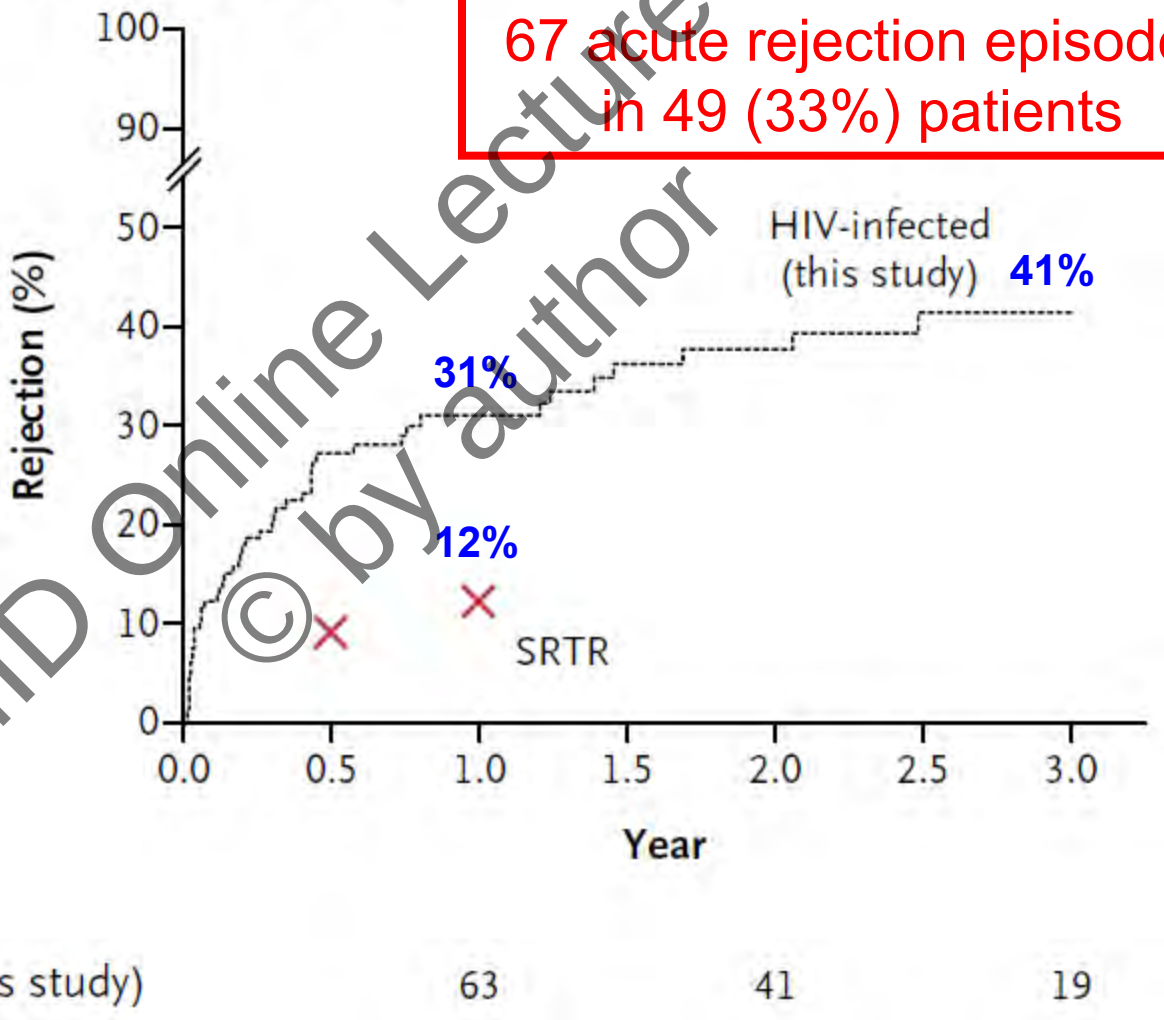
- Causes of 13 graft failures:
  - Chronic rejection or allograft nephropathy (5)
  - Vascular thrombosis (3)
  - Acute rejection (3)
  - Other (2)

Stock et al. NEJM 2010

Unexpectedly High Rates of Acute Rejection

- Graft rejection associated with deceased donor (HR 2.3, p=0.03) and cyclosporine use (HR 2.1, p=0.02)
- Higher tacrolimus trough level associated with decreased risk of acute rejection (HR 0.9. p=0.04)

67 acute rejection episodes in 49 (33%) patients



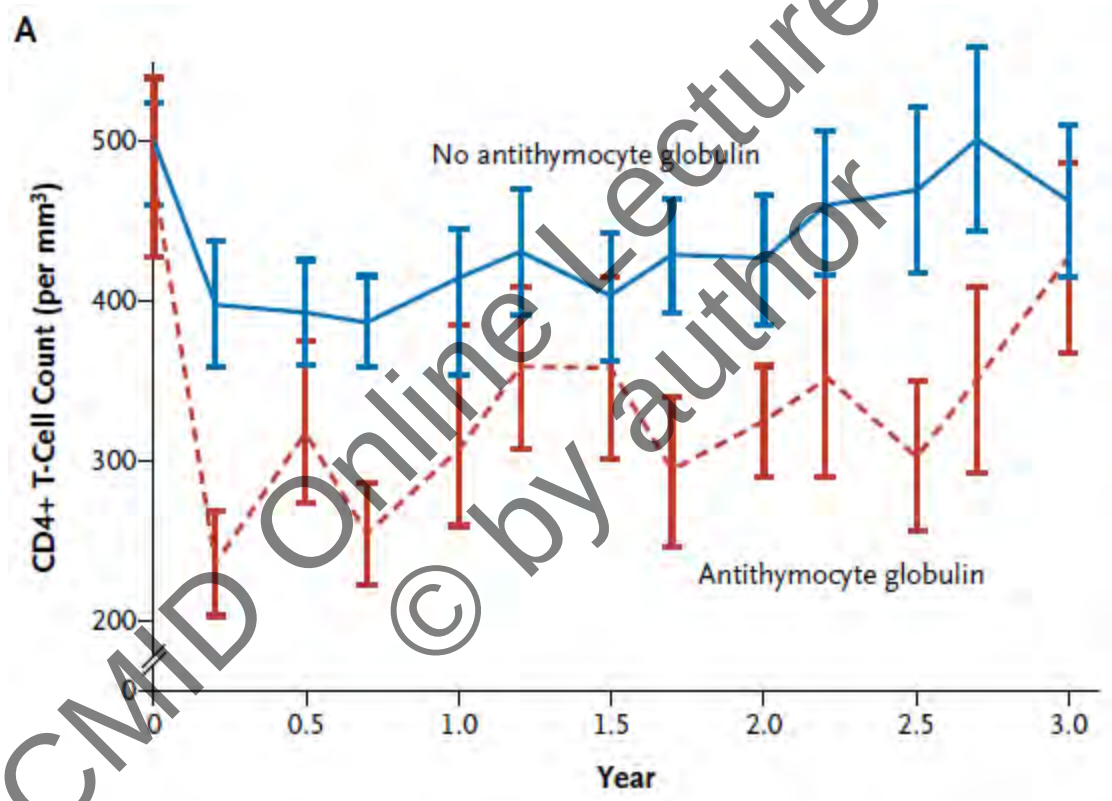
Stock et al. NEJM 2010

HIV-Related Outcomes Not a Significant Problem

- AIDS-defining conditions were rare
  - Cutaneous Kaposi's sarcoma (2)
  - *Candida* esophagitis (1)
  - Presumptive PCP (1)
  - Cryptosporidiosis (1)
- Two patients with biopsy-proven newly diagnosed HIVAN despite virologic suppression
- 48 (32%) with detectable HIV-1 RNA after transplant
  - 29 with a single episode
  - 19 with transient viremia (median peak, 604 copies/ml)
  - Only 1 patient with detectable HIV-1 RNA at three years

Stock et al. NEJM 2010

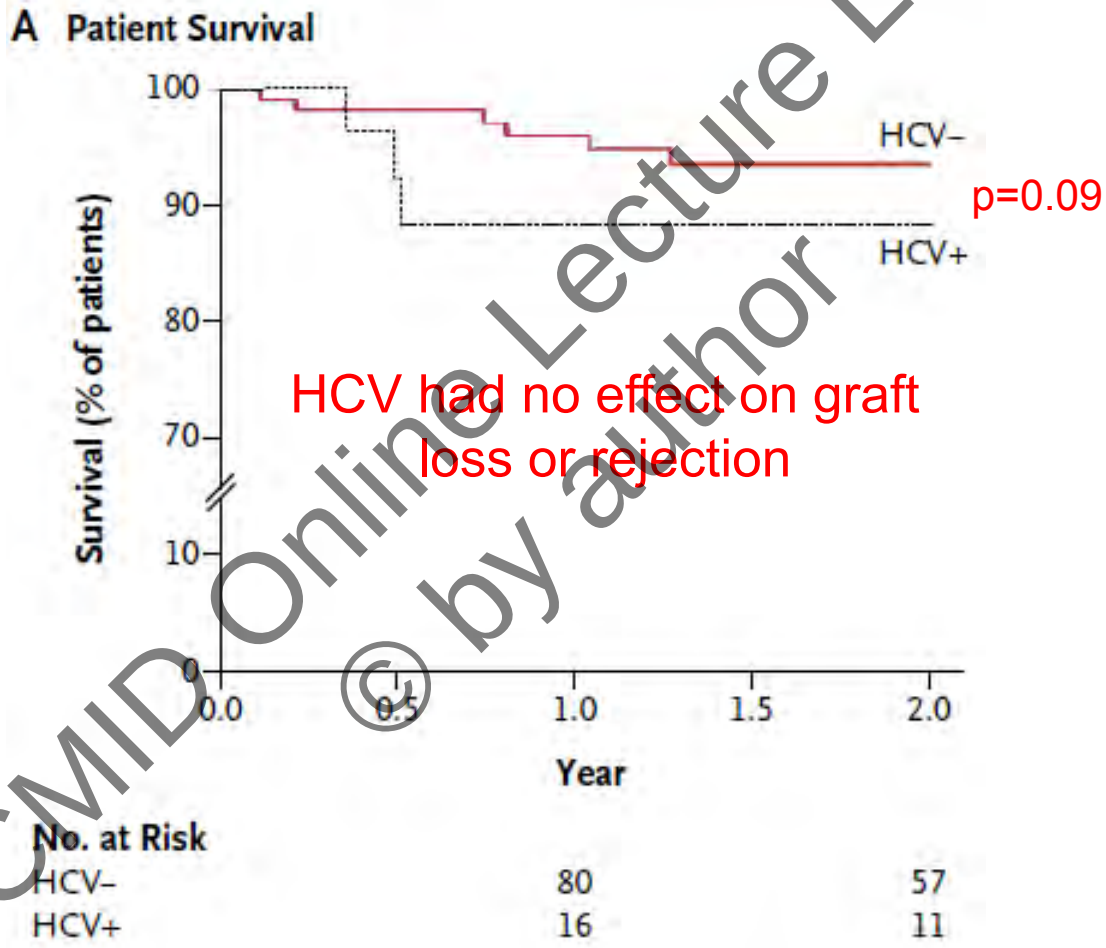
Significant Reductions in CD4 Counts with Thymoglobulin



Twice as many serious infections per follow-up year observed with thymoglobulin in the first week (0.9 vs. 0.4, p=0.002)

Stock et al. NEJM 2010

Hazard of Death Marginally Higher in HIV-HCV Patients



HCV had no effect on graft loss or rejection

HCV associated with higher rate of serious infections per follow-up year (0.8 vs. 0.5, p=0.02)

Stock et al. NEJM 2010

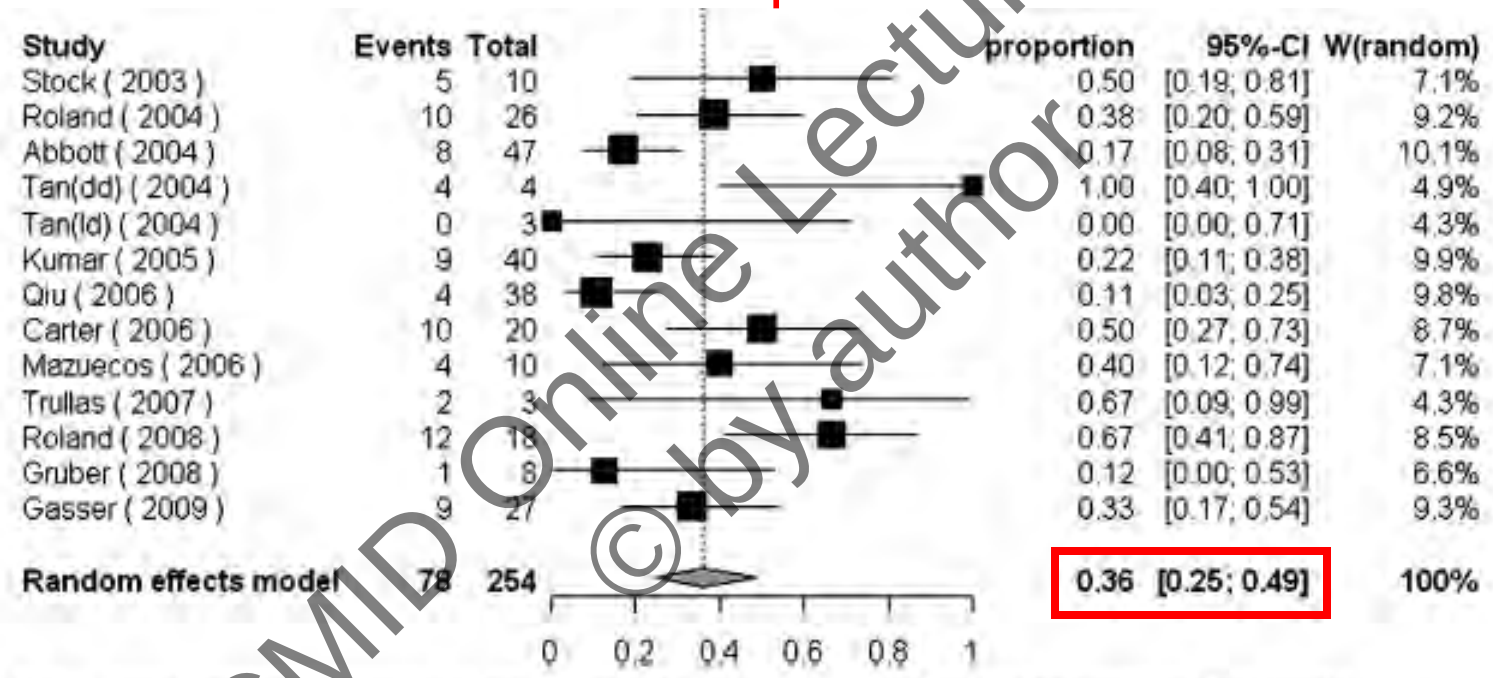
Updated Outcomes and Survival in 150 HIV Kidney Transplants

- Median follow-up of 2.3 years
- 1- and 3-year survival: 95% and 91%
- Factors associated with mortality
  - HCV (HR 3.17; CI 1.10, 9.09; p=0.03)
  - Age (HR 1.06; CI 1.01, 1.11; p=0.03)
  - ATG induction (HR 2.63; CI 0.94, 7.31; p=0.06)
- No recurrences or survival differences in patients with history of an opportunistic infection
- HIV factors are not associated with mortality

Roland et al. (presented orally at ATC in May 2011)

High Rates of Kidney Rejection Consistently Observed Across Cohorts

78 episodes of rejection among 254 HIV kidney transplant recipients



Study	Events	Total	proportion	95%-CI	W(random)
Stock (2003)	5	10	0.50	[0.19; 0.81]	7.1%
Roland (2004)	10	26	0.38	[0.20; 0.59]	9.2%
Abbott (2004)	8	47	0.17	[0.08; 0.31]	10.1%
Tan(dd) (2004)	4	4	1.00	[0.40; 1.00]	4.9%
Tan(ld) (2004)	0	3	0.00	[0.00; 0.71]	4.3%
Kumar (2005)	9	40	0.22	[0.11; 0.38]	9.9%
Qiu (2006)	4	38	0.11	[0.03; 0.25]	9.8%
Carter (2006)	10	20	0.50	[0.27; 0.73]	8.7%
Mazuecos (2006)	4	10	0.40	[0.12; 0.74]	7.1%
Trullas (2007)	2	3	0.67	[0.09; 0.99]	4.3%
Roland (2008)	12	18	0.67	[0.41; 0.87]	8.5%
Gruber (2008)	1	8	0.12	[0.00; 0.53]	6.6%
Gasser (2009)	9	27	0.33	[0.17; 0.54]	9.3%
Random effects model	**78**	**254**	**0.36**	**[0.25; 0.49]**	**100%**

0 0.2 0.4 0.6 0.8 1

Fig. 2. Pooled estimated proportion of patients suffering organ rejection, analysed using a random effects model.

Analysis could not clarify which immunosuppression protocols were associated with complications

Landin et al. Nephrol Dial Transplant 2010

High Rates of Rejection in European HIV KT Recipients

Cross-sectional multicenter survey of EuroSIDA clinics in 2008

Rejection observed in 8/26 (30%) HIV KT recipients

TABLE 4. HIV-Infected Kidney Transplant Recipients With Graft Rejection

Patient	1	2	3	4	5	6	7	8
Transplant date*	8/2005	8/2000	5/2005	8/2005	12/2005	2/2004	2/2006	5/2005
Cadaveric donor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immuno suppression								
Initial induction	DAC	—	—	PAA	PAA	—	BAS	—
Initial maintenance	FK + MMF	—	FK + MMF + St	MMF + RAP + St	MMF + RAP + St	CyA + MMF + St	FK + MMF + St	FK + St
Current regimen	FK + MMF	CyA + MMF + St	—	FK + MMF+ St	FK + MMF+ St	—	St	—
Date rejection*	2/2006	8/2003	11/2007	9/2005	3/2006	9/2007	8/2006	5/2005
Treatment	St	St	—	St	St	St	St	St, AA
Type of rejection†	IB	IIA	AR	BC	IA	CR, VAS	IA	—
Graft currently functioning?	Yes	No	No	Yes	Yes	No	No	No
Date started RRT	—	—	12/1/2007	—	—	12/15/2007	4/1/2008	5/18/2005

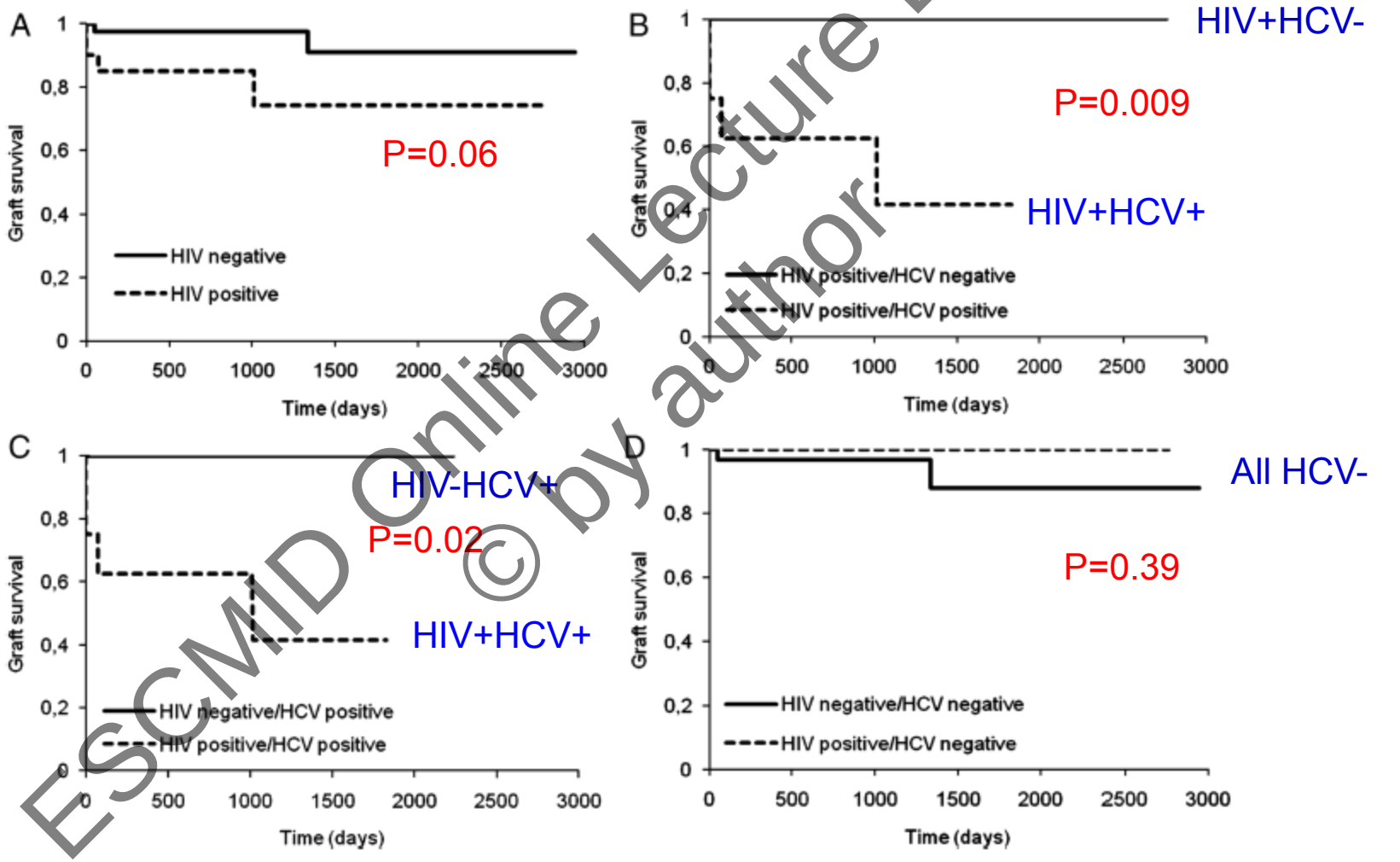
Trullas et al. JAIDS 2010

Potential Factors Associated with Lower Rates of Rejection

- Acute rejection in only 15% of 27 HIV KT recipients in France
- Proposed factors (speculative)
  - Use of anti-CD25 induction therapy
  - Predominant use of tacrolimus
  - Absence of mTOR inhibitor use
  - Withdrawal of protease inhibitors
    - Stable tacrolimus treatment

Touzot et al. AJT 2010

Lower Death-Censored Graft Survival with HCV in Spanish Cohort of 20 HIV KT Recipients



Mazuecos et al. Nephrol Dial Transplant 2011

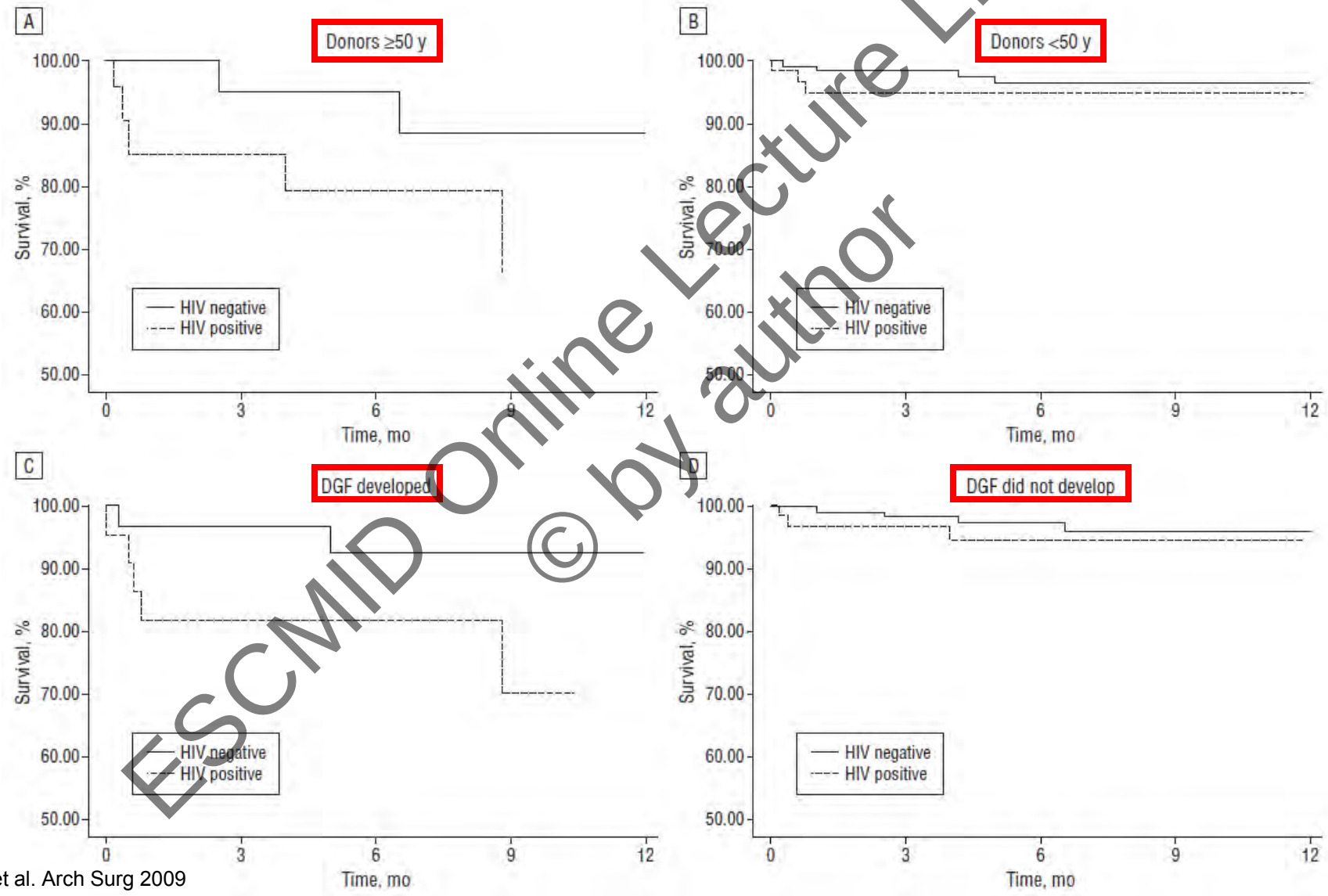
Risk Factors for Graft Loss Among HIV+ Kidney Transplant Recipients

Retrospective Cohort Study of 100 HIV+ KT Recipients from UNOS Database

Risk Factor	1-y Graft Survival Rate, %	*P* Value[a]	Risk of Graft Loss (HR)	*P* Value
Donor				
Age ≥50 y				
No (n=75)	95.1	.009	1 [Reference]	.02
Yes (n=25)	66.3		5.43	
Hypertension				
No (n=80)	90.8	.02	1 [Reference]	.04
Yes (n=17)	76.0		4.42	
ECD				
No (n=88)	90.3	.04	1 [Reference]	.06
Yes (n=12)	72.2		4.01	
CIT ≥16 h				
No (n=65)	96.4	.007	1 [Reference]	.02
Yes (n=35)	64.7		6.88	
Recipient				
DGF				
No (n=77)	94.7	.02	1 [Reference]	.03
Yes (n=22)	70.1		4.81	

Locke et al. Arch Surg 2009

Impact of Donor Age and Delayed Graft Function on Survival



Locke et al. Arch Surg 2009

24 Management Algorithm for Transplantation in Patients with Human Immunodeficiency Virus

Shirish Huprikar

24.1 Initial pre-transplant evaluation of patients with human immunodeficiency virus (HIV)

HIV-specific	General
• HIV RNA levels in the past 12 months • Baseline HIV RNA level • CD4 cell counts in the past 12 months • CD4 cell count nadir • Current and previous antiretroviral regimen history • Prior HIV genotypic and phenotypic information • Previous opportunistic infections and treatment history	• Hepatitis A IgG • Hepatitis B: HBsAg, anti-HBs, anti-HBc • HBV DNA and HBeAg (for HBsAg+ patients) • Hepatitis C: HCV Ab, HCV RNA and genotype (for HCV Ab+ patients) • HCV RNA and Prior HCV treatment history • Screening for latent TB: TST or IGRA • CMV IgG, EBV IgG,VZV IgG • Syphilis screen • *Strongyloides stercoralis* IgG (for patients who have lived in endemic regions) • *Toxoplasma* IgG • G6PD

Careful patient selection is still important and it is essential to obtain a detailed HIV history to determine eligibility and guide management

24.2 HIV patient selection criteria for transplantation

Suitable candidates for transplantation must adhere to all transplant center-specific selection criteria and have stable HIV (Table 24.2).

Organ	HIV RNA	CD4+ T-cell count
Kidney[a]	Undetectable (< 48 copies/mL) for 3 months	> 200 /μL for 3 months
Liver	Undetectable (< 48 copies/mL) for 3 months[b]	> 100 /μL for 3 months in liver candidates without a history of opportunistic infection > 200 /μL for 3 months in liver candidates with a history of opportunistic infection

[a]The criteria for kidney candidates should be followed in heart, lung, or pancreas transplant candidates where experience is quite limited.
[b]Detectable HIV RNA is acceptable in selected liver transplant candidates who currently cannot tolerate antiretroviral therapy due to hepatoxicity provided that genotypic testing does not reveal significant resistance that would prevent complete virologic suppression after transplantation.

Refer stable HIV patients with advanced chronic kidney disease for transplant evaluation as early as possible

24.3 Preferred antiretroviral drugs in HIV1 transplant candidates or recipients

Class	Preferred	Alternative	Comments
Dual NRTI	Tenofovir/emtricitabine *or* Abacavir/lamivudine	Zidovudine (avoid in HCV co-infected patients who may need therapy with interferon and ribavirin)	Individual components of fixed-dose combinations need to be administered in patients with renal failure Tenofovir/emtricitabine is preferred in HIV-HBV co-infected patients
	+		
NNRTI	Efavirenz	Nevirapine *or* Etravirine	Avoid nevirapine in liver transplant candidates
	OR		
PI (boosted)	Atazanavir *or* Darunavir	Lopinavir-ritonavir *or* Fos-amprenavir	Decreased levels of atazanavir may occur with gastric acid suppression
Integrase inhibitor	Raltegravir	N/A	
CCR5 inhibitor	Maraviroc	N/A	

- Antiretrovirals that avoid drug interactions with calcineurin inhibitors (CNIs) and sirolimus should be considered to minimize post-transplant complications (see Table 24.4). Raltegravir is a preferred key third agent that avoids drug interactions with CNIs and sirolimus.Efavirenz is a preferred key third agent with limited drug interactions with CNIs and sirolimus (see Table 24.4).

Consider changing to a “transplant-friendly” regimen while the patient is on waiting list if clinically feasible

AST Handbook of Transplant Infections (ed. Kumar and Humar)

Tenofovir (TDF) Not Associated with Renal Dysfunction Following Kidney Transplantation

- TDF frequently used in the NIH cohort study (n=150)
  - 43 (29%) pre-transplant
  - 52 (35%) post-transplant
- TDF was discontinued in 15/52 (29%)
  - Not known if TDF was discontinued due to toxicity
- No significant association between TDF and post-transplant creatinine in univariate analysis (p=0.58)
  - Unknown at this time if continued use would be associated with renal impairment in multivariate analysis
- Follow-up is ongoing to determine the impact of long-term post-transplant use of TDF

Roland et al. ATC 2011 (abstract)

Dose Adjustments with Boosted versus Unboosted Protease Inhibitors

Group	Case no.	Time to start ARV_s post-LT_x (days)	$CD4^+$ at resumption (cells/mm^3)	HIV viral load at resumption (copies/mL)	PI_s dosages (mg)	IS	IS C_t pre-ARV_s (ng/mL)	IS C_t 48h post-ARV_s resumption (ng/mL)	IS dosage fold decrease
A	1	1	132	<40	LPV/RTV 400/100 BID	FK	0	19	8
	2	11	98	<40	APV/RTV 450/100 BID	CsA	284	1161	14
	4	37	194	<40	LPV/RTV 400/100 BID	CsA	241	1884	6
	10	29	416	<40	LPV/RTV 400/100 BID	CsA	178	294	7
B	3	21	155	332	fosAPV 1400 BID	CsA	431	629	2.25
	5	12	65	<40	ATV 400 QD	CsA	344	587	2.75
	6	12	276	27 999	ATV 400 QD	CsA	161	360	2
	7	19	221	>500 000	ATV 400 QD	CsA	163	219	2.5
	8	13	531	<40	ATV 400 QD	CsA	104	324	3.5
	9	25	160	<40	ATV 400 QD	RPM	9	>30	4
	11	13	93	<40	ATV 400 QD	CsA	212	379	3
	12	18	30	<40	ATV 400 QD	RPM	13	10	4

The necessary fold decrease in IS dosage was higher with boosted PIs than with unboosted PIs

Guaraldi et al. AJT 2009

24.4 Drug–drug interactions and post-transplant management in transplanted patients with HIV

Antiretroviral(s)	Potential interaction	Approximate dosing adjustment	CNI/sirolimus serum levels
Ritonavir-boosted PIs Nelfinavir	Increased levels of CNI or sirolimus	Tacrolimus 0.5–1.5 mg weekly Cyclosporine 25–50 mg daily Sirolimus 1–1.5 mg weekly	Early and frequent monitoring are required to establish dose and frequency
Unboosted PIs Atazanavir Fos-amprenavir	Increased levels of CNI or sirolimus	Tacrolimus 0.5–1.5 mg weekly (may need more) Cyclosporine 100–200 mg daily Sirolimus 1–1.5 mg daily	
NNRTI (efavirenz, nevirapine, etravirine)	Decreased levels of CNI or sirolimus	No baseline adjustments	Early monitoring is needed as higher doses may be required
NNRTI + PI	Increased levels of CNI or sirolimus	Tacrolimus 0.5–1.5 mg weekly Cyclosporine 25–50 mg daily Sirolimus 1 mg weekly	Early and frequent monitoring are required to establish dose and frequency
Integrase inhibitor (ralregravir)	None	No dose adjustment	Standard monitoring
CCR5 inhibitor (maraviroc)	May increase maraviroc levels	No dose adjustment	Standard monitoring

Lower rejection rates observed in kidney transplant patients who are homozygous for CCR5Δ. Future role of maraviroc needs to be studied

Kidney Transplantation in HIV Patients

Summary

- Patient and graft survival are acceptable and at least comparable to other high risk kidney transplant recipients
  - Can be considered standard of care at experienced centers
- No evidence for progression of HIV after kidney transplantation
- Risk factors associated with mortality
  - HCV (associated with higher rates of infection)
  - ATG (associated with higher rates of infection)
- Risk factors associated with graft loss
  - Treated rejection
  - ATG
  - Donor age ≥50
  - Delayed graft function
- Risk factors associated with rejection
  - Deceased donors (live donors associated with graft survival)
  - Cyclosporine use (higher tacrolimus levels protective)

Kidney Transplantation in HIV Patients

Future Directions

- Future studies should continue to explore the factors associated with patient and graft survival
  - Deceased vs. live donors?
  - Is HCV a problem?
- Risk factors for rejection should be emphasized in future studies
  - Is there an ideal immunosuppressive regimen?
  - Is there an ideal antiretroviral regimen?
- Define optimal timing for re-initiating HAART in conjunction with immunosuppressants
- Can we expand donor pool to include HIV+ donors?

Thank you
Questions?

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