The Pre-Transplant Evaluation

HIV Edition

West Coast TID Meeting

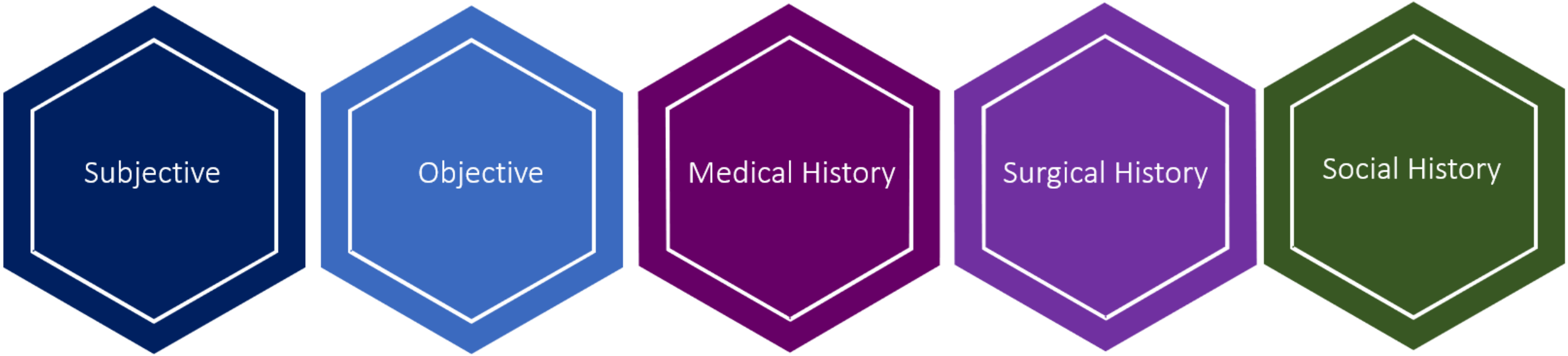
10/25/2022

Alan Koff
Assistant Professor
UC Davis

Patient Visit

- [redacted] year-old male with HIV is referred for **pre-transplant evaluation** for kidney transplant.
- Referral question: Please **review HIV medications** for transplant

Patient Visit



Subjective	Objective	Medical History	Surgical History	Social History
"I feel fine. I have hemodialysis three times a week and it doesn't bother me at all."	Normal exam, functioning fistula, no cutaneous lesions. Clothing +'ve for cat hair.	FSGS with ESRD on HD HIV Cutaneous KS HTN Gout CVA GERD	AV fistula	Not currently employed Not sexually active Lives *alone*, independent Has *several* cats Born in US No significant travel

Patient Visit

-Dolutegravir and ritonavir-boosted Darunavir

-Lisinopril

-Clopidogrel

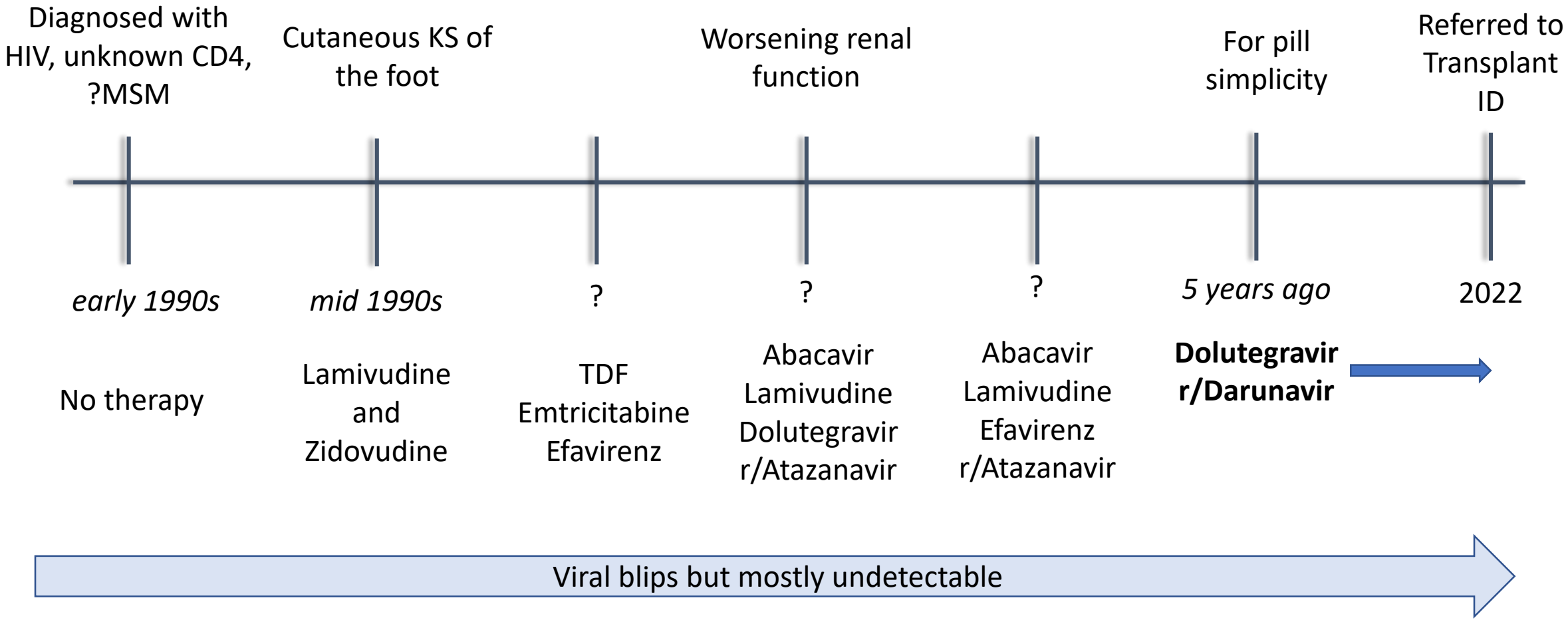
-Pravastatin

-Sevelamer

-Vitamin D

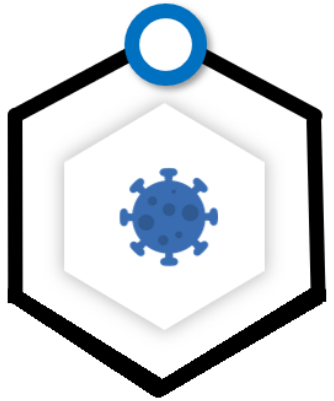
-Vitamin B complex

HIV History

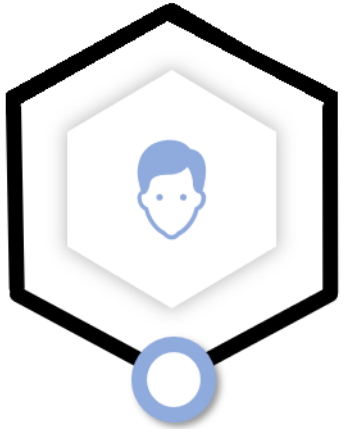

Diagnosed with HIV, unknown CD4, ?MSM
Cutaneous KS of the foot
Worsening renal function
For pill simplicity
Referred to Transplant ID
early 1990s
mid 1990s
?
?
?
5 years ago
2022
No therapy
Lamivudine and Zidovudine
TDF Emtricitabine Efavirenz
Abacavir Lamivudine Dolutegravir r/Atazanavir
Abacavir Lamivudine Efavirenz r/Atazanavir
Dolutegravir r/Darunavir
Viral blips but mostly undetectable

Patient Visit

Microbiologic Workup



- HHV-8 antibody **positive** (1:80, normal <1:20)
- **HIV VL undetectable, CD4 862 (31%),** no genotype available
- Hepatitis B **core** antibody positive, surface antibody 33



Patient Management

- History of KS
- HIV management
- Hepatitis B core antibody positive

Standard induction for KTR is **thymoglobulin**, maintenance is **tacrolimus, mycophenolate +/- prednisone**

Patient Visit

- Is history of cutaneous KS a contraindication to transplant?
  - -Yes
  - -No

- What about visceral KS?
  - -Yes
  - -No

HIV, KS and Renal Transplant

- Patients undergoing transplant with **HHV-8 antibody positivity** have been fairly well described
- Previous studies often excluded those with history of OIs including KS (ie Stock et al. NEJM. 2010)
- Transplant with a history of HIV **and** KS is not so well described.

Kaposi Sarcoma in HIV-positive Solid-Organ Transplant Recipients: A French Multicentric National Study and Literature Review

Chloé Charpentier, MD,[1] Julie Delyon, PhD,[1,2,3] Denis Glotz, PhD,[3,4] Marie-Noelle Peraldi, PhD,[3,4] Jean-Philippe Rerolle, MD,[5] Benoît Barrou, PhD,[6] Emilie Ducroux, MD,[7] Audrey Coilly, MD,[8] Camille Legeai, MD,[9] Stéphane Barete, MD,[10] and Céleste Lebbé, PhD[1,2,3]

Transplantation ■ January 2019 ■ Volume 103 ■ Number 1

- Multicenter retrospective study in France

Database	KS Prevalence (non-HIV)	KS Prevalence (HIV)
CRISTAL	0.18%	0.66%
DIVAT	0.46%	0.50%

TABLE 3. Patients characteristics

HIV and KS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Biological data at SOT:							
CD4, /mm^3	464	600	1007	520	140	302	200
VL, copies/mL	0	200					0
Biological data at KS diagnosis:							
CD4, /mm^3	366	600	600	660	200	495	200
VL, copies/mL	0	0					0
Transplantation							
Age at SOT	70	38	35	48	53	50	65
Organ	Kidney	Kidney	Kidney	Kidney	Liver	Kidney	Kidney
Etiology	HSF	Diabetes	HIV	HIV	HIV and HBV	HIV	HSF
Complication	PNA (m4)	—	CMV (m2) Acute R (m12) PNA (m15)			HEV (m8)	CMV (m6) Norovirus (m8) Chronic R (m20)
Manifestations							
Vutaneous	+	+	+	+	+	+	+
Mucosal	+	–	–	–	–		
Lymph node							
Gastrointestinal tract							
HHV-8 detection:							
Serology at SOT							
PCR at SOT							
PCR after KS diagnosis	NA	+	+	+	+	+	+
Treatment	MMF > AZA Radiotherapy local 5-FU	CNI > mTORi	CNI > mTORi	CNI > mTORi	CNI > mTORi PI>other PI	CNI > mTORi	CNI > other CNI ↓ CS
Response	PR	CR	CR	PR	PR	CR	CR
Follow-up							
Follow-up after KS diagnosis, y	3	2	2	8	1	6	3
Death	No	No	No	No	Yes	No	No

Median CD4 count **at transplant** was 464/mm^3

Median CD4 at **KS diagnosis** was 495/mm^3

7 cases: 6 KTR, 1 liver.

IS decreased in 5 cases
Change to mTOR in 5 cases
1 with topical 5-FU and XRT

4 with CR
3 with PR
No KS-related death, graft loss, or loss of HIV control

>, conversion to; –, negative; +, positive; AZA, azathioprine, F, female; HBV, hepatitis B virus; HEV, hepatitis E virus; HHV-8, human herpes virus-8; mTORi, mTOR inhibitors; m, month; M, male; NA, not available; PNA, pyelonephritis; R, rejection.

Kidney Transplantation in HIV Positive Patients: Current Practice and Management Strategies

Elmi Muller, MD PhD[1], Francois C. J. Botha, MBChB[2], Zunaid A. Barday, MBChB[3], Kathryn Manning, MPH[1], Peter Chin-Hong, MD PhD[4], Peter Stock, MD PhD[5]

Transplantation. 2021 July 01; 105(7): 1492–1501. doi:10.1097/TP.0000000000003485.

- Evaluated data from PLWH undergoing organ transplant from 19 cohort studies
- Authors felt that cutaneous or visceral KS was no longer a contraindication if it was felt it “could be eradicated”.
- Option to switch to mTOR for management of KS was felt to be important.

- Per 2019 AST guidelines, HHV-8 seropositivity is not a contraindication to transplantation.

Prevalence, Incidence and Correlates of HHV-8/KSHV Infection and Kaposi's Sarcoma in Renal and Liver Transplant Recipients

M. Andreoni[1], D. Goletti[2], P. Pezzotti[3], A. Pozzetto[4], P. Monini[2], L. Sarmati[1], F. Farchi[3], G. Tisone[5], A. Piazza[5], F. Pisani[5], M. Angelico[6], P. Leone[2], F. Citterio[4], B. Ensoli[2] and G. Rezza[3,*]

- Retrospective study at two transplant centers in Italy
- Patients were screened for **HHV-8 antibodies** prior to transplantation, with 21 (16.1%) being positive.
- 4/97 kidney recipients developed KS after transplant

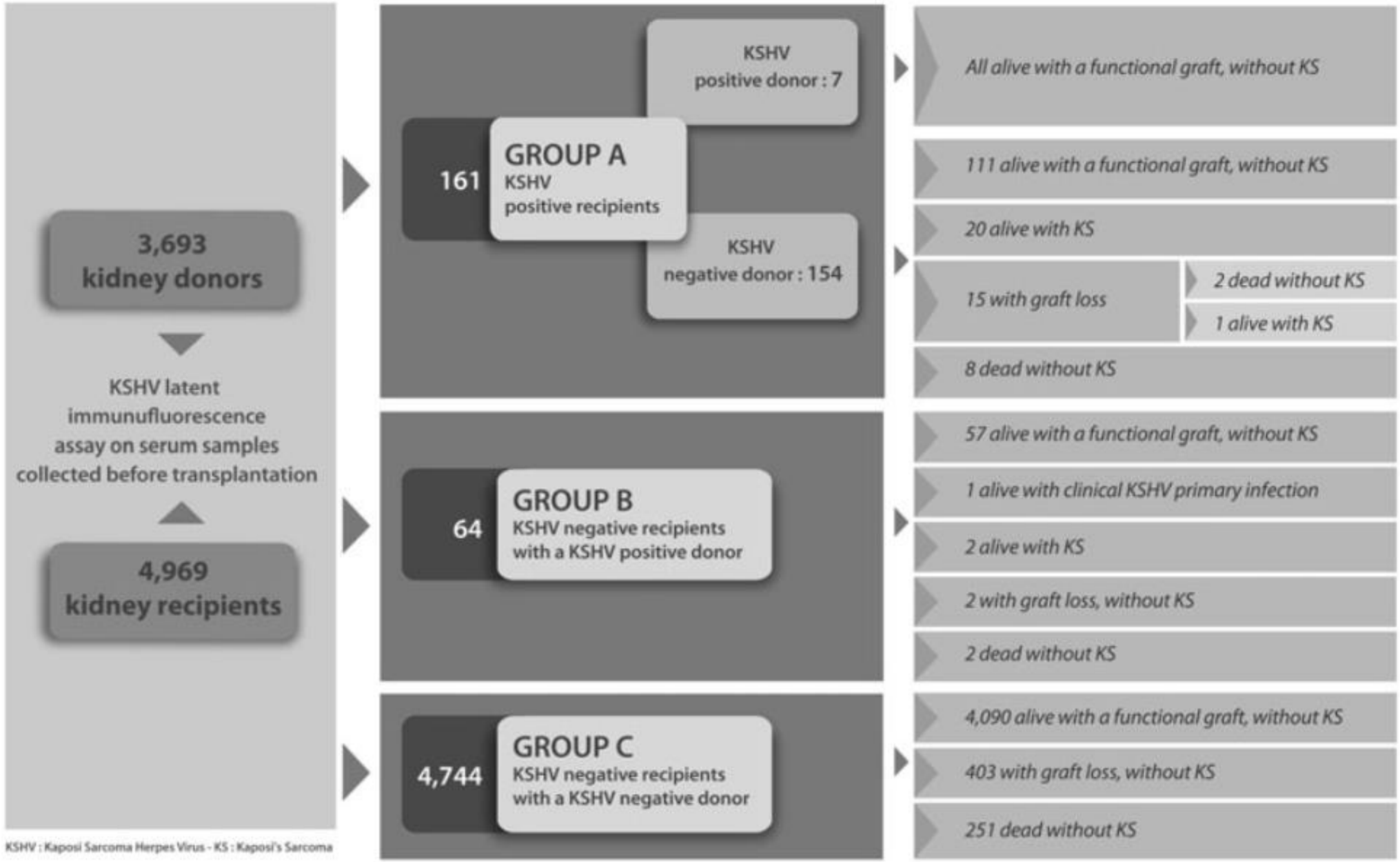
→ 3/4 were seropositive before transplant

- 0/33 liver recipients developed KS after transplant

The Impact of Preexisting or Acquired Kaposi Sarcoma Herpesvirus Infection in Kidney Transplant Recipients on Morbidity and Survival

C. Francès[a,*], A. G. Marcelin[b], Ch. Legendre[c], S. Chevret[d], E. Dussaix[e], J. Lejeune[d], S. Euvrard[f], A Bigorie[g], T. F. Schulz[h], F. Agbalika[i], C. Lebbé[j] and the skin and organ transplantation group of the French Society of Dermatology

- Evaluated risk of post-transplant KS based on HHV-8 serostatus
- Serum samples in KTR with HHV-8 D+/R- or R+ status were tested for HHV-8 PCR every 3 months
- Dermatologic exam every 3 months
- Group A: HHV-8 R+ → 21 KS cases out of 161 recipients (13%)
- Group B: HHV-8 D+/R- → 3 KS cases out of 64 recipients (4.7%)
- Group C: HHV-8 D-/R- → 0 KS cases



KSHV : Kaposi Sarcoma Herpes Virus - KS : Kaposi's Sarcoma

HOPE Act: Kidney

Outcomes	HIV D+/R+ N = 25	HIV D−/R+ N = 50	*P* value
Median follow-up time, y (IQR)	1.4 (1.1-2.3)	1.8 (1.4-2.6)	.14
Patient survival, no. (%)*	25 (100%)	75 (100%)	
Graft survival, no. (%)	23 (92%)	45 (90%)	>.99
Participants with delayed graft function, no. (%)	3 (12%)	21 (42%)	.01
Serious adverse events, per person-year**	1.1	1.1	.78
Participants with hospitalization due to infection, no. (%)	7 (28%)	13 (26%)	.85
Participants with opportunistic infection, no. (%)	4 (16%)	6 (12%)	.72
CMV viremia, no. (%)	3 (12%)	3 (6%)	.39
Esophageal candidiasis, no. (%)	0 (0%)	2 (4%)	.55
Candida glabrata fungemia, no. (%)	0 (0%)	1 (2%)	>.99
Bartonella infection of liver, no. (%)	1 (4%)	0 (0%)	.33
Participants with breakthrough HIV viremia, no. (%)	1 (4%)	3 (6%)	>.99
Participants with malignancy, no. (%)	0 (0%)	3 (6%)	.55
Kaposi sarcoma, no. (%)	0 (0%)	1 (2%)	>.99
Gastric adenocarcinoma, no. (%)	0 (0%)	1 (2%)	>.99
Oropharyngeal cancer, no. (%)	0 (0%)	1 (2%)	>.99
1-y eGFR filtration rate, mean, SD***	63 (28)	57 (17)	0

HOPE Act: Liver

Outcomes	HIV D+/R+ (*N* = 24)	HIV D−/R+ (*N* = 21)	*p*-value
Median follow-up time (months), (IQR)	18 (12, 24)	28 (21, 40)	.002
Deaths, no. (%)	6 (25)	2 (10)	.25
Graft failure, no. (%)	2 (8)	1 (5)[a]	>.99
Recipients with any liver rejection[b], no. (%)	4 (17)	4 (19)	>.99
SLK recipients with any kidney rejection, no. (%)	1 (33)	0 (0)	.38
Recipients with a SAE[c], no. (%)	15 (68)	16 (80)	.66
Recipients with an infectious hospitalization[c], no. (%)	8 (36)	5 (25)	.43
Recipients with an opportunistic infection, no. (%)	6 (25)	3 (14)	.47
Opportunistic infection episodes[d], no.	8	3	.049
Pulmonary aspergillosis, no.	1	0	
Candida esophagitis, no.	0	1	
CMV[e], no.	7	2	
Recipients with HIV breakthrough, no. (%)	2 (8)	2 (10)	>.99
Recipients with cancer, no. (%)	6 (25)	2 (10)	.25
Bowen's disease (squamous cell carcinoma in situ), no.	1	0	
Kaposi's sarcoma and/or HHV8-related lymphoma[f], no.	3	0	
Myoepithelial carcinoma of right parotid gland, no.	1	0	
Anal cancer, no.	1	0	
Recurrent hepatocellular carcinoma, no.	0	2	

Durand et al. AJT. 2021.
Durand et al. AJT. 2022.

Seroprevalence of HHV8 Among Donors and Recipients with HIV

Christine Durand

ATC 2022 Abstract

- Analysis of HOPE act for **HHV-8 seroprevalence**
- 85 recipients (**54 kidney, 26 liver, 5 SLK**) analyzed
- **Recipient** HHV-8 **seroprevalence was 38%**
- **Recipient** HHV-8 positivity associated with male sex (OR 13.6, p=0.02), MSM (OR 4.2, p=0.01)
- **Donor** HHV-8 **seroprevalence was 28%** for HIV+ donors and 6% among false positive (HIV-) donors.
- **Donor** HHV-8 positivity associated with male sex (OR 8.9, p=0.04), MSM (OR 3.3, p=0.02), HepB cAb + (OR 3.8, p=0.006)

10 Years of DTAC Experience with Kaposi's Sarcoma – Not Just Another PTLD!

M. Nalesnik,[1] M. Clark,[2] S. Tlusty,[2] M. Michaels,[1] C. Wolfe.[1]

[1]DTAC, Richmond
[2]United Network for Organ Sharing, Richmond

Meeting: 2017 American Transplant Congress

- Reviewed cases of donor-derived KS from 1/2007 to 11/2016
- Proven or probable DD-KS occurred in 7 recipients from 5 deceased donors
- Possible cases occurred in 3 recipients from 3 donors.
- All but one of the 8 donors was born overseas or had a history of higher risk sexual exposure
- Involvement of transplanted organ was common, often mimicked PTLD
- Median time to KS was 7 months, all within 1 year

(Thinking of cutting this study for time purposes, what do you think?)

Patient Visit

- HIV Management

	Generic Name	Brand Name	Assessment	Drug Resistance Associated Mutations Detected
NRTI	Abacavir	Ziagen	Resistant	D67D/N, K70K/R, M184M/V
	Didanosine	Videx	Resistant	D67D/N, M184M/V
	Emtricitabine	Emtriva	Resistant	D67D/N, K70K/R, M184M/V
	Lamivudine	Epivir	Resistant	D67D/N, K70K/R, M184M/V
	Stavudine	Zerit	Sensitive	D67D/N, K70K/R
	Tenofovir	Viread	Sensitive	D67D/N, K70K/R
	Zidovudine	Retrovir	Sensitive	D67D/N, K70K/R
NNRTI	Doravirine	Pifeltro	Sensitive	A98A/G, I178I/M
	Efavirenz	Sustiva	Sensitive	A98A/G
	Etravirine	Intelence	Sensitive	A98A/G
	Nevirapine	Viramune	Resistance Possible	A98A/G
	Rilpivirine	Edurant	Sensitive	None
INI	Bictegravir	Bictegravir	Sensitive	None
	Dolutegravir	Tivicay	Sensitive	None
	Elvitegravir	Vitekta	Sensitive	None
	Raltegravir	Isentress	Sensitive	None
PI	Atazanavir	Reyataz / r‡	Sensitive	I62V
	Darunavir	Prezista / r‡	Sensitive	None
	Fosamprenavir	Lexiva / r‡	Sensitive	None
	Indinavir	Crixivan / r‡	Sensitive	None
	Lopinavir	Kaletra‡	Sensitive	None
	Nelfinavir	Viracept	Sensitive	None
	Ritonavir	Norvir	Sensitive	None
	Saquinavir	Invirase / r‡	Sensitive	I62V
	Tipranavir	Aptivus / r‡	Sensitive	None

NRTI Mutations: D67DN • K70KR • M184V

NNRTI Mutations: A98AG

RT Other Mutations: K43KE • V60VI • I63IT • I135IV • D177E • I178IM • G196E • F214L • K219G • V245LM • E248Q • D250E • I257V • A272P • T286A • E297A • G335D • R356K • M357T • K366R • A376T • V381I • K395R • A400T

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Intermediate Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Drug resistance mutation scores of NRTI: Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
D67DN	5	15	0	0	5
K70KR	5	30	0	0	5
M184V	15	-10	60	60	-10
Total	25	35	60	60	0

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Low-Level Resistance
efavirenz (EFV)	Low-Level Resistance
etravirine (ETR)	Potential Low-Level Resistance
nevirapine (NVP)	Intermediate Resistance
rilpivirine (RPV)	Low-Level Resistance

Drug resistance mutation scores of NNRTI: Copy to clipboard

Rule	DOR	EFV	ETR	NVP	RPV
A98AG	15	15	10	30	15

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Susceptible
cabotegravir (CAB)	Susceptible
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Potential Low-Level Resistance
raltegravir (RAL)	Potential Low-Level Resistance

Drug resistance mutation scores of INSTI: Copy to clipboard

Rule	BIC	CAB	DTG	EVG	RAL
E157Q	0	0	0	10	10

What regimen would you choose at his upcoming visit (virally suppressed on r/DRV + DTG)?

-Continue r/DRV + DTG

-Change to TAF/FTC/BIC

-Change to DTG/RPV

-Other

Patient Visit

How would you manage this patient's hepatitis B risk post-transplant (hepatitis B core antibody positive, surface antibody 33 IU/mL)?

-Ensure *the* ART regimen includes tenofovir

-Ensure *the* ART regimen has lamivudine or emtricitabine

-This would not influence the ART regimen I'd choose, and I would not recommend Hepatitis B prophylaxis after transplant.

-This would not influence the ART regimen I'd choose, but I would offer Hepatitis B prophylaxis with entecavir if *the* ART did not have hepatitis B activity.

Outcomes and risk factors for hepatitis B virus (HBV) reactivation after kidney transplantation in occult HBV carriers

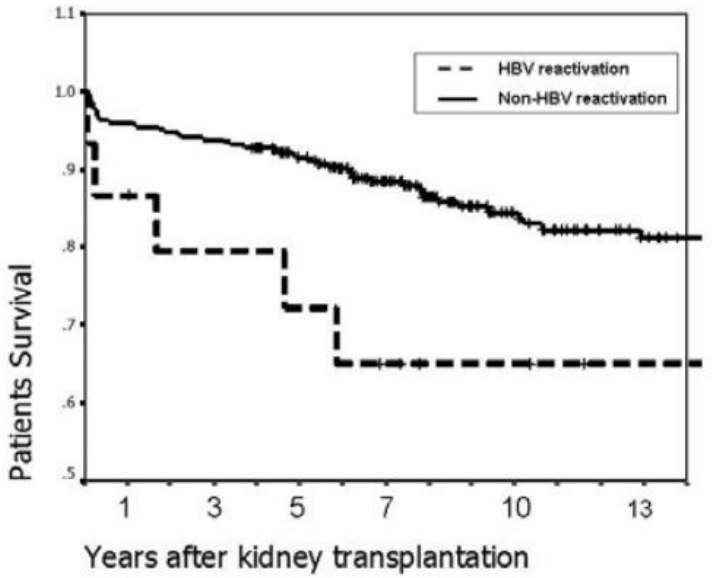
G.-D. Chen, J.-L. Gu, J. Qiu, L.-Z. Chen

First published: 08 March 2013 | https://doi.org/10.1111/tid.12065 | Citations: 39

- Retrospective study of KTRs
- Assessed 322 patients with isolated **hepatitis B core positive**
- Prophylaxis not given prior to 2002.
- Lamivudine prophylaxis was given for 3 months for all patients after 2002.
- HBsAg and HBV DNA checked months 1, 2, 3 and q3 months thereafter.

Results

15 patients (4.7%) experienced reactivation (lamivudine started at that time)



Logistic multivariate analysis of risk factors for hepatitis B virus reactivation

	OR value	95% CI	*P*-value
Age >60 years	11.69	2.844–48.12	0.001
Anti-T-cell antibodies	4.87	1.184–20.03	0.028
HBsAb (+)	0.046	0.009–0.241	<0.001
Lamivudine prophylaxis	0.038	0.004–0.348	0.004

OR, odds ratio; CI, confidence interval; HBsAb, hepatitis B surface antibody.

Comparison of complications after kidney transplantation

	HBV reactivation (n = 15)	Non-HBV reactivation (n = 307)	*P*-value
Liver function impairment	12 (80.0%)	93 (30.3%)	<0.001
Liver function failure	2 (13.3%)	0 (0%)	0.002
Hepatocellular carcinoma	2 (13.3%)	4 (1.3%)	0.017
Delayed graft function	1 (6.7%)	17 (5.5%)	0.853
Acute rejection	7 (46.7%)	67 (21.8%)	0.026
Chronic rejection	3 (20.0%)	55 (17.9%)	0.840
New-onset diabetes	1 (6.7%)	16 (5.2%)	0.812

HBV, hepatitis B virus.

Comparison of risk factors for hepatitis B virus (HBV) reactivation between two groups

	HBV reactivation (n = 15)	Non-HBV reactivation (n = 307)	*P*-value
Age >60 years old	7 (46.7%)	29 (9.4%)	<0.001
Gender male	9 (60.0%)	202 (65.8%)	0.645
Dialysis time >12 m	2 (13.3%)	76 (24.8%)	0.484
HBsAb (+)*	2 (13.3%)	178 (58.0%)	0.001
Delayed graft function	1 (6.7%)	17 (5.5%)	0.853
Acute rejection	7 (46.7%)	67 (21.8%)	0.026
FK506	5 (33.3%)	97 (31.6%)	0.888
MMF	9 (60.0%)	215 (70.0%)	0.591
Anti-T-cell antibodies	12 (80.0%)	122 (39.7%)	0.002
Lamivudine prophylaxis	1 (6.7%)	109 (35.5%)	0.021

*HBsAb (+) refers to serum HBsAb titer >10 mIU/mL.
HBsAb, hepatitis B surface antibody; FK506, tacrolimus; MMF, mycophenolate mofetil.

Significant rate of hepatitis B reactivation following kidney transplantation in patients with resolved infection

Journal of Clinical Virology
Volume 55, Issue 3, November 2012, Pages 233-238

Nada Kanaan [a], Benoit Kabamba [b], Céline Maréchal [a], Yves Pirson [a], Claire Beguin [c], Eric Goffin [a], Ziad Hassoun [d]

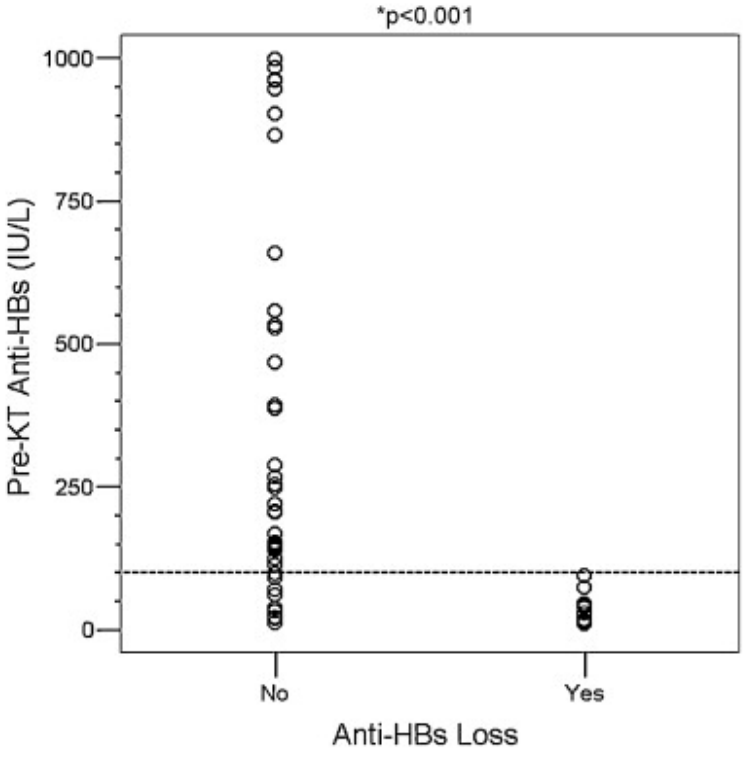
- Retrospective study of 93 KTRs with isolated hepatitis B core antibody
- No prophylaxis given

HBsAg +

HBsAg +
And
HBV DNA >2000 IU/mL

Patient	TP date	Time to reversion (months)	Reactivation		
			Time to reactivation (m)	ALT	HBV DNA
# 1	1996	5	49	48	Positive
# 2	2005	11	30	46	260×10^3
# 3	2006	42	42	286	47×10^3
# 4	2006	44	44	57	7.3×10^8
# 5	2007	4	24	20	$>10^9$
# 6	2008	36	36	22	$>10^9$

No patients with HBsAb >100 IU/L experienced complete loss of sAb or reactivation



Results

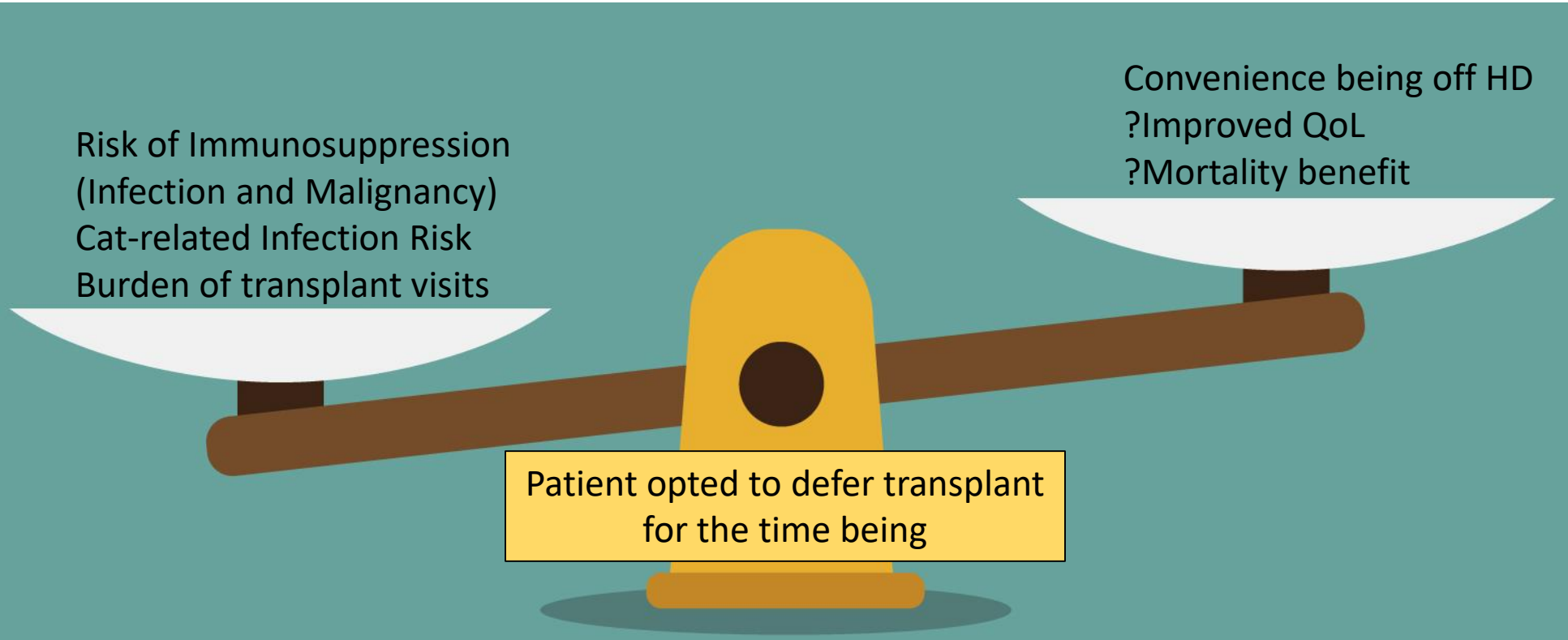
Table 3. Risk factors for HBV reactivation.

Parameters	All cohort N = 93	HBV reactivation patients N = 6	No HBV reactivation N = 87	*p*-Value
Geographical distribution, *n* (%)				
Northern Europe	45 (48)	1 (17)	44 (51)	0.11
Mediterranean area	33 (36)	5 (83)	28 (32)	0.01
Sub Saharan Africa	14 (15)	0 (0)	14 (16)	0.30
Other	1 (1)	0 (0)	1 (1)	0.99
Time on dialysis (median) (years)	2.6 [1.1–4.1]	3.82 [2.67–5.23]	2.43 [1.05–3.87]	0.48
Donor source (deceased), *n* (%)	85 (91)	6 (100)	79 (91)	0.44
Induction, *n* (%)	42 (45)	2 (33)	40 (46)	0.55
Maintenance immunosuppression, *n* (%)				
Triple therapy	87 (94)	6 (100)	81 (93)	0.51
Tacrolimus	69 (74)	5 (83)	64 (74)	0.60
Cyclosporine	24 (26)	1 (17)	24 (28)	0.56
Mycophenolate Mofetil	78 (84)	6 (100)	72 (83)	0.27
Azathioprine	10 (11)	0 (0)	10 (11)	0.38
Anti-HBs antibodies, *n* (%)	74 (80)	1 (17)	73 (84)	0.001
Anti-HBs titer (median) [P25–P75]	115 [13–546]	0 [0–11]	143 [16–660]	0.002
Anti-HCV positive, *n* (%)	14 (15)	0 (0)	14 (16)	0.29

Patients without sAb at time of transplant were **26 times more likely** to experience reactivation

Follow-Up

- ART changed to DTG/RPV. VL ND.
- TAF added after genotype run through Stanford DB.



Takeaway Points

- HIV regimens may have DDIs with many post-transplant medications (e.g. CNIs, PPIs)
- Suppression of viremia and optimization of regimen should be ensured well in advance of transplant when possible
- History of AIDS-defining illness, if well controlled, is not necessarily a contraindication to transplant
- Post-transplant KS is associated with morbidity and mortality but may be manageable with reduction in IS or mTOR switch, and risk may be acceptable
- Risk of hepatitis B reactivation with positive HBcAb appears strongly correlated to the to degree of surface antibody positivity