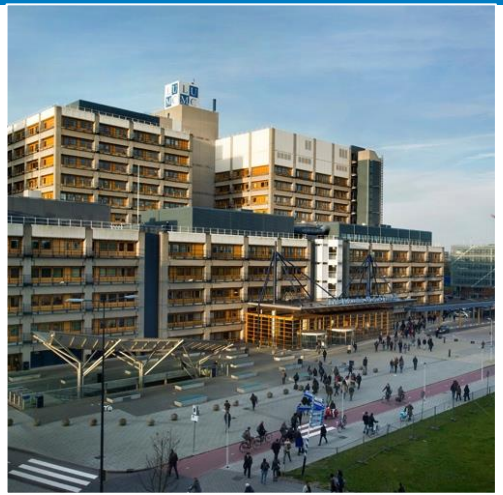
Leiden University
Medical Center

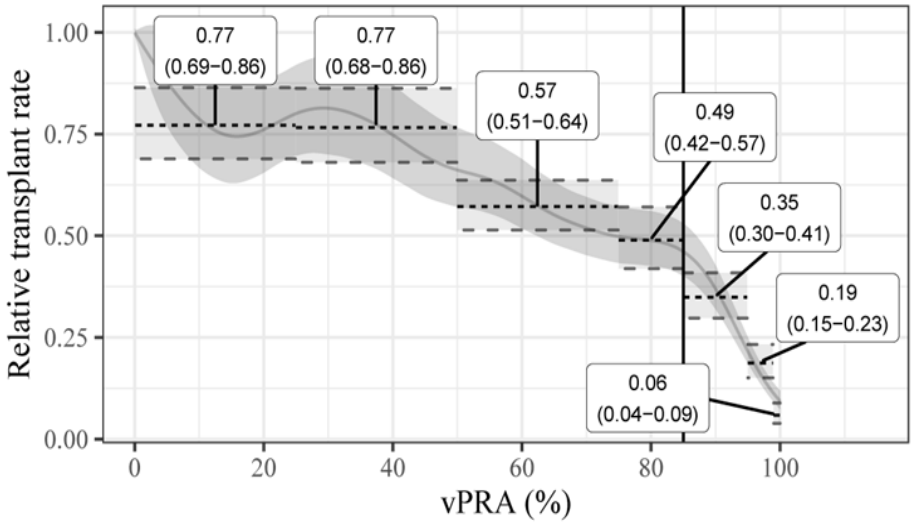
Desensitizasyon tedavisi alan yuksek oranda sensitize hastalarda anti-HLA antikor kinetigi: Hollanda deneyimi



Gonca E. Karahan, PhD
TIGED
19-04-2024/ANTALYA

Transplanting highly sensitized patients is a major challenge

- Exposure to allogeneic HLA can result in anti-HLA antibody formation (sensitization)
- Patients with HLA antibody profiles reacting to ≥ 85–100% of donors **(vPRA%)** in the donor population are called **highly sensitized**
- Within Eurotransplant, 5% of patients awaiting a transplant are highly sensitized
- These patients have a long waiting time and a high mortality rate



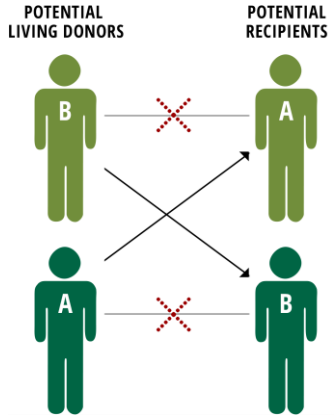
anti-HLA antibody profile in relation to HLA makeup of the donor population

Heidt et al., Kidney Int, 2018

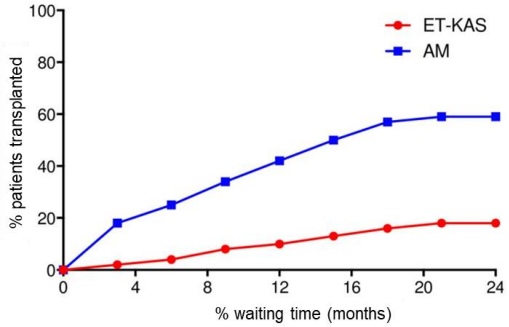
De Ferrante, Heidt et al., Transplantation, 2023

Options for facilitating transplantation in highly immunized patients

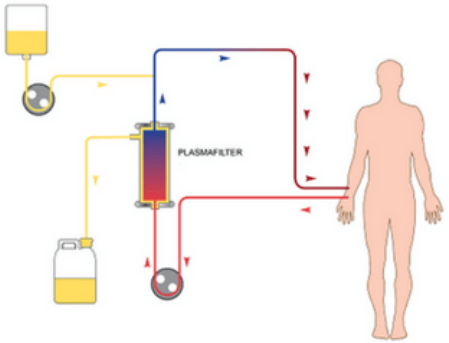
HLA compatible living-donor transplantation
Paired-exchange program/National cross-over program



HLA compatible deceased-donor transplantation via prioritized allocation
Eurotransplant Acceptable Mismatch program

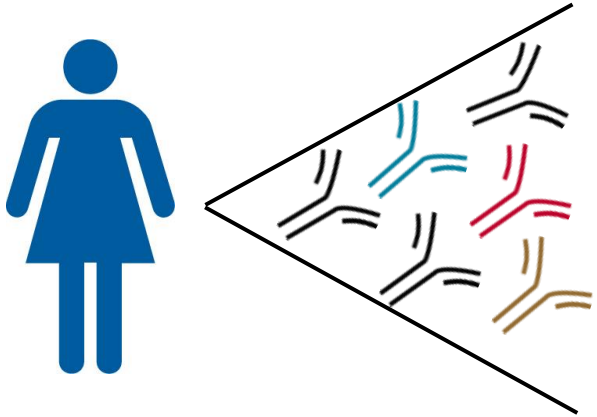


HLA incompatible (HLAi) transplantation
Antibody removal therapy (<u>Desensitization</u>)



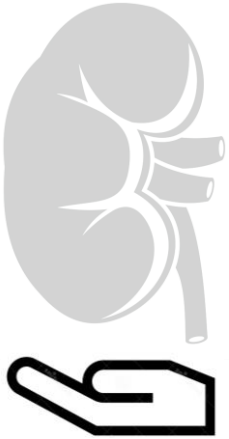
- laborious
- time consuming
- risk for infection
- costly
- no guarantee for tx

Desensitization: a window of opportunity for transplantation

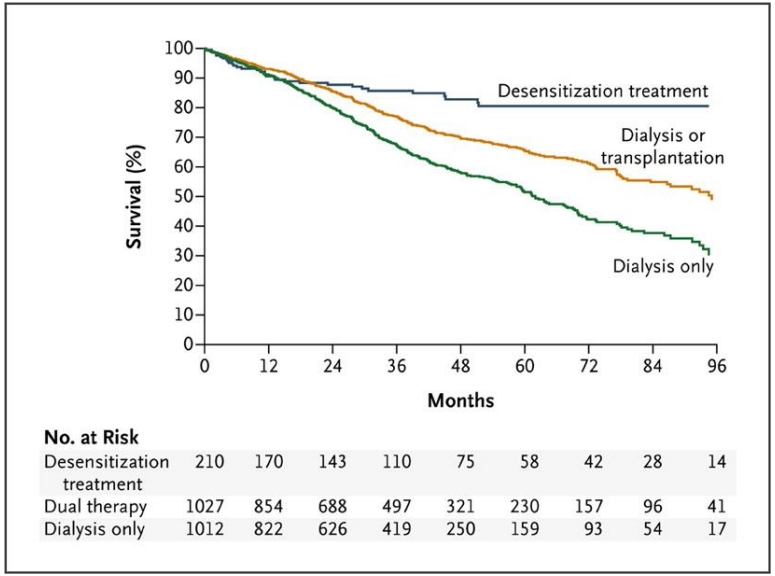


Desensitization treatments

Living donor
transplantation



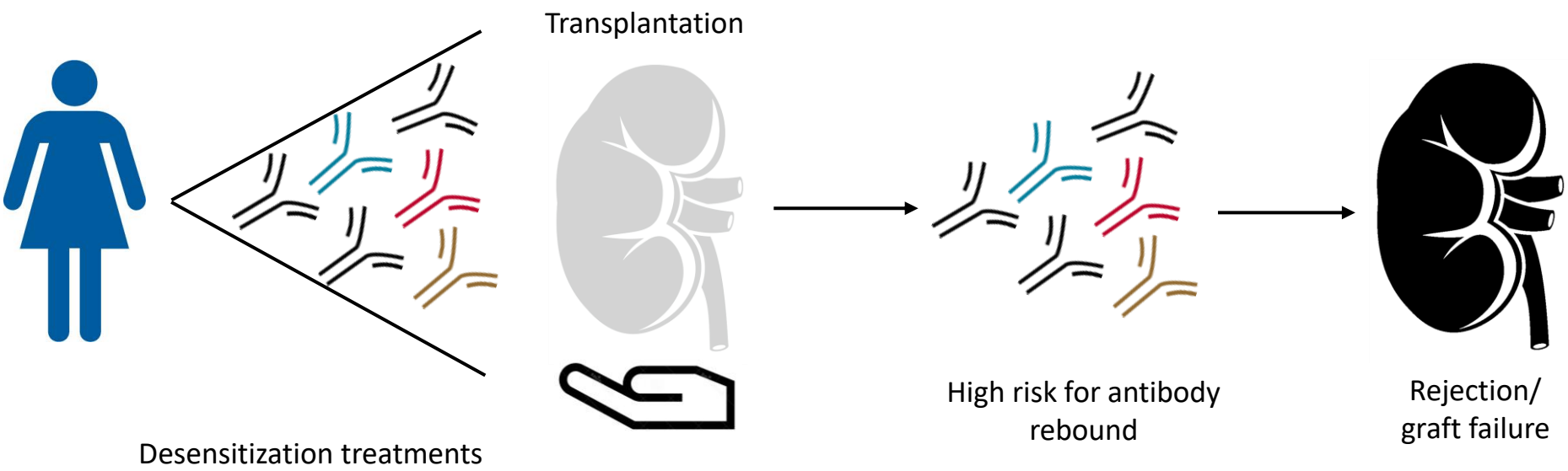
Plasmapheresis (PE) + low dose IVIg



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

Montgomery et al, NEJM, 2011

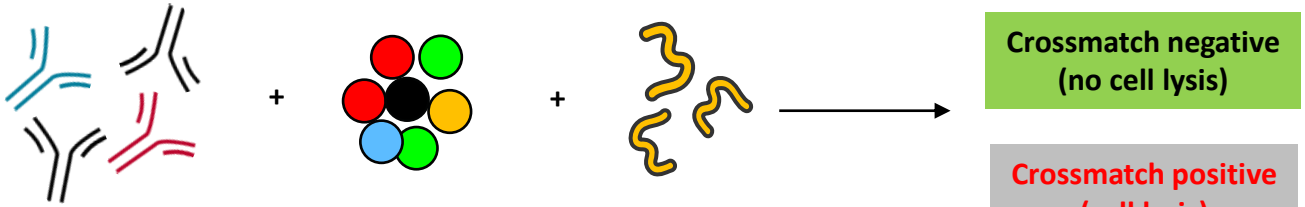
Desensitization: a window of opportunity for transplantation, but with increased risks



30-70% of patients transplanted after successful desensitization experience **acute** antibody-mediated rejection **(ABMR)** due to **DSA rebound**, which may **rapidly progress to chronic ABMR** and graft loss.

Immunological risk assessment is based on serum antibody detection

1) Crossmatching (Complement dependent cytotoxicity-CDC)



Assay limitatios:
-need for viable cells
-labor intensive

Assay limitations:
-recombinant HLA
-bead saturation problem
-most common 100 HLA on beads

Protocol-National Desensitization Program

NEDERLANDSE TRANSPLANTATIE VERENIGING

Eligibility: no offer for 2 years in AM program or unsuccessful participation in 4 rounds of national cross-over program

Decision to proceed with transplantation is based on CDC-XM result:

- Conversion of positive CDC-XM to negative CDC-XM
- Maintenance of negative CDC-XM

Study aim

To provide a detailed overview of the HLA-based immunological test results of patients desensitized at Erasmus Medical Center, the Netherlands, between 2013 and 2022)

- To assess anti-HLA and DSA antibody kinetics in a cohort of highly sensitized kidney transplant candidates who underwent desensitization
- To explore whether the efficacy of antibody removal therapy can be predicted

Study cohort (n:16, 2013-2022)

	Group 1 (5 PE-TX) n=9	Group 2 (10 PE-tx) n=4	Group 3 (10 PE-no tx) n=3
Patient age (at 1st PE session), years	35 (28-69)	43 (33-53)	46 (37-68)
Sex, female	4	3	2

Study cohort (n=16) (Feb 2013-Jan 2022)

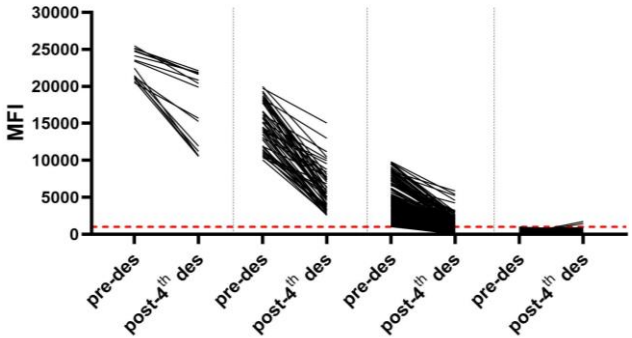
	Group 1 (5 PE-TX) n=9	Group 2 (10 PE-tx) n=4	Group 3 (10 PE-no tx) n=3
Donor characteristics			
Age	52 (31-61)	56 (45-60)	53 (35-66)
Living-related	6	3	2
Living-unrelated	3	1	1
HLAi	7	2	3
HLAi and ABOi	2	2	0
Clinical outcome			
Biopsy-proven ABMR	7 (78%)	4 (100%)	N/A
Time to ABMR, days	8 (7-27)	18 (7-41)	N/A
Biopsy-proven cABMR	5 (56%)	3 (75%)	N/A
Time to cABMR, months	11 (5.2-56)	24 (9.3-51.3)	N/A
Follow-up time, months	57 (16-110)	58 (52-91)	N/A
Functioning graft within follow-up	7 (78%)	2 (50%)	N/A

- HLA-A, B, C, DR, DQ **matching** and **DSA** assigment at **split antigen level** (routine)
- **One Lambda** SAB kits, baseline (normalized) MFI, average of multiple beads
- Luminex **DSA cutoff >1000 MFI**

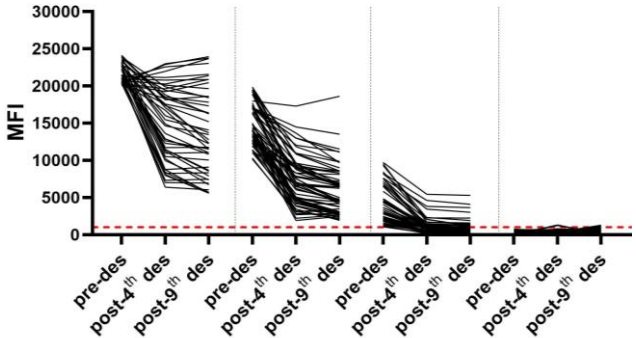
Not all patients/antibody specificities respond similarly to desensitization

MFI → ≥ 20000 | ≥10000 <20000 | ≥ 1000 <10000 | <1000

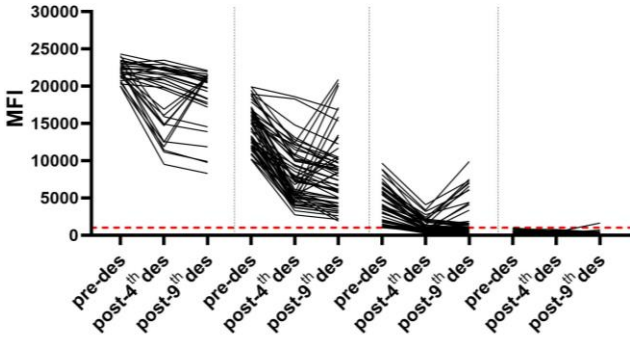
5 PE-tx



10 PE-tx



10 PE-no tx



*All beads

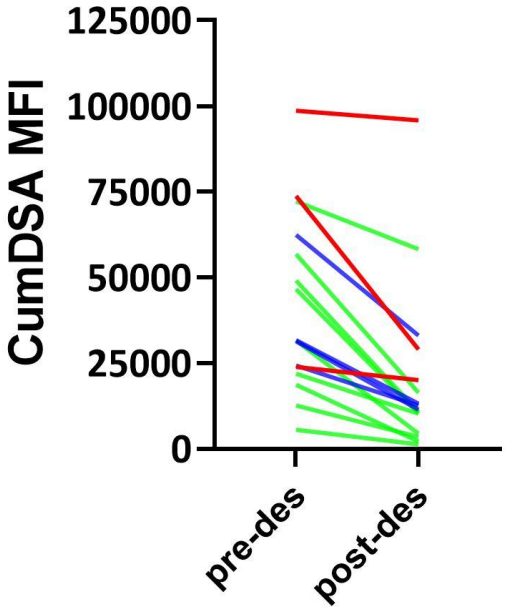
Cumulative Donor Specific Antibody MFI

5 PE-tx (n=9)
10 PE-tx (n=4)
10 PE-no tx (n=3)

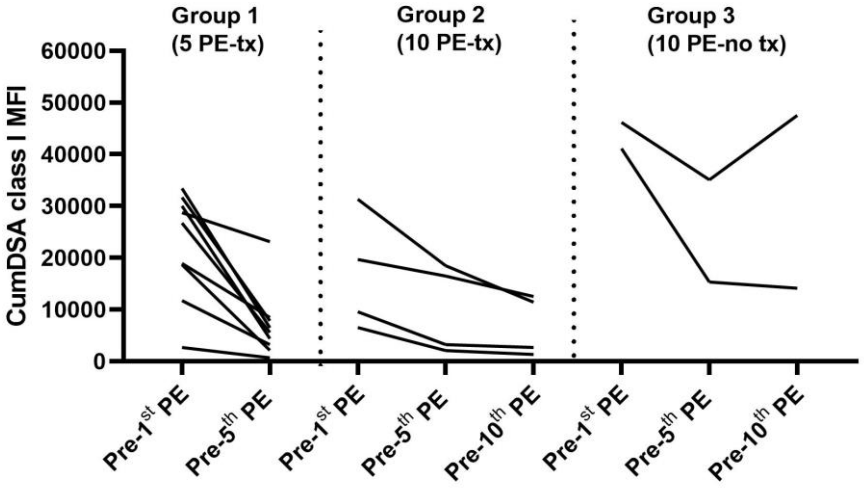
Cumulative DSA (cumDSA) MFI

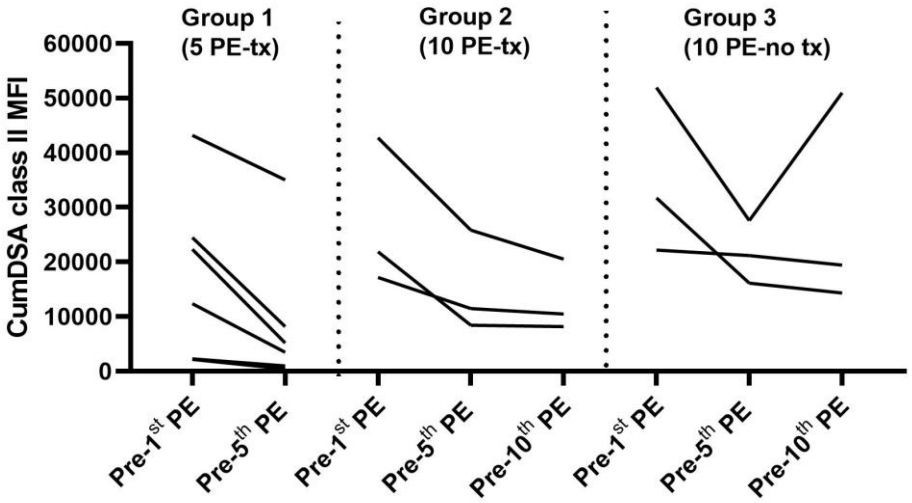
anti-HLA A2 (MFI:15000)
anti-HLA A3 (MFI:10000)
anti-HLA DR4 (MFI: 12000)
\+

CumDSA MFI= 37000



Decrease in MFI was the lowest for Group 3

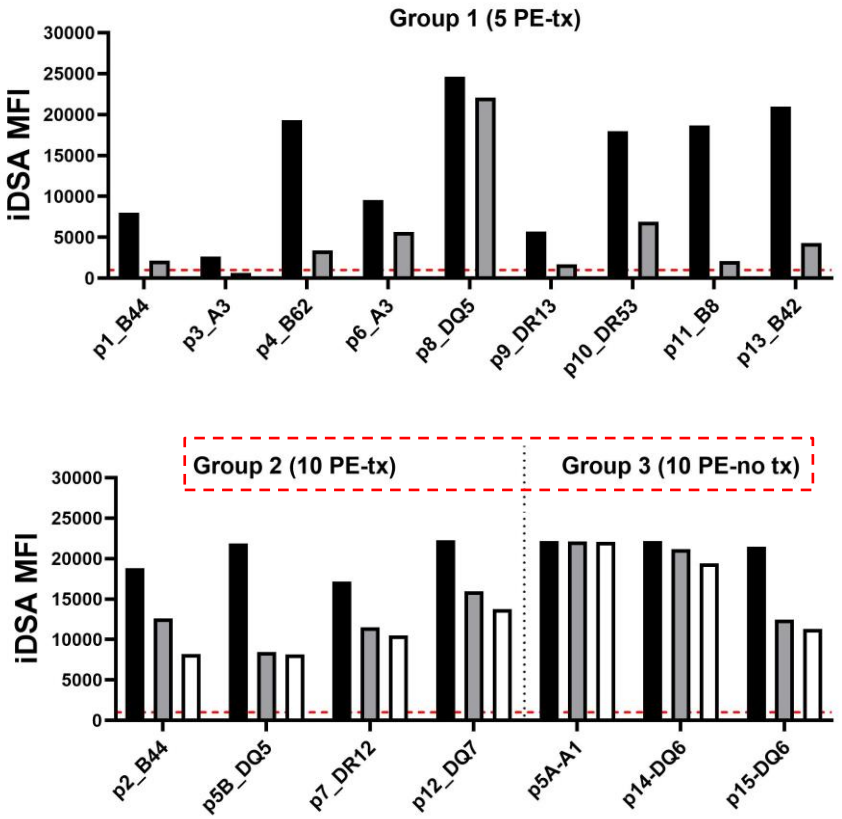




Immunodominant Donor Specific Antibody MFI

Immunodominant DSA (iDSA) MFI

Anti-HLA A2 (MFI:15000)
Anti-HLA A3 (MFI: 10000)
Anti-HLA DR4 (MFI: 12000)



Using antibody titer to stratify patients with vPRA>99.9% for desensitization treatments

Received: 12 July 2020 | Revised: 30 September 2020 | Accepted: 5 October 2020
DOI: 10.1111/ajt.16363

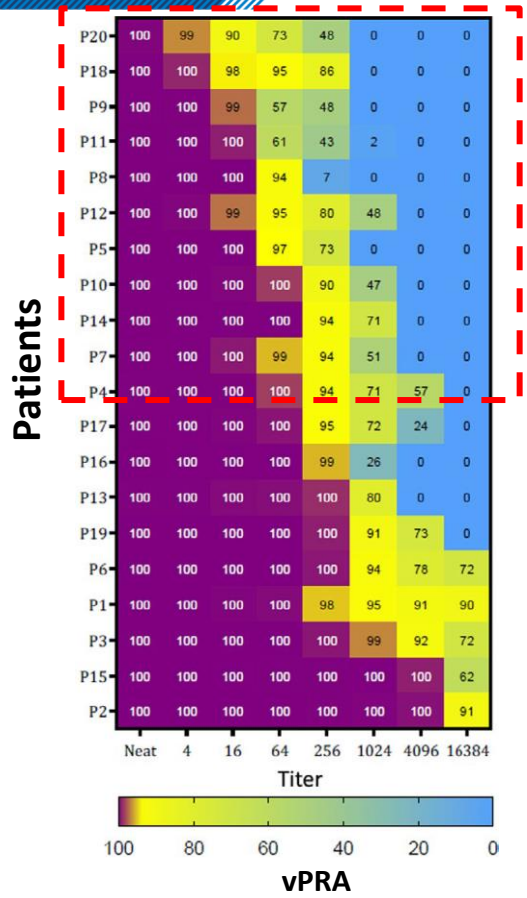
BRIEF COMMUNICATION

AJT

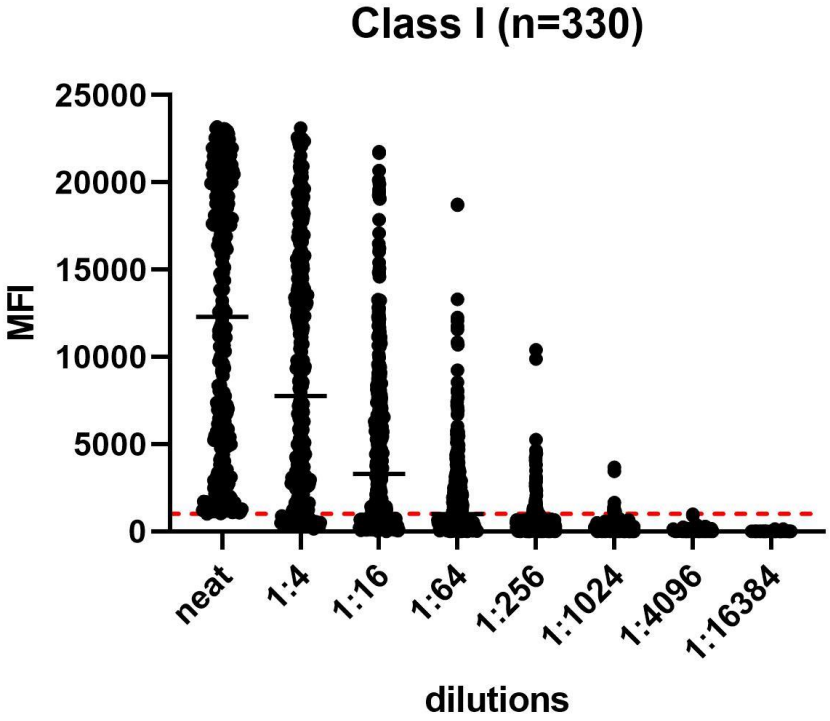
Estimating alloantibody levels in highly sensitized renal allograft candidates: Using serial dilutions to demonstrate a treatment effect in clinical trials

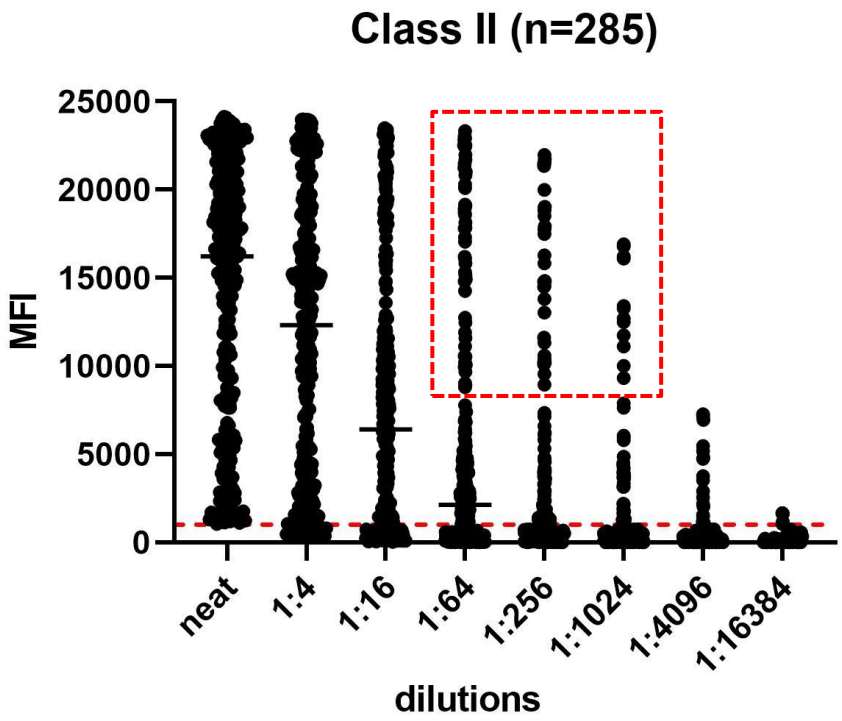
Anat R. Tambur[1] | Carrie Schinstock[2] | Chelsea Maguire[1] | David Lowe[3] | Byron Smith[2] | Mark Stegall[2]

- *…Stepwise dilution of the serum will gradually eliminate antibody positivity and thus decrease the vPRA because the corresponding antigens would no longer be considered unacceptable…*
- *….This approach will help stratify patients prior to inclusion in studies and help in discerning partial therapeutic effects..*



Decrease in MFI upon serial dilution of pre-desensitization serum





Serial dilution reveals high titer anti-HLA class II antibodies

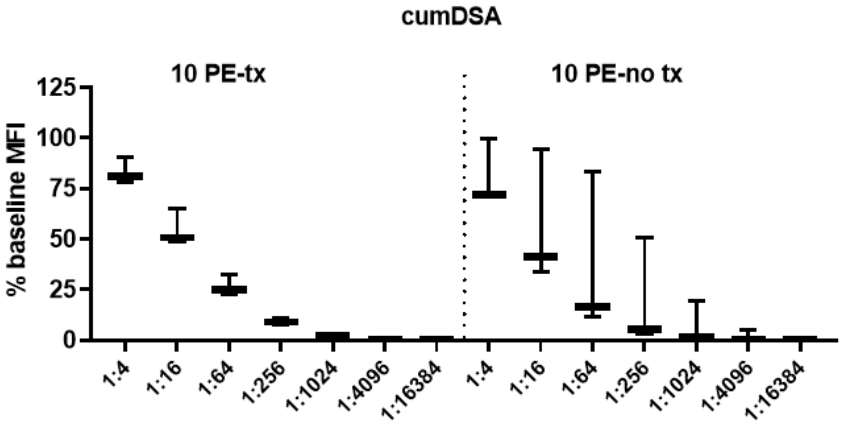
*All 10-PE patients

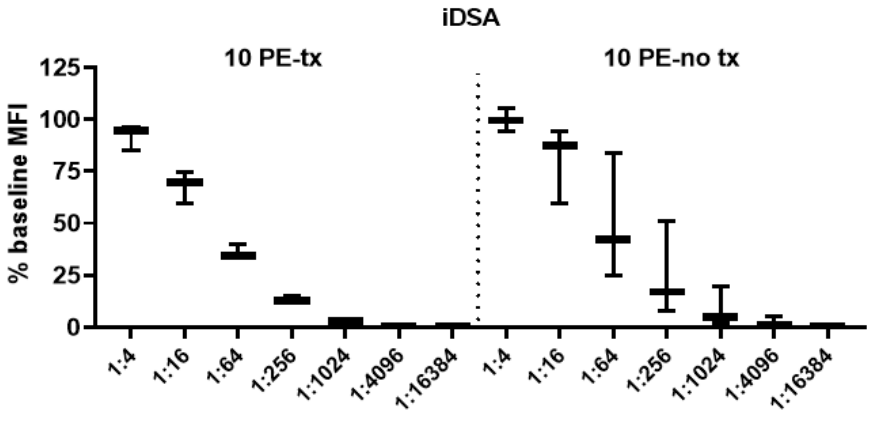
Reduction in vPRA upon dilution does not predict desensitization efficacy

Max=red	100,00
white	85,00
Min=blue	0,00

	vPRA Total					
	10 PE-tx			10 PE-no tx		
	P2	P7	P12	P5a	P14	P15
pre-des (neat)	99,16	99,97	99,98	100,00	100,00	99,58
(pre-des) 1:4	99,23	99,97	99,98	99,97	100,00	99,30
1:16	99,20	99,82	99,98	99,90	99,94	98,79
1:64	96,54	99,17	99,95	99,78	97,94	96,10
1:256	76,07	95,81	99,60	55,68	97,57	62,48
1:1024	0,00	81,91	95,97	0,00	94,08	0,00
1:4096	0,00	59,67	0,00	0,00	66,66	0,00
1:16384	0,00	0,00	0,00	0,00	55,26	0,00

Reduction in cumDSA or iDSA MFI upon titration does not predict desensitization efficacy

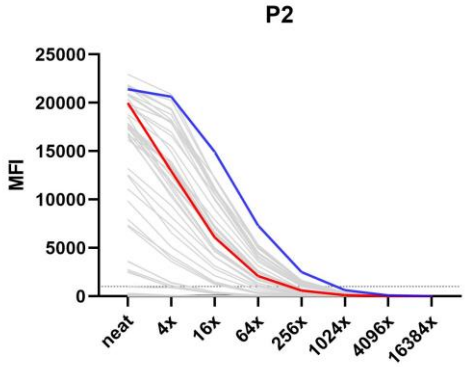


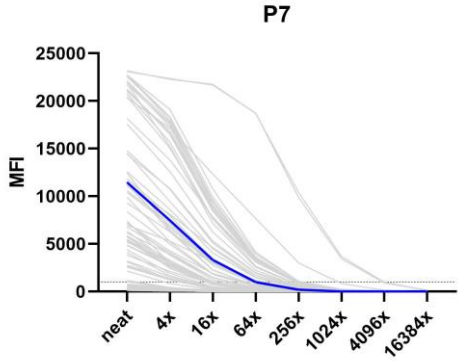


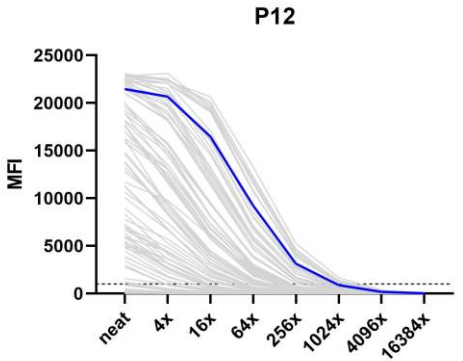
No common iDSA for class I

HLA-A
HLA-B
HLA-C
non-DSA

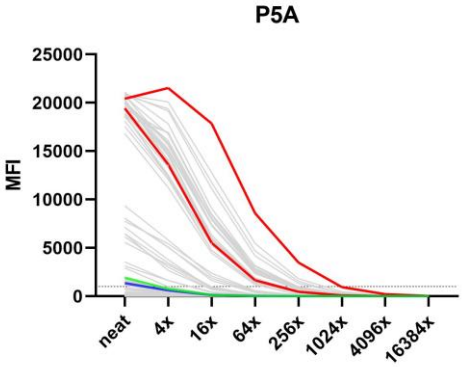
10 PE-tx

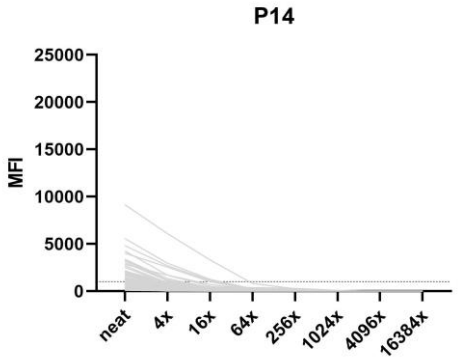


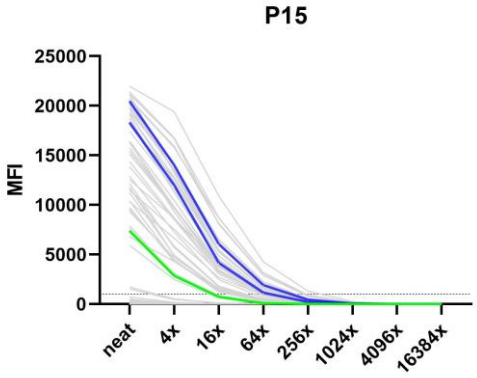




10 PE-no tx





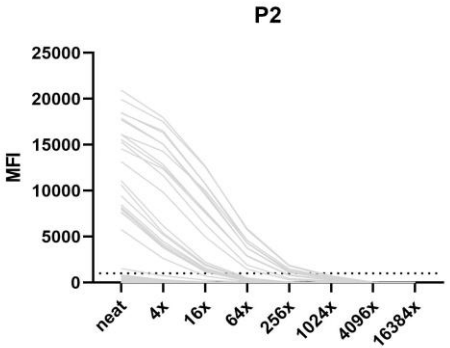


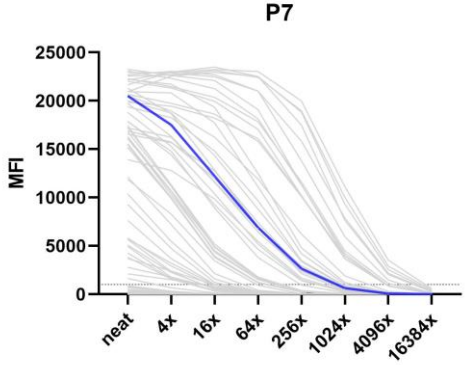
HLA-DQ6: common iDSA in desensitization resistant cohort

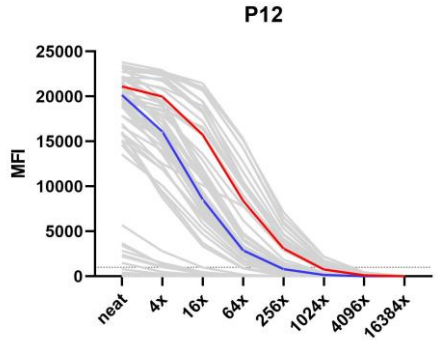
HLA-DR
HLA-DQ
HLA-DP
non-DSA

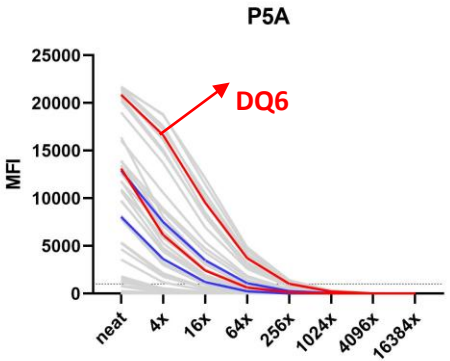
10 PE-tx

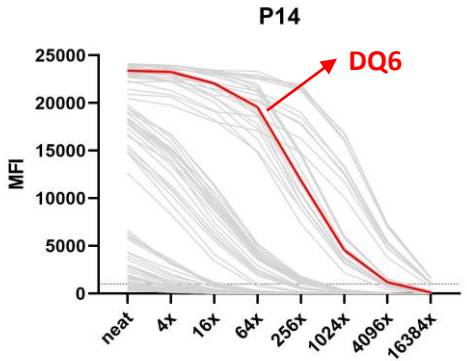
10 PE-no tx

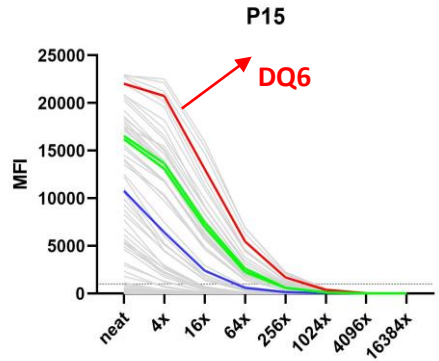






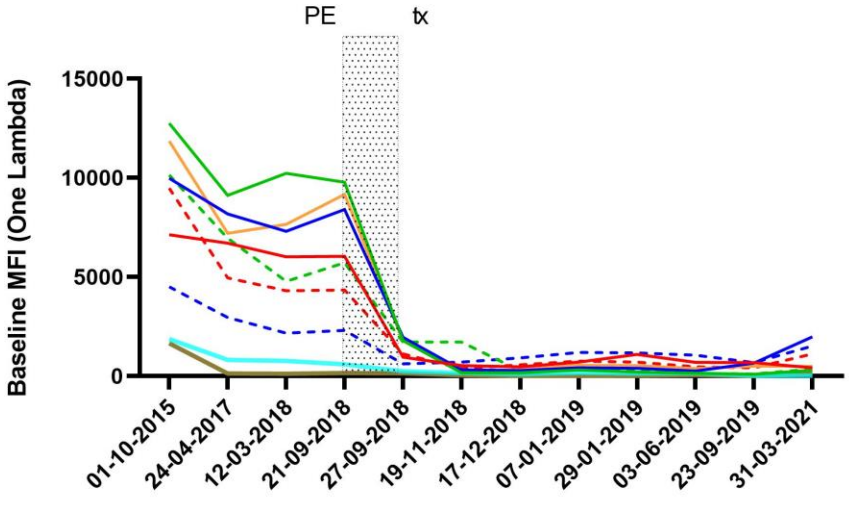




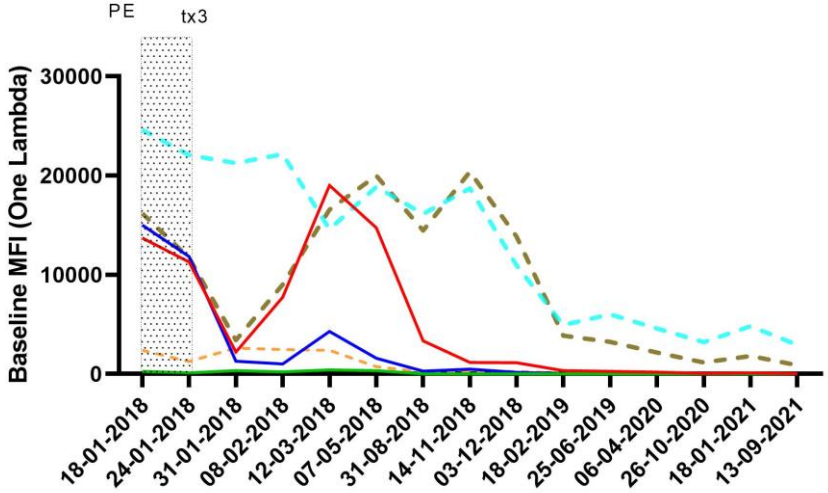


Post-transplant DSA kinetics

No rebound DSA

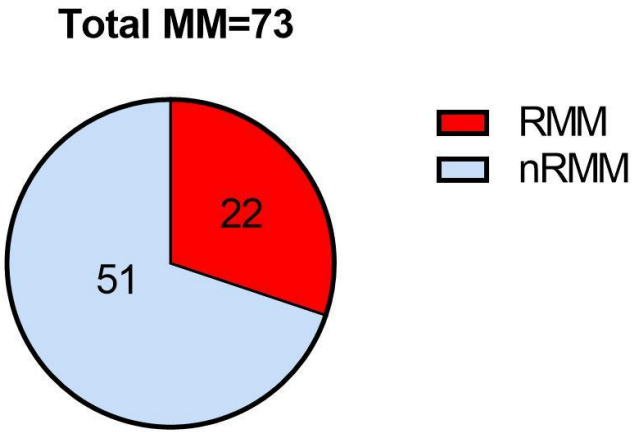


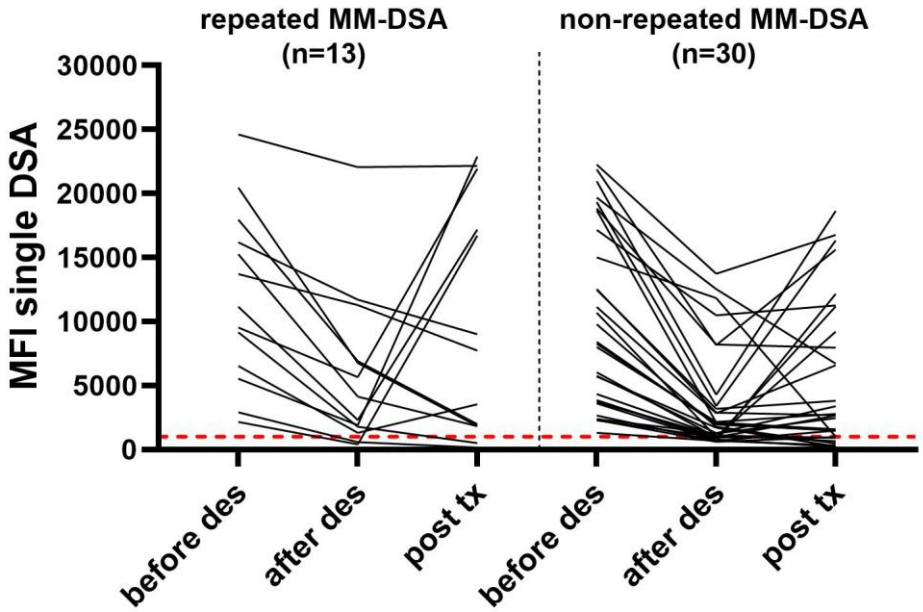
Rebound+no rebound DSA



DSA rebound due to RMM?

RMM and DSA kinetics post-transplant



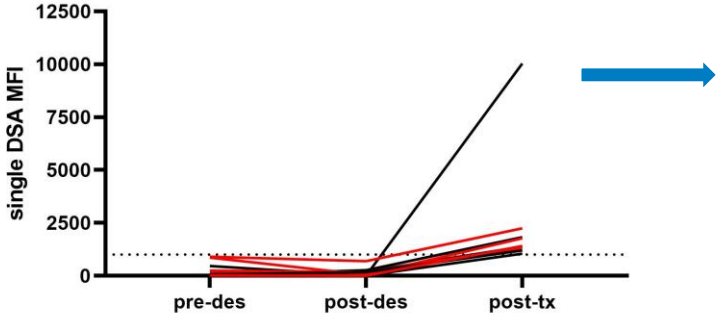


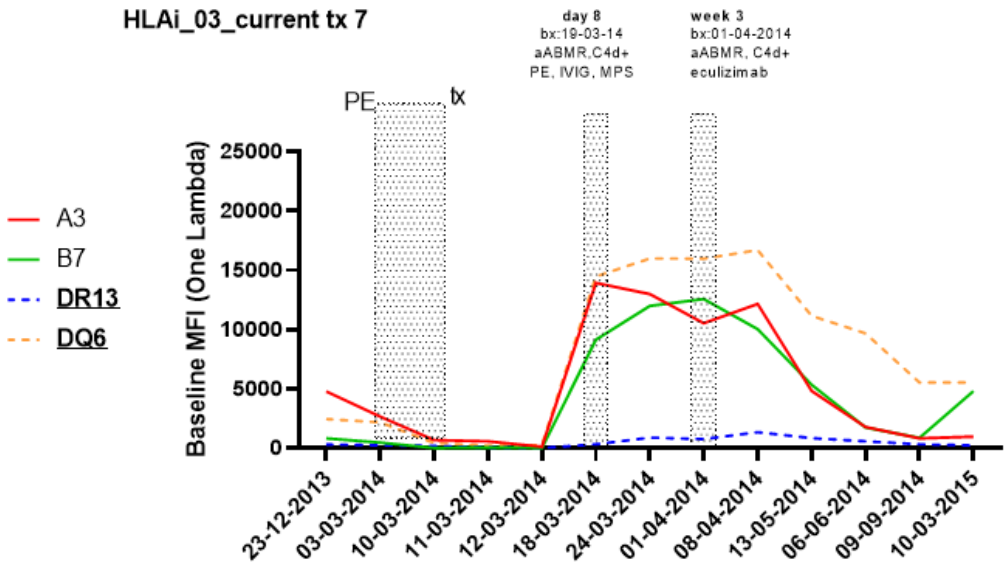
- In the first post-tx month, RMM-DSA MFIs were 56% of the baseline MFI in comparison to 39% for non-RMM.

De novo DSA within first post-tx month

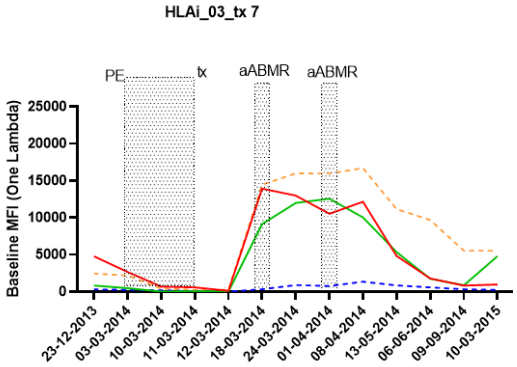
De novo DSA (n=10) in 5 patients

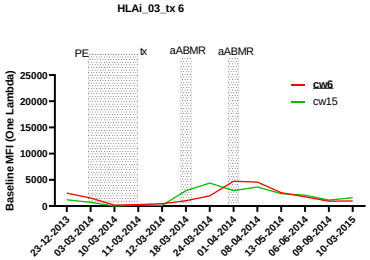
5 dnDSA were directed at RMM (memory response?)

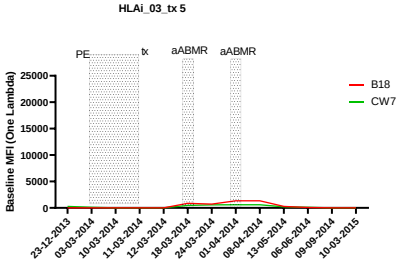


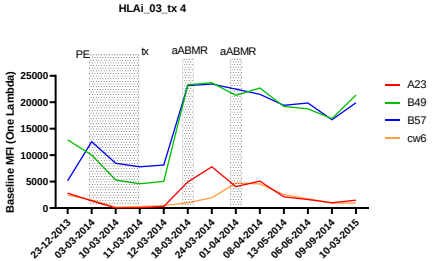


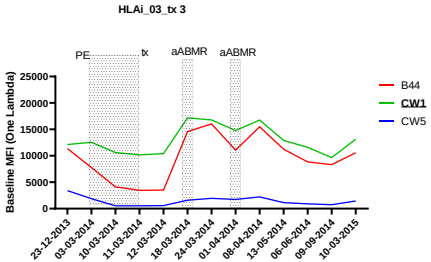
Repeated mismatch at epitope level

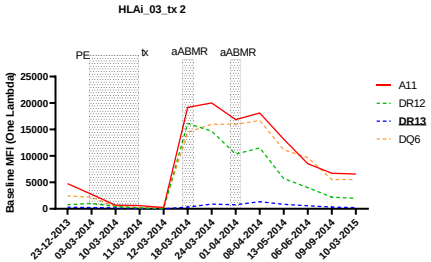


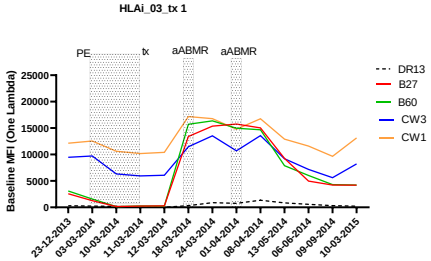












Conclusions

- Response to antibody removal treatments varies between patients and withing a patient for different antibody specificities
- Desensitization after 4th PE is resulting in relatively less decrease in MFI
- HLA class II antibodies are more resistant to desensitization
- Multiple factors play a role on the efficacy of desensitization
  - antibody strength, affinity
  - immunoglobulin homeostasis (production & catabolism)

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