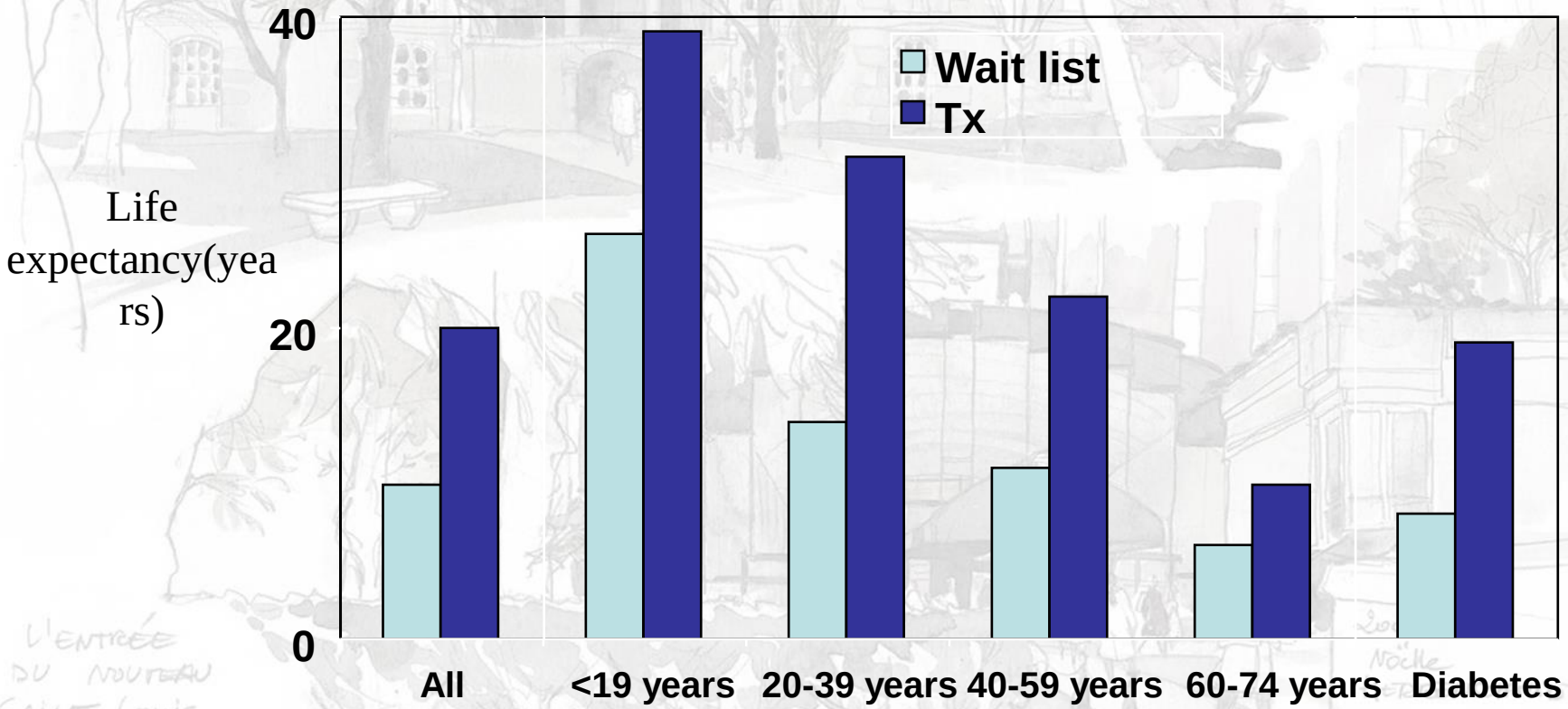
Desensitization in kidney transplantation

17th International Congress of Iranian Society of Nephrology

D. Glotz 2019

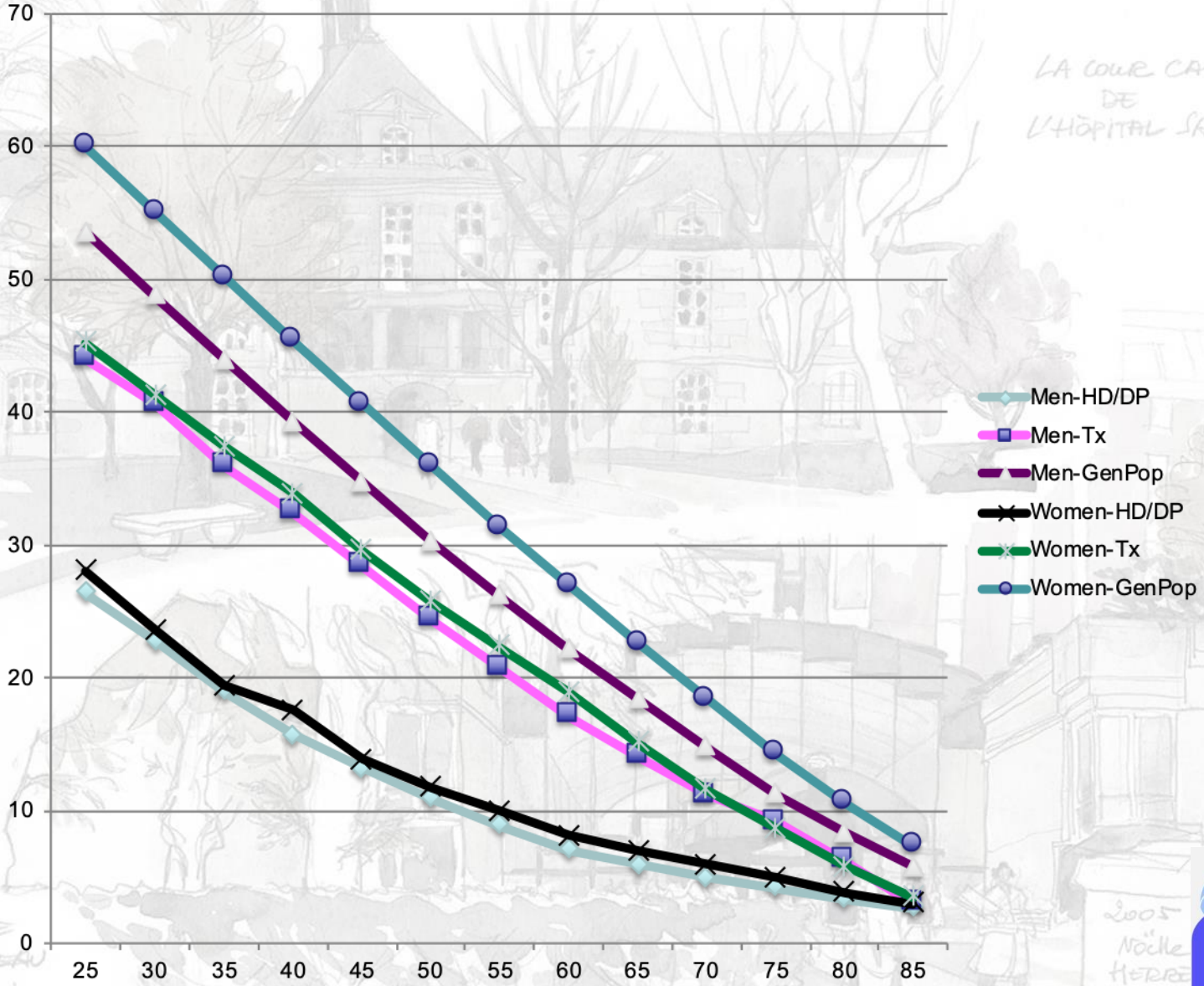
Transplantation and patient survival….

A benefit in all cases!



Wolfe NEJM 1999

The end result….



Time on dialysis and graft survival

Paired kidney analysis

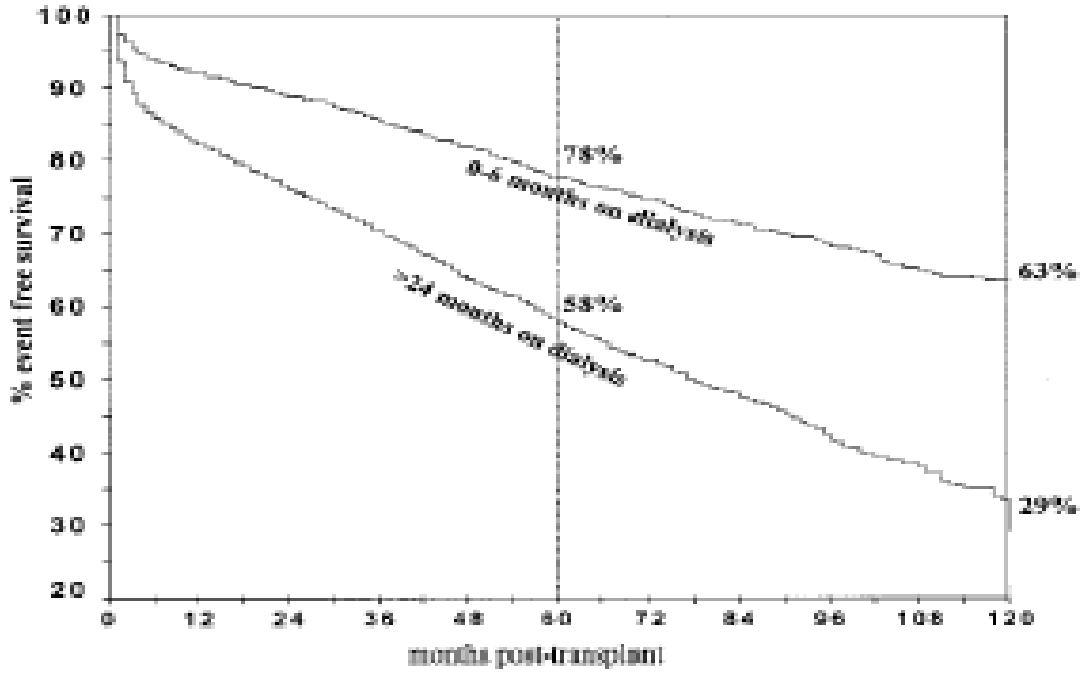


FIGURE 1. Unadjusted graft survival in of 2,405 recipients of paired kidneys with short compared to long ESRD time.

Meier-Kriesche Transpl 2002

Time on dialysis and graft survival

Both for LD and CAD donors

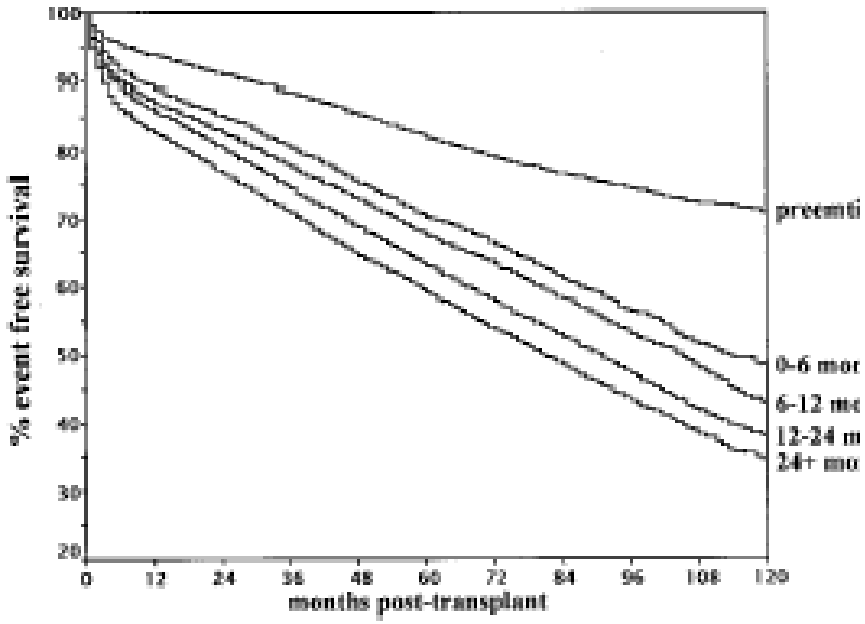


FIGURE 2. Unadjusted graft survival in 56,587 recipien cadaveric transplants by length of dialysis treatment be transplant.

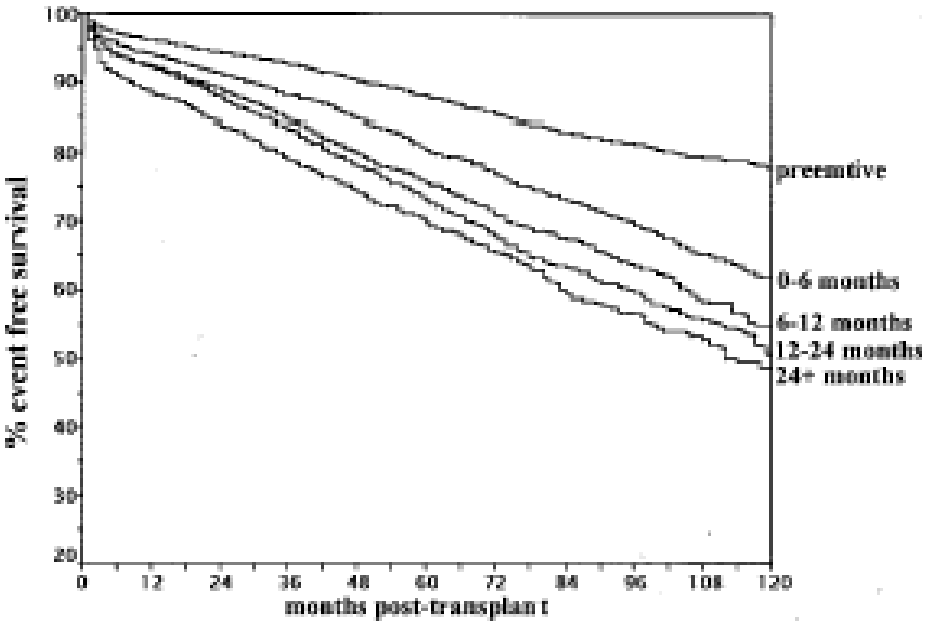


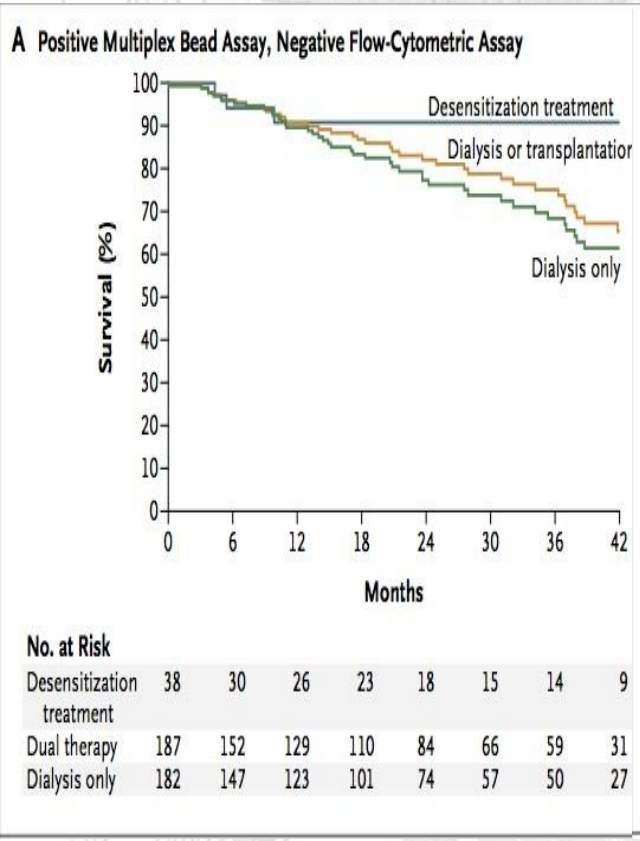
FIGURE 3. Unadjusted graft survival in 21,836 recipients of living transplants by length of dialysis treatment before transplant.

Transplantation expands life expectancy, and early transplantation is the most successful!

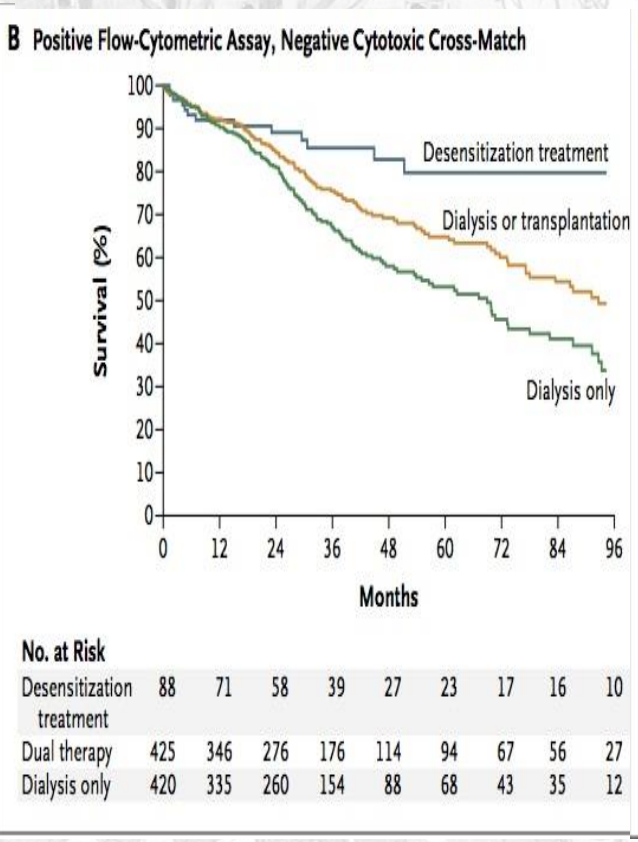
Transplantation expands life expectancy, and early transplantation is the most successful!

What about HLA incompatible Transplants?

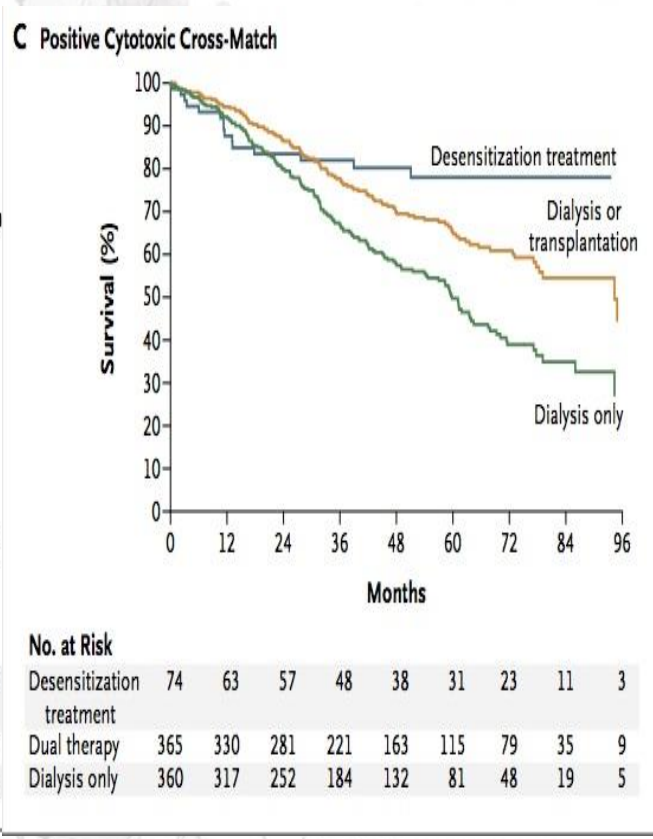
HLA incompatible survival



No. at Risk								
Desensitization treatment	38	30	26	23	18	15	14	9
Dual therapy	187	152	129	110	84	66	59	31
Dialysis only	182	147	123	101	74	57	50	27



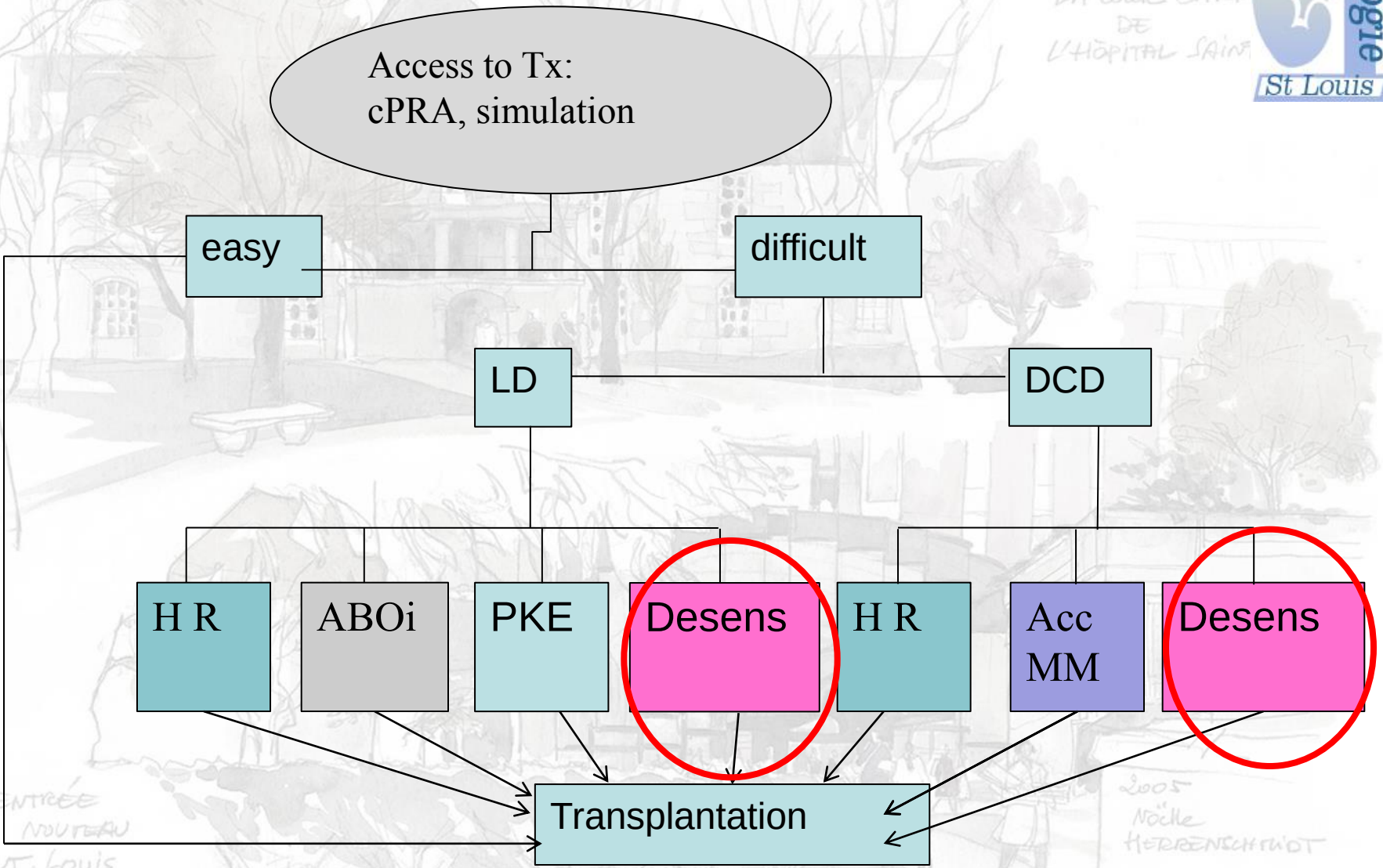
No. at Risk									
Desensitization treatment	88	71	58	39	27	23	17	16	10
Dual therapy	425	346	276	176	114	94	67	56	27
Dialysis only	420	335	260	154	88	68	43	35	12



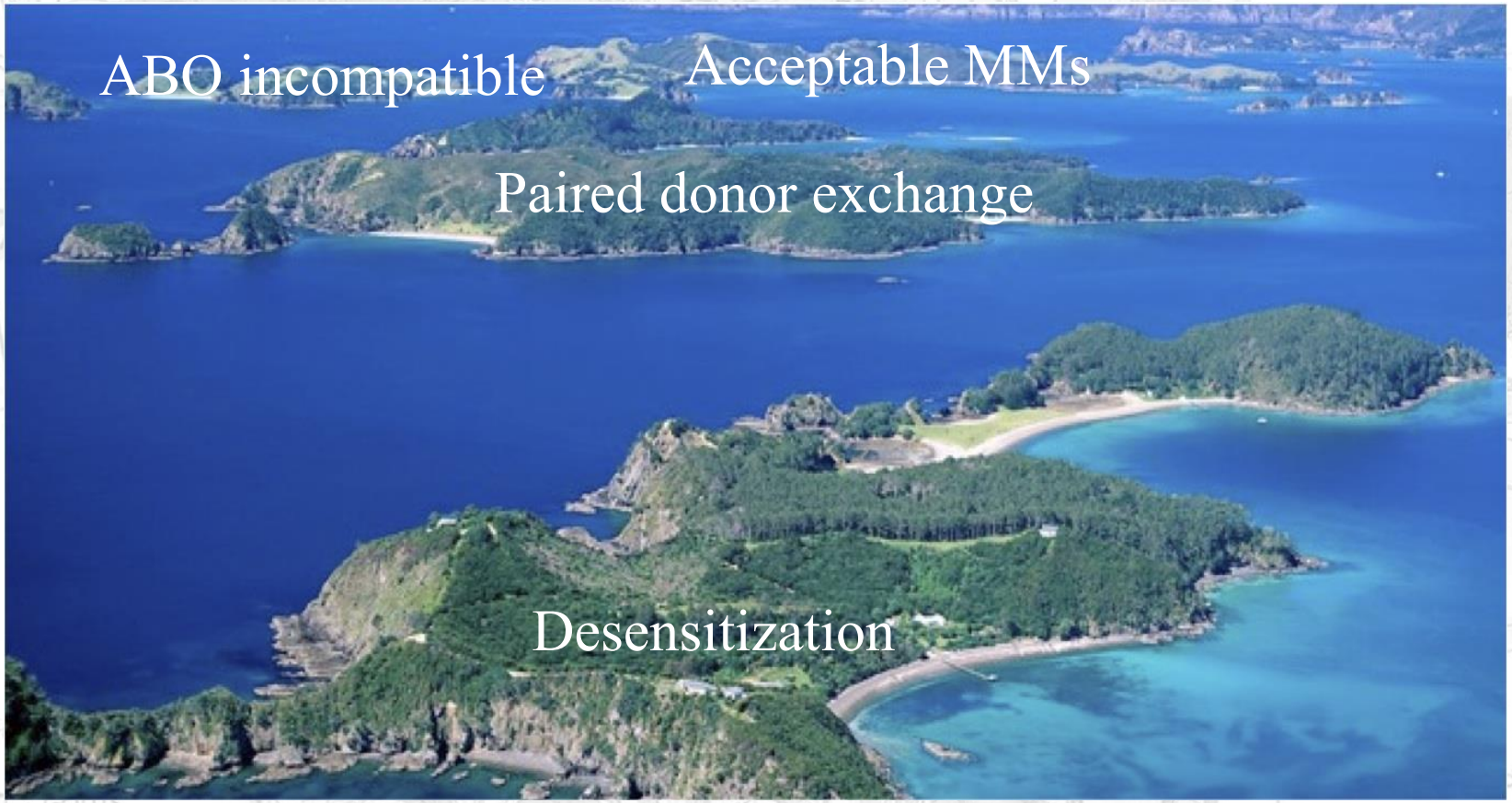
No. at Risk									
Desensitization treatment	74	63	57	48	38	31	23	11	3
Dual therapy	365	330	281	221	163	115	79	35	9
Dialysis only	360	317	252	184	132	81	48	19	5

Montgomery, NEJM 2011

There are many ways to Transplant….



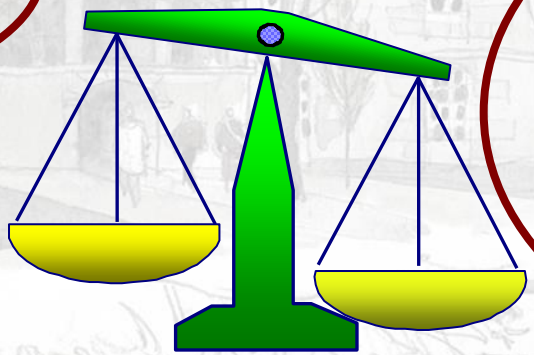
Desensitization is part of a strategy…



Kidney transplantation in sensitized patients awaiting transplants from deceased donors

Increased waiting times

No graft



Efficiency

- ***Graft survival***
- ***AMR***
- ***CAMR***
- ***Immunosuppression***
- ***High risk (infections, tumors)***

Contraints

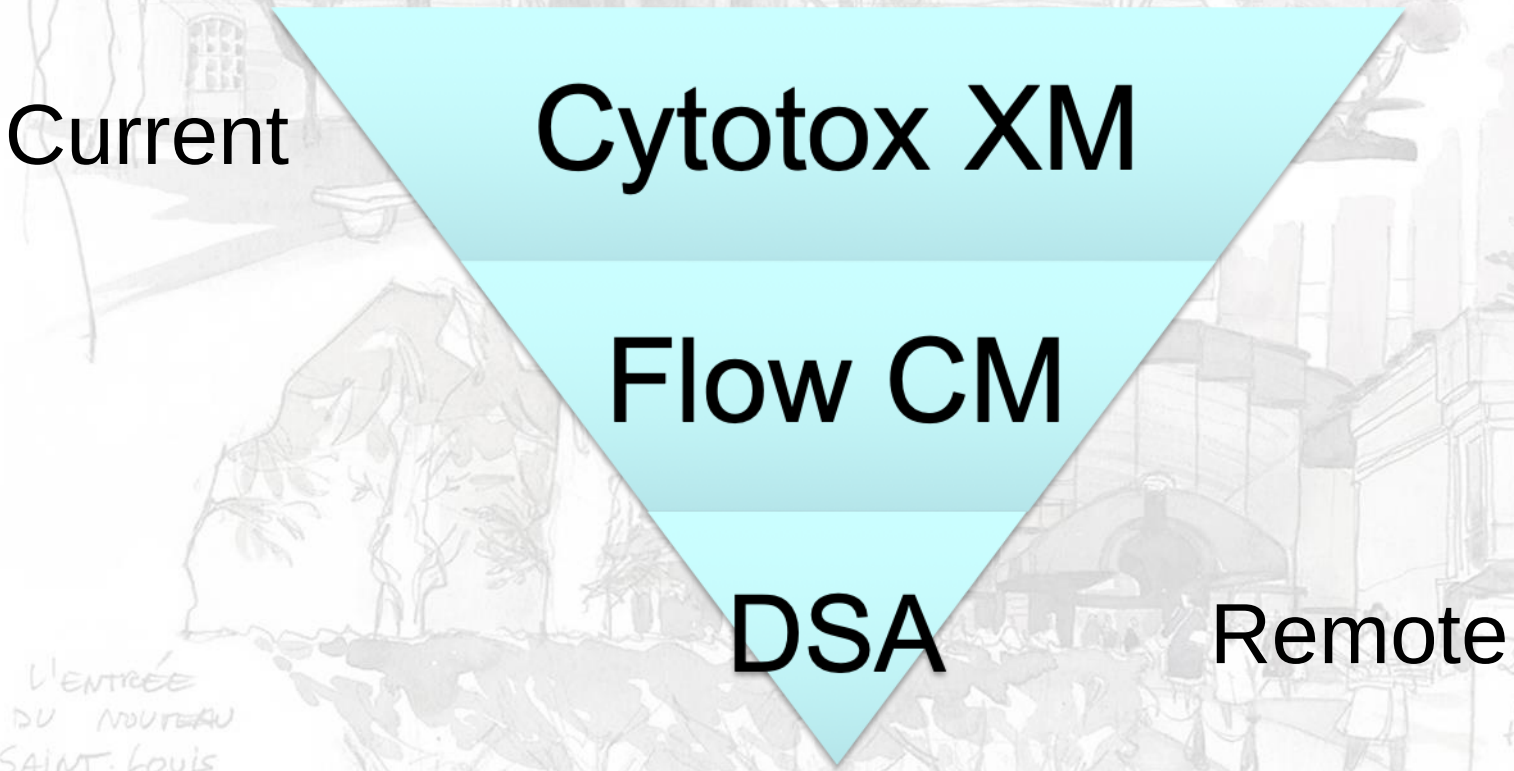
- **Organ scarcity**

  3.4 potential recipients for each kidney transplant

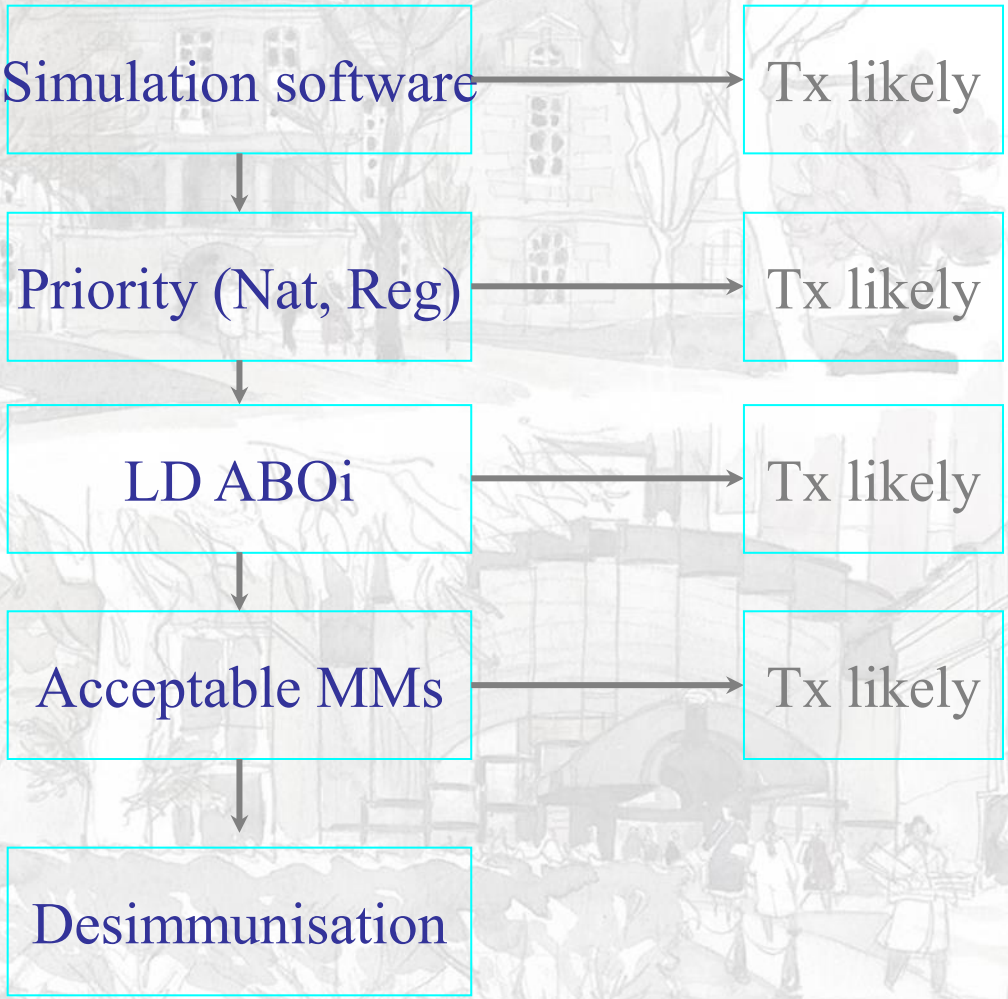
- **Logistical (geographic, cold ischemia)**
- **Financial**

Access to transplant

- Avoid immunological conflict!
- If impossible, minimize it !



The Saint-Louis algorithm



Estimate the chances of Tx….

Simulation software

- Database of all french donors of the last 5 years
- Enter patient's immunological characteristics

↓

Get the number of possible donors
Estimate the competition….

Expertise Accès à un greffon

Tho PI	82078
REGION	7
Dept1	• AN PREL1 •
Dept2	• AN PREL2 •
Dept3	• Site1 •
Dept4	• Site2 •
Dept5	• Site3 •
	0 Site4 •
AGE≤	• Site5 •
ABO1	B Site6 •
ABO2	• Site7 •
ABO3	•
ABO4	• POIDS≤ •
PRL ORG	0
Supertype A1=	1
Supertype A68=	28
Supertype B7=	7
Supertype B8=	8
Supertype DR3=	3
Supertype DR15=	2

Ag Interdits (recodés)

A	B	DR
9	14	5
10	12	
11	17	
19		
36		
3		

Requête

Mismatch (MM)	nb donneurs ≤ MM	nb donneurs = MM	% donneurs prélevés	Incompatibilités	n	% donneurs prélevés	Identités HLA
0 MM	0	0	-	0	0	-	2DR2B2A
1 MM	0	0	-	1A	0	-	2DR2B1A
				1B	0	-	2DR1B2A
				1DR	0	-	1DR2B2A
2 MM	0	0	-	2A	0	-	2DR2B
				2B	0	-	2DR2A
				1A1B	0	-	2DR1A1B
				1DR1A	0	-	1DR2B1A
				1DR1B	0	-	1DR2A1B
				2DR	0	-	2B2A
3 MM	0	0	-	1A2B	0	-	2DR1A
				2A1B	0	-	2DR1B
				1DR2B	0	-	2B1DR
				2A1B	0	-	2A1DR
				1DR1A1B	0	-	1DR1A1B
				2DR1B	0	-	2A1B
				2DR1A	0	-	1A2B
4 MM	2	2	2,30	2A2B	0	-	2DR
				2DR2B	1	1,15	2A
				2DR2A	0	-	2B
				1DR1A2B	0	-	1DR1A
				1DR2A1B	0	-	1DR1B
				2DR1A1B	1	1,15	1A1B
5 MM	3	1	1,15	1DR2A2B	1	1,15	1DR
				2DR1A2B	0	-	1A
				2DR2A1B	0	-	1B
6 MM	4*	1	1,15	2DR2A2B	1	1,15	0 identité
	Donneurs B, • • • prélevés à l'échelon considéré =				87	100,00	
	dont 83 (95%) présentaient des Ag interdits						
	urs prélevés répondant à tous les critères de la requête						
	s possibilités de greffe si l'on ne tient pas compte de la compatibilité HLA.						
	0 Ag Interdits	4					

Résultat

A.T.: 0

I.G.S.: >95%

Ancienneté LNA= 4,15 Age Patient = 35 an Ac %= 68 Greffes antérieures: 1

Total donneurs potentiels 4

Evaluation des possibilités d'accès à la greffe pour un receveur donné, conclusion :

2,5

Access to transplant

Inscription | **Immuno.** | Coord. attente | Suivis | Observ.

▸ **HLA**

A1	A2	B1	B2	DR1	DR2	DQ1	DQ2
1	31	37	62	9	10	5	9

▸ **Anticorps** - renseignés par Isabelle DUPUY

Taux IgG anti-Ly T ou totaux : 100%

Taux d'anticorps anti-HLA Classe 2 : 100%

Taux de greffons incompatibles : **96%** **Taux de greffons incompatibles historisé :** **96%**

▸ **Date de dernière recherche Ac anti-HLA validée :** 16/06/2010

❖ **Données saisies par l'équipe (utilisées pour l'aide au choix)**

Transférer automatiquement les Ac de classe I et II saisies par le laboratoire vers les données cliniques :Oui

▸ **Spécificités des anticorps Classe 1**

A2 A3 A11 A24 A25 A28 A32 A66 B5 B7 B17 B27 B35 B38 B48 B49 B53 B56 B59 B60 B63 B67 B77 B78 B81

▸ **Spécificités des anticorps Classe 2**

▸ **Antigènes interdits**

❖ **Données saisies par le laboratoire**

▸ **Spécificités des anticorps Classe 1**

A2 A3 A11 A24 A25 A28 A32 A66 B5 B7 B17 B27 B35 B38 B48 B49 B53 B56 B59 B60 B63 B67 B77 B78 B81

▸ **Spécificités des anticorps Classe 2**

▸ **Antigènes permis**

A26 A29 A34 A36 A43 A74 A80 B8 B12 B13 B39 B41 B44 B45 B46 B47 B50 B72 B76 DR1 DQ2 DQ4 DQ8

▸ **Commentaire**

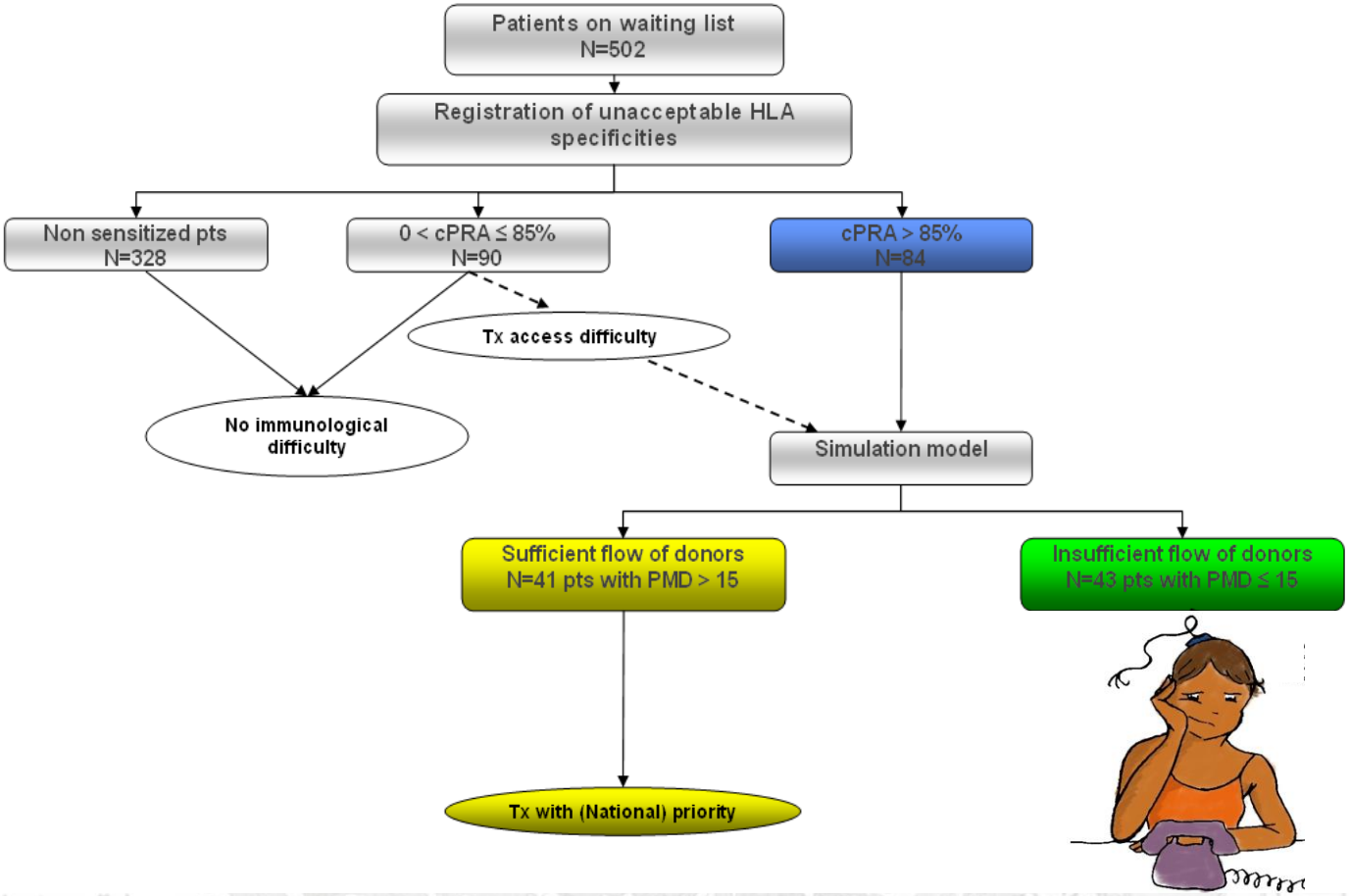
❖ **Nombre d'incompatibilités acceptables**

A : 2 **B :** 2 **DR :** 0 **Maximum :** 4

❖ **Accès à la greffe**

FAG : 0 **FAG A :** 0 **FAG B :** 0 **FAG AB :** 0 **FAG O :** 0

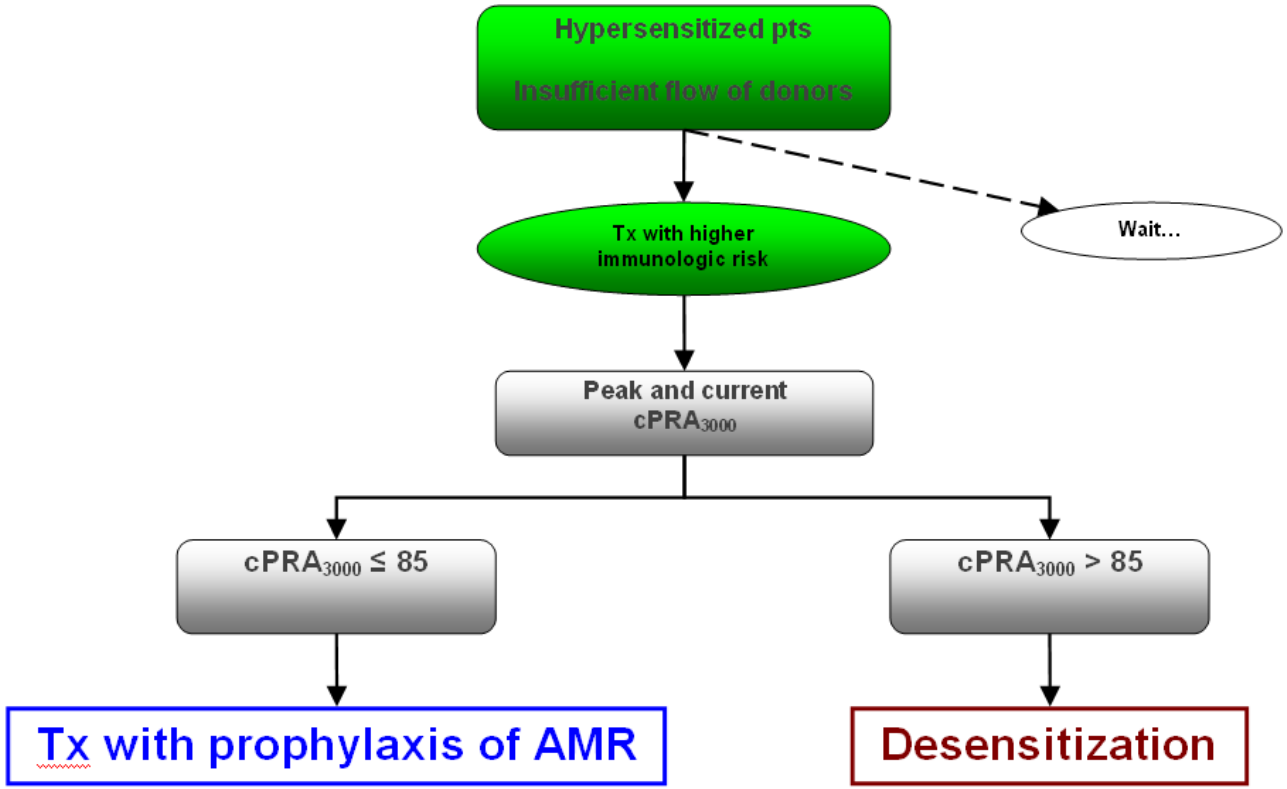
Waiting list management



Lefaucheur, AJT 2011

Waiting list management

Hypersensitized pts with insufficient flow of donors



Lefaucheur, AJT 2011

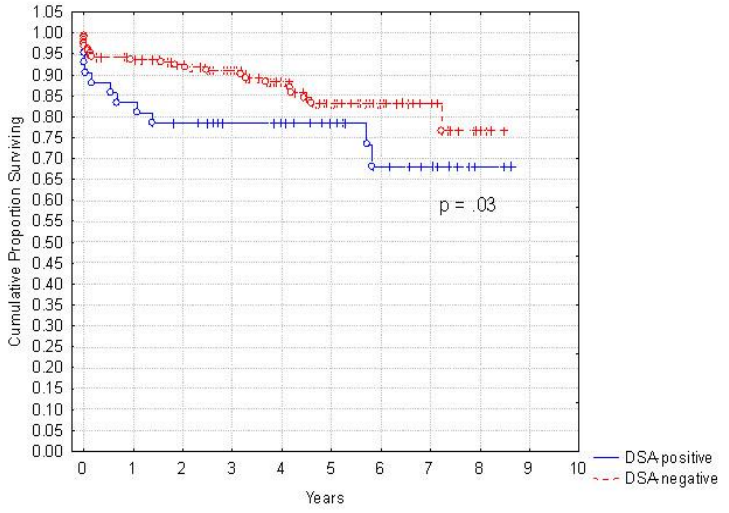
Our main challenge: Defining the risk

Presence/absence of antibody is not enough

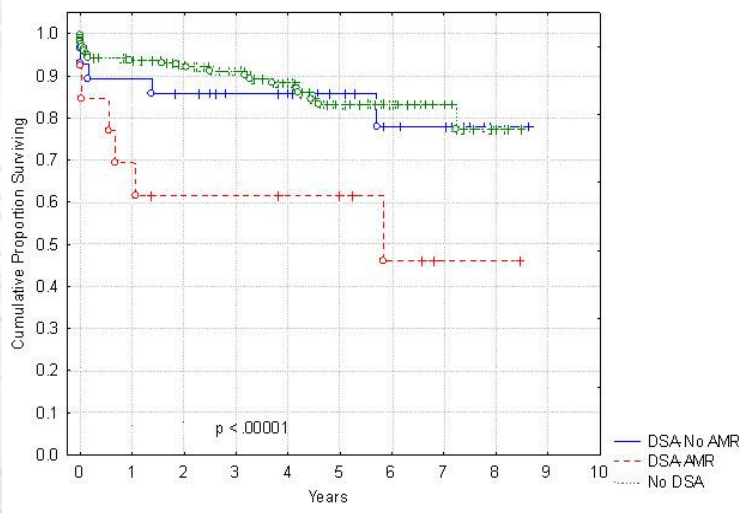
- XM: flow crossmatch
- DSA: ELISA/Luminex

Presence/absence of DSA

- 237 pts, CDC-XM -, ELISA on peak
- 43 pts (18%) DSA +, AMR: 35%
- 194 pts (82%) DSA -, AMR: 3%



8 year graft survival curve according to DSA (+/-)



8 year graft survival curve according to DSA (+/-) and AMR (+/-)

Lefaucheur, AJT 2008

Presence/absence of DSA

Impact of a positive flow crossmatch

	Pt (n)	% T+ FXCM	Early graft loss (< 3 mo) FP vs FN	Acute Rej. FP vs FN	1 year Surv. FP vs FN
Iwaki et al. 1987	113	16%	22% vs 4%		
Cook et al. 1987	196	18%	22% vs 7%		
Mahoney et al. 1990	67	18%	33% vs 7%		67% vs 85%
Ogura et al. 1993	841	18%	20% vs 7%		75% vs 82%
Pelletier et al. 1997 *	102	18%		67% vs 51%	86% vs 98%
Kerman et al. 1999 *	97			44% vs 40%	81% vs 83%
Karpinski et al. 2001	143	13%	33% vs 11%	25% vs 5%	

FXCM = flow crossmatch, **FP = flow positive, FN = flow negative**

* No significant difference between FP and FN

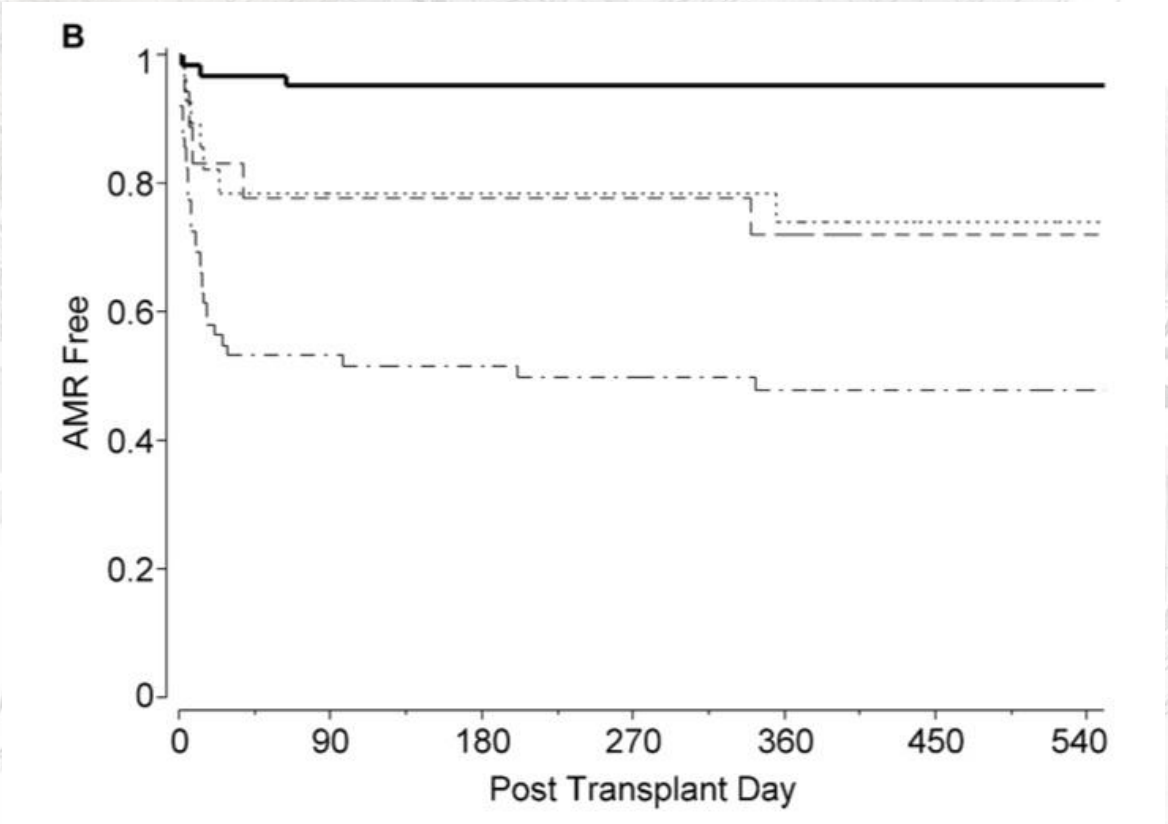
Our main challenge: Defining the risk

How much is too much ?

Defining the relevant threshold of

- **DSA: MFI in Luminex**
- **XM: MCS in flow crossmatch**

Relative risk of AMR according to max DSA MFI



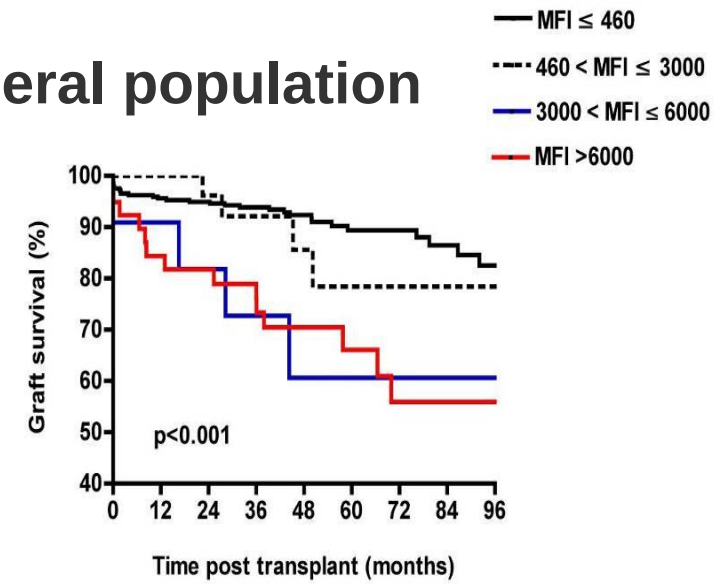
0-5 000
5-10 000

>10 000

Gloor, AJT 2010

Graft survival according to max DSA MFI

General population

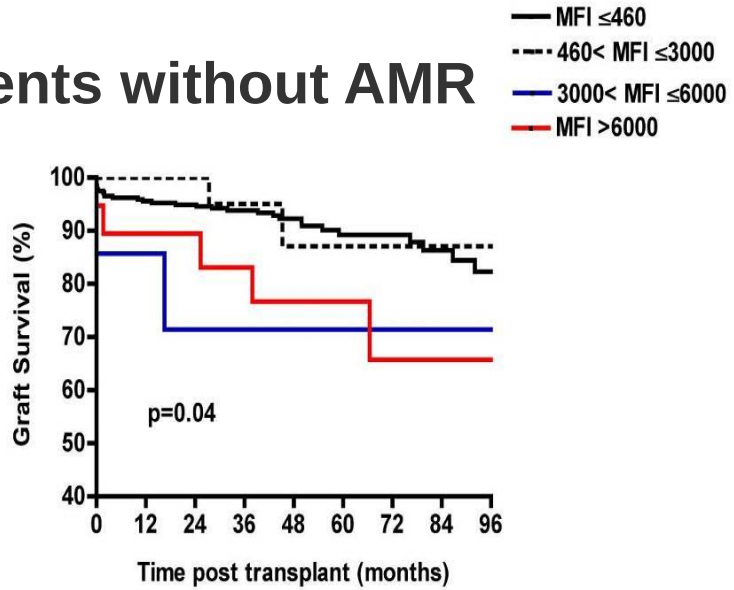


Number at risk

MFI ≤ 460	325	297	285	224	151	103	75	51	33
460 < MFI ≤ 3000	27	27	26	22	13	10	8	7	6
3000 < MFI ≤ 6000	11	11	10	8	4	3	3	2	2
MFI >6000	39	33	30	28	19	16	12	9	5

RR of graft loss in pts with DSA > 3000: 3.8 (95 CI, 3.5-18.4, p<.0001)

Patients without AMR



Number at risk

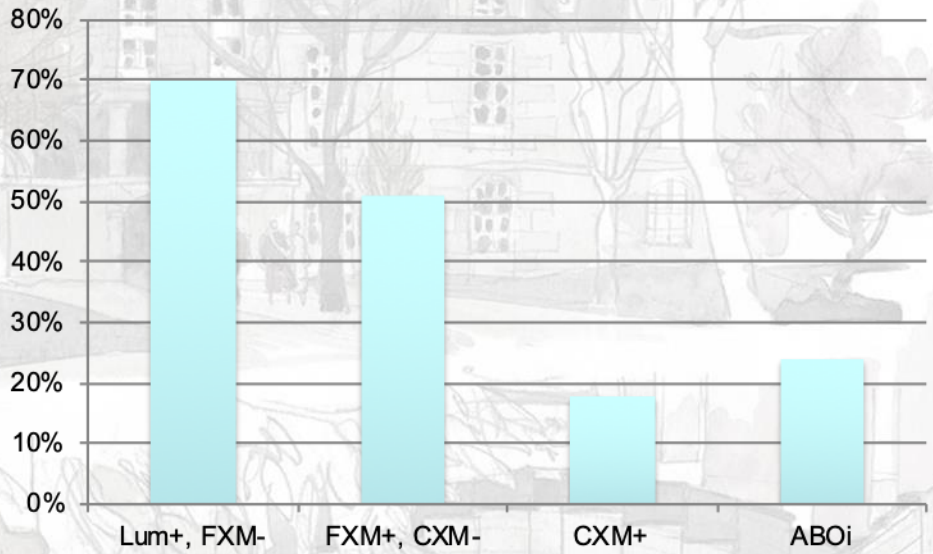
MFI ≤460	322	294	283	222	141	101	74	49	34
460< MFI ≤3000	22	22	22	18	12	10	8	7	6
3000< MFI ≤6000	7	7	6	5	4	3	3	2	2
MFI >6000	19	17	15	14	11	9	7	5	3

RR of graft loss in pts with DSA > 3000: 2.8 (95 CI, 1.5-16.9, p=.009)

Lefaucheur, JASN 2010

The team is the limit !

- USA



- France:
  - 43 centers, 4 with HLA incompatible programs

The team is the limit !

- Desire and manpower
- Necessary tools:
  - DSA by Luminex SA, Histology with C4d in 48 hours or less
  - Plasmapheresis, Rituximab, IVIg available

Choosing the desensitization regimen

Desensitization

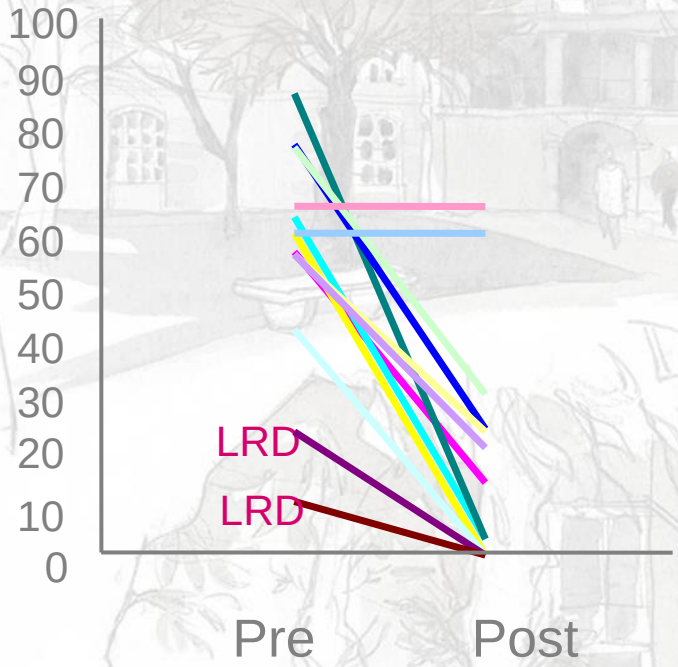
Pre-Tx suppression of anti-HLA Abs

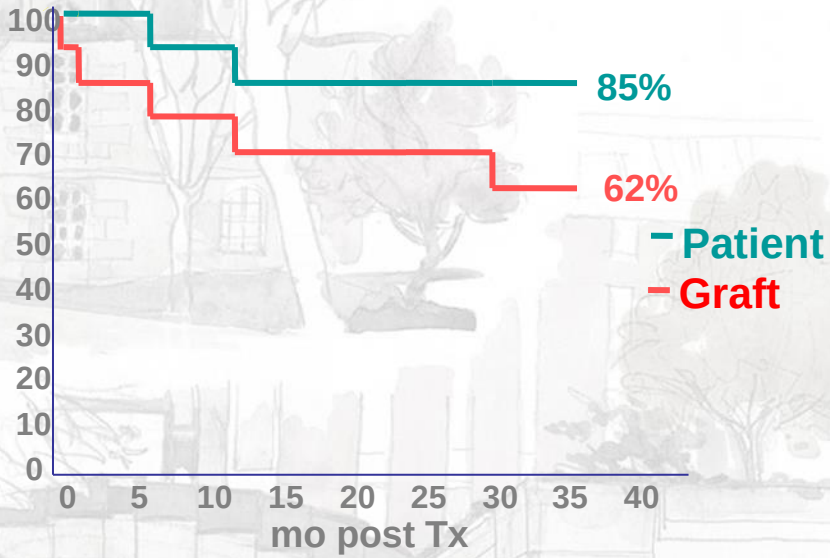
- IVIg high dose
- IVIg/plasmapheresis
- Rituximab ?
- Rituximab/IVIg
- Bortezomib ?
- Eculizumab, IdeS??
- BAFF, TACI…??

1. High dose IVIg

French protocol

Results





- Follow-up 48 months (3-90)
- 1 graft loss to thrombosis day 1
- 1 graft lost to BK infection
- 3 grafts lost to humoral rejection
- 2 deaths (PTLD 6 months, Stroke 12 months)

Glotz D, AJT, 2002
Glotz D, Transplant Int, 2004

Desensitization

2. IVIg/PP

John Hopkins Protocol

- 18 patients
- **Inclusion**: 8 cytotoxic XM +, 10 flow XM + (class I or II)
- Combination of PP and IVIg (0,1 mg/Kg)
- **Success**: negativation of CXM
- 5 acute rejections, C4d positive

… not adapted to DD waiting list

Montgomery R, Trans Proc, 2002

Desensitization

4. IVIg/Rituximab

- 20 pts
- **Inclusion:** “highly sensitized” or LD CXM pos
- **Success:** T CDCXM neg at 1:2 or T flow CXM < 250

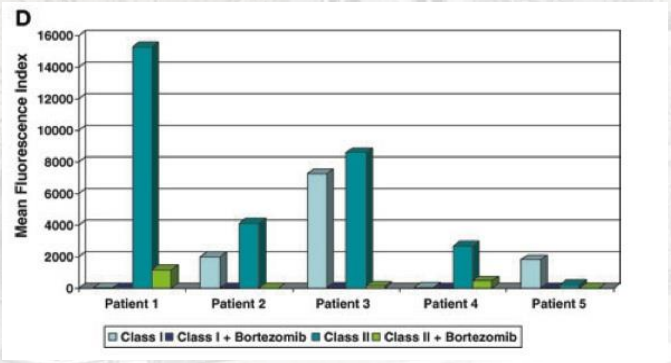
Jordan SC, NEJM, 2008

Desensitization

5. Bortezomib …?

… Promise

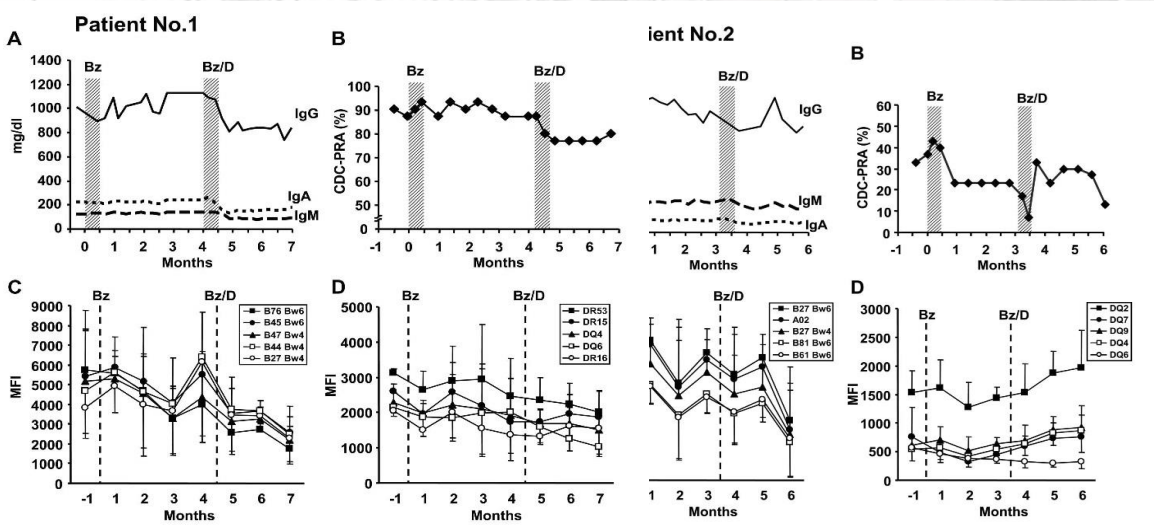
- *In vitro*



- *« Effectively removed DSAs with one cycle pre-Tx and one cycle immediat post-Tx »*

Everly MJ, Trivedi HL,Terasaki PI et al., 2009, ATC, abstract LB05

… Reality



Wahrmann, AJT, 2010

Desensitization Protocols

Conclusion

- **IVIg high dose (DD) and PP/IVIg (LD)**

  ↪ **are the backbone desensitization therapies**

- **The value of adding Rituximab is still debated**

  ↪ **Interesting association: IVIg/Rituximab**

- **New agents look promising …**

A new paradigm….

Prophylaxis by C5 inhibition

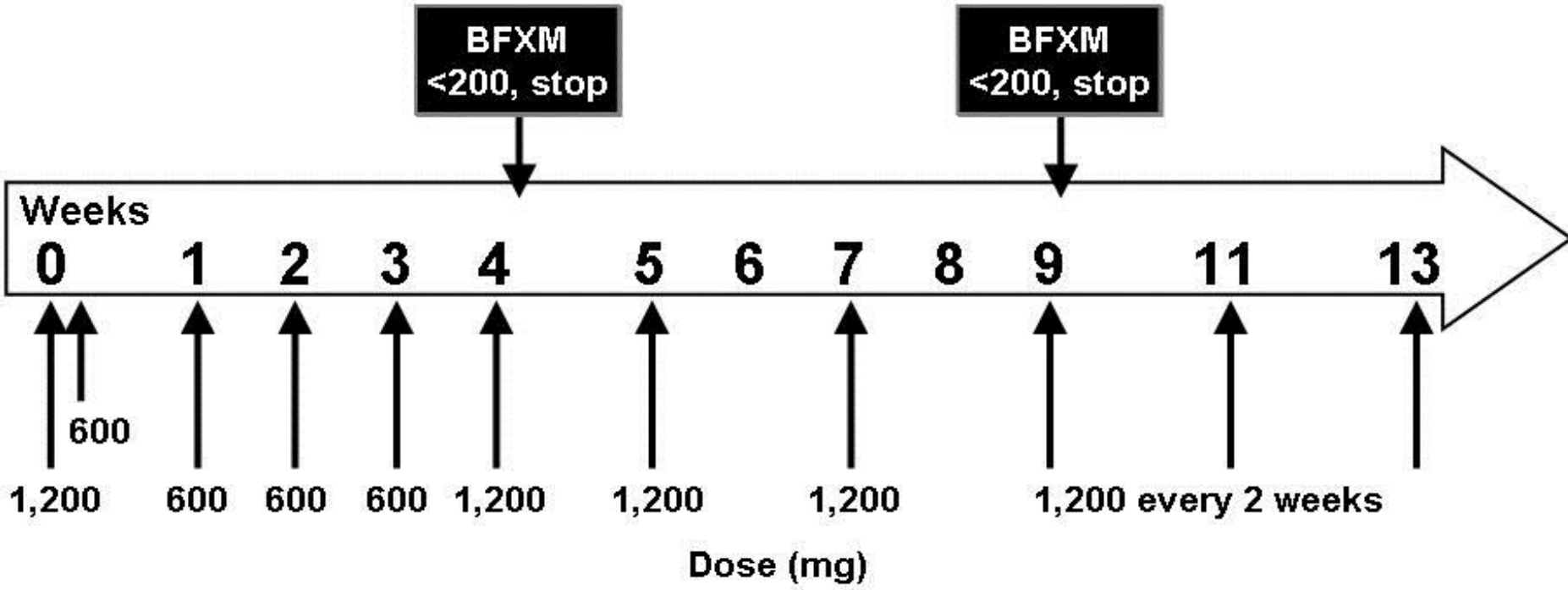
Monoclonal anti C5 Ab: Eculizumab

- 26 patients
- Inclusion: positive B cell flow XM
- Success: diminution of B cell flow XM
- PP pre-Tx if B cell flow XM > 300
- Eculizumab: D0, weeks 1, 2, 3, 4…. and more
- Only 2 rejections

Historical control group (n=51): 41% AMR

Stegall, AJT 2011

Anti-C5 Treatment Protocol



No post-transplant plasmapheresis.
Biopsy on days 4, 7, 14, 28, and 90.

Stegall, Gloor

Prevention of Acute Antibody-Mediated Rejection in Sensitized Deceased-Donor Kidney Transplant Recipients: 1-Year Outcomes

D. Glotz,[1] G. Russ,[2] L. Rostaing,[3] C. Legendre,[4] S. Chadban,[5] J. Grinyo,[6] N. Mamode,[7] G. Tufveson,[8] L. Couzi,[9] P. Rigotti,[10] Y. Lebranchu,[11] S. Sandrini,[12] W. Marks[13]

[1]Saint-Louis Hospital, Paris, France and INSERM U 940; [2]Royal Adelaide Hospital, Adelaide, Australia; [3]CHU Rangueil, Toulouse, France; [4]Hopital Necker, Paris, France; [5]Royal Prince Alfred Hospital, Camperdown, Australia; [6]H U de Bellvitge, Barcelona, Spain; [7]Guy's Hospital, London, United Kingdom; [8]Uppsala University Hospital, Uppsala, Sweden; [9]H Pellegrin, Bordeaux, France; [10]Via Giustiniani, Padua, Italy; [11]Hopital Bretonneau CHU, Tours, France; [12]Spedali Cvl di Brescia, Brescia, Italy; and [13]Alexion Pharmaceuticals, Inc., Cheshire, CT, United States

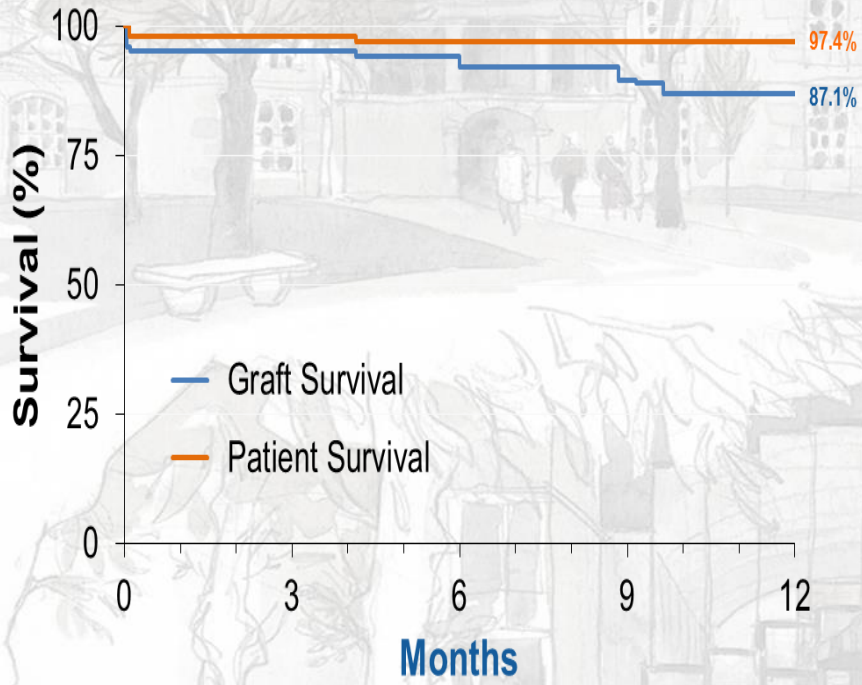
Baseline Demographics and Clinical Characteristics

Characteristic	Patients (N = 80)
Median age, y (range)	52 (24–70)
Time on waiting list[a] , y (range)	5.5 (0.3-33.6)
Sex, n (%) (male / female)	32 (40) / 48 (60)
Current DSA[b], n (%) Class I only, n (%) Class II only, n (%) Class I and II, n (%)	69 (86.3) 30 (37.5) 12 (15.0) 27 (33.8)
Historical[c] DSA, n (%)	11 (13.8)

Efficacy Endpoints

Outcome	9 Weeks (N = 80)	1 Year (N = 80)
Post-transplant failure rate,[a] n (%)	10 (12.5) (95% CI: 6.2%, 21.8%)	15 (18.8) (95% CI: 10.9%, 29.0%)
Biopsy-proven AMR, n (%)	6 (7.5)	8 (10.0)
Graft loss, n (%)	4 (5.0)	9 (11.3)
Primary cause		
Renal artery thrombosis	2 (2.5) 2 (2.5)	
Primary nonfunction	1 (1.3)	2 (2.5)
Death, n (%)	0	6 (7.5)
Lost to follow-up, n (%)		

Graft and Patient Survival, Renal Function Through 1 Year



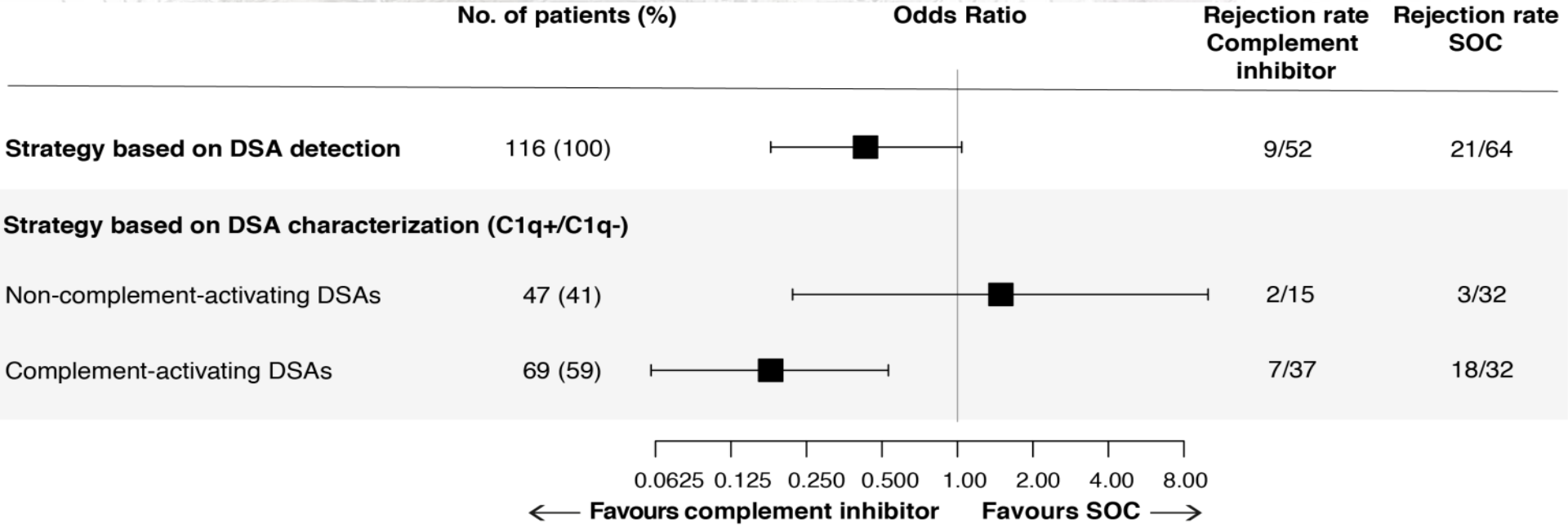
Patient Survival #s at risk	80	76	72	51	43
Graft Survival #s at risk	80	76	72	51	43

Renal Function

Time Point	Serum Creatinine (mg/dL), mean ± SD (n)	Proteinuria (≥2+), n (%)
0	7.44 ± 2.52 (n=78)	—
1 month	1.86 ± 1.07 (n=74)	9/59 (15.3%)
3 months	1.70 ± 0.09 (n=75)	8/55 (14.5%)
12 months	1.80 ± 1.11 (n=45)	8/36 (22.2%)

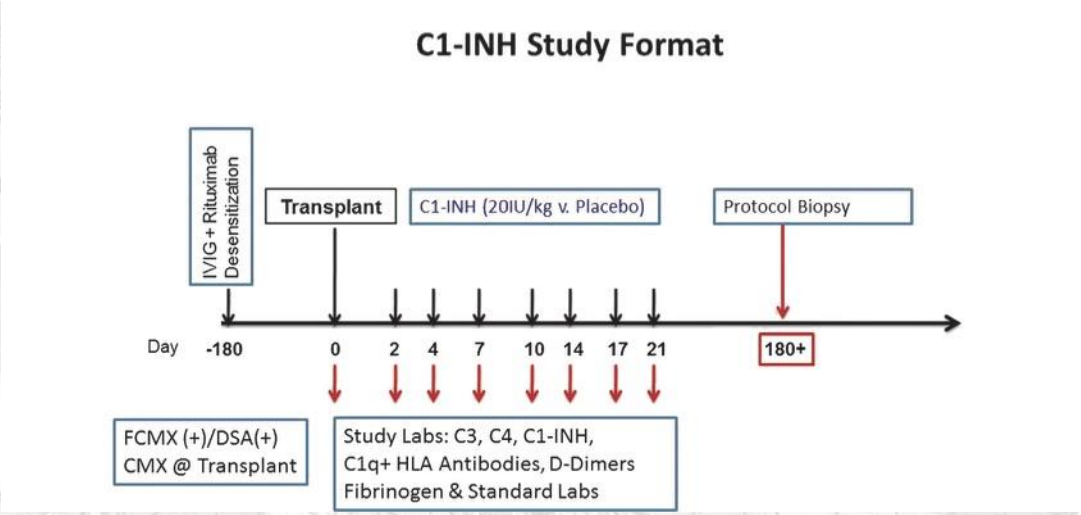
IMPACT OF A THERAPEUTIC STRATEGY BASED ON DSA C1q STATUS *vs.* DSA DETECTION

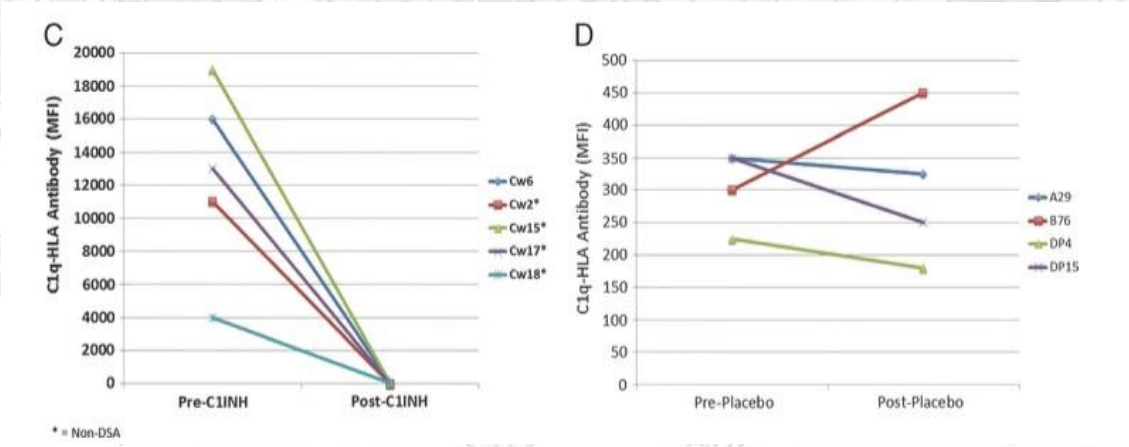
Response rate to complement inhibition improved when characterizing DSA C1q status at transplantation



A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients

Ashley A. Vo,[1] Adriana Zeevi,[2] Jua Choi,[1] Kristen Cisneros,[1] Mieko Toyoda,[3] Joseph Kahwaji,[1] Alice Peng,[1] Rafael Villicana,[1] Dechu Puliyanda,[1] Nancy Reinsmoen,[4] Mark Haas,[5] and Stanley C. Jordan[1]





Vo, Transpl 2015

Tocilizumab

Anti-IL6

Interleukin (IL)-6 is a cytokine that has powerful stimulatory effects on B cells and plasma cells and is responsible, in conjunction with other cytokines, for normal antibody production.

-Desensitization

-Treatment of refractory AMR

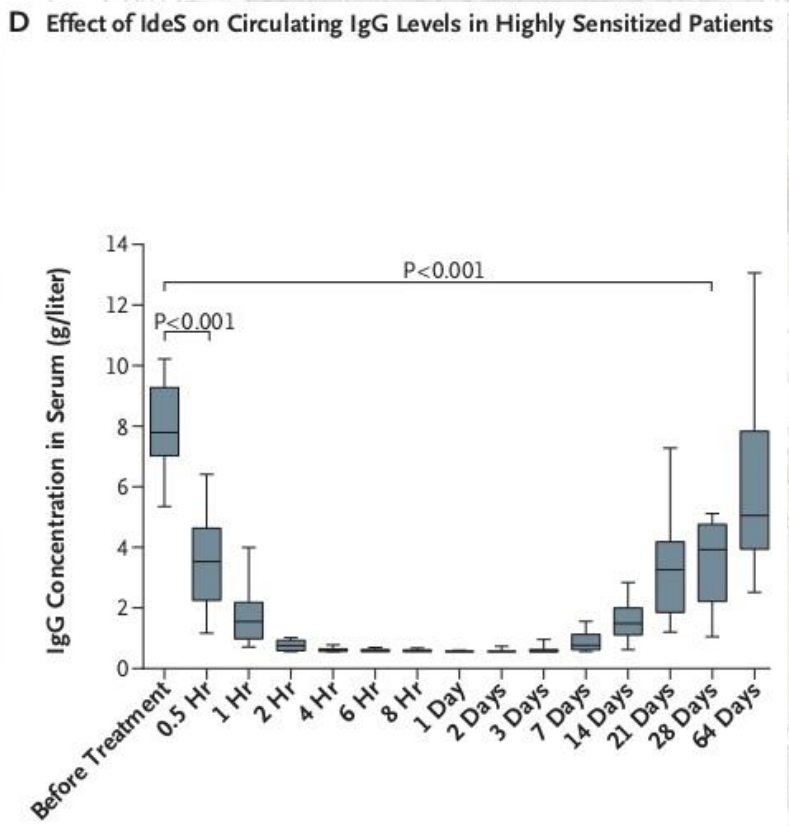
Vo, Transpl 2015

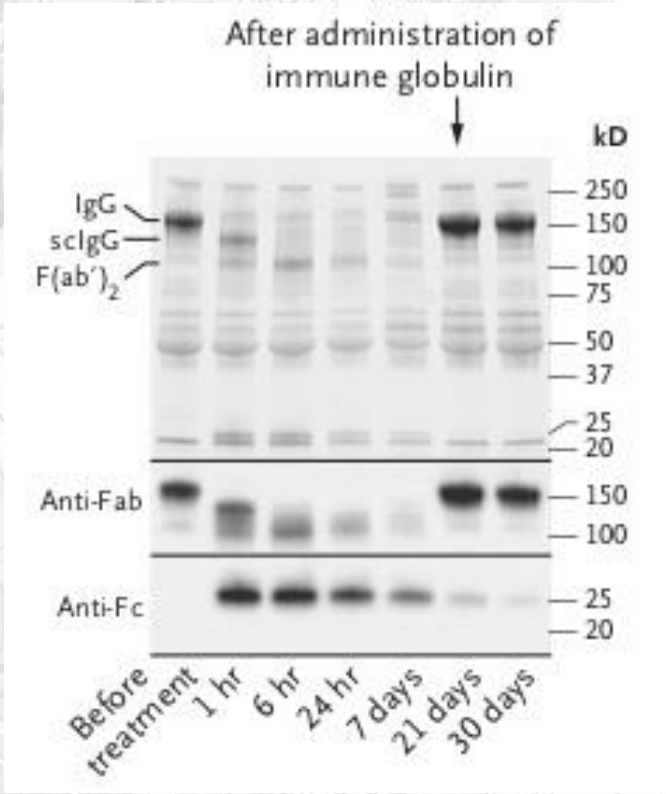
Jordan, personal comm

IdeS

The new kid in the block…

IgG degrading enzyme (from Strep pyogenes)





Jordan, NEJM 2017

IdeS

25 sensitized patients (mean cPRA 95%)
24 transplanted
10 humoral rejections

Immunologic variables	
Anti-HLA donor-specific antibody positive — no. (%)	23 (92)
No. of anti-HLA donor-specific antibodies	2.3±1.8
Mean fluorescence intensity	
Class I	5660±2364
Class II	8199±5639
Negative anti-HLA donor-specific antibodies at 1 to 6 hr after treatment — no. (%)	25 (100)
Positive cross-match at transplantation — no. (%)†	20 (80)
Estimated GFR at 1 to 6 mo after transplantation — ml/min/1.73 m^2	58±30
Follow-up — mo	4.7±1.9
Graft loss — no. (%)	1 (4)

One shot….

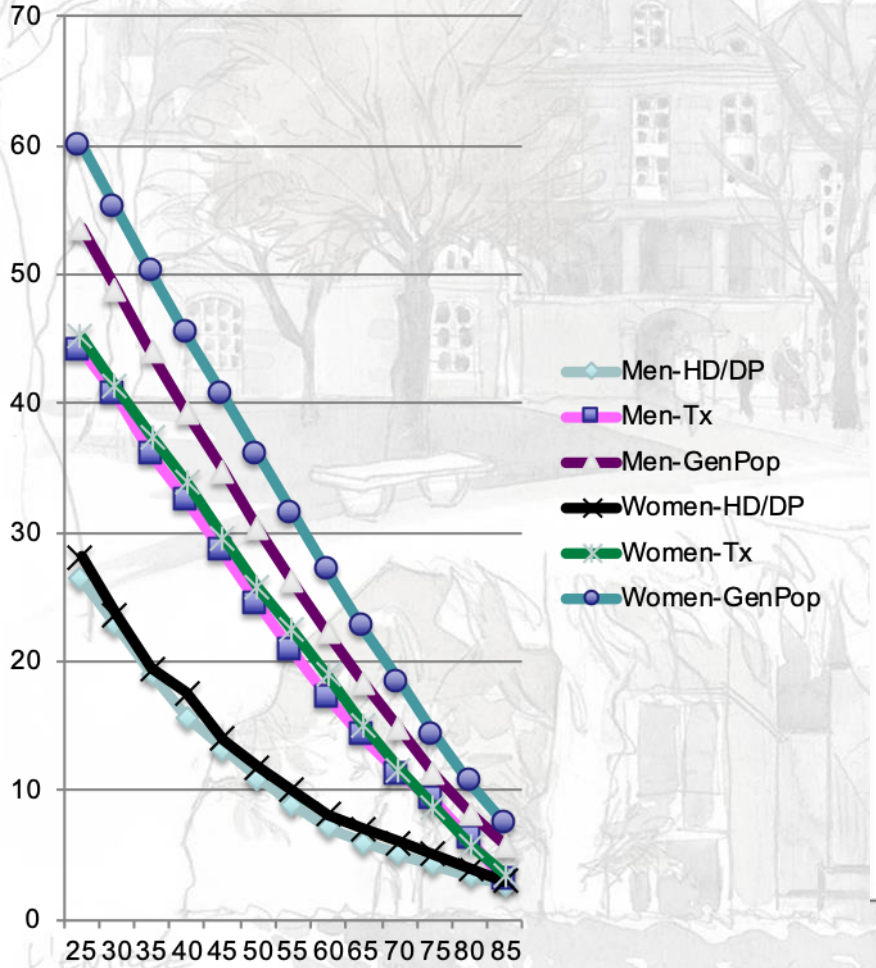
Jordan, NEJM 2017

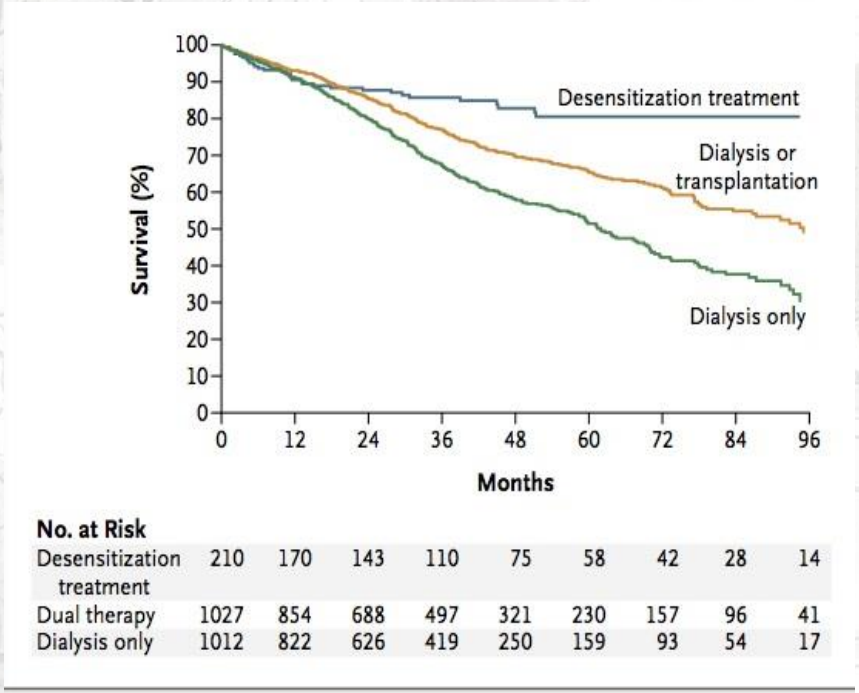
Choosing the desensitization regimen: Saint Louis choices

Immunosuppression

	DSA MFI < 1000	DSA MFI 1000-3000	DSA MFI 1000-3000	DSA MFI > 3000	DSA MFI > 3000
	CXM-	CXM-	CXM-	CXM-	CXM+
	FCM -	FCM -	FCM +	FCM +	FCM +
Desensitization pre-Tx	none	none	High dose IVIg or PP/IVIg	High dose IVIg or PP/IVIg	PP/IVIg, Ec, IdeS ????
Desensitization post-Tx	none	High dose IVIg	High dose IVIg	High dose IVIg	High dose IVIg
Immunosuppressive regimen	Depletive induction, CNI, Mycophenolate, Steroïds				

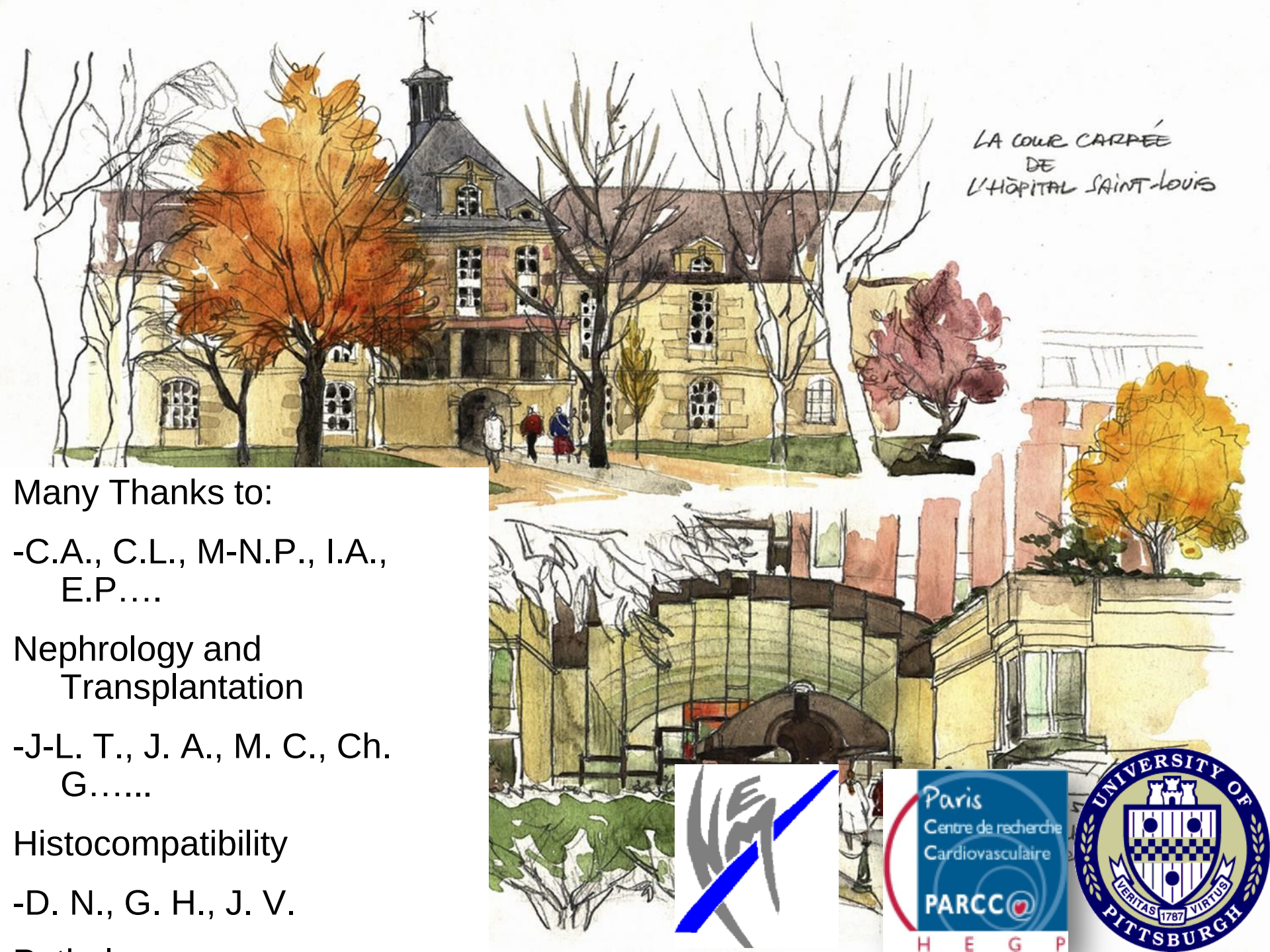
Transplantation is the best solution….





No. at Risk									
Desensitization treatment	210	170	143	110	75	58	42	28	14
Dual therapy	1027	854	688	497	321	230	157	96	41
Dialysis only	1012	822	626	419	250	159	93	54	17

….with a limit



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Nephrology and Transplantation

-J-L. T., J. A., M. C., Ch. G…...

Histocompatibility

-D. N., G. H., J. V.