Weight-adjusted ATG dosing improves relapse-free survival in obese allo-HSCT recipients

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Background

- Incidence of obesity now >30% in many Western countries[1]
  - Has doubled in the last 30 years[2]
  - Almost 1 in 3 MUD allo-HSCT recipients were obese at RAH over last 10 years
- Obesity incidence peaks at age 50-60s, as does median allo-HSCT age

- In SA, rabbit anti-thymocyte globulin (ATG) remains standard of care for GVHD prophylaxis in MUD allo-HSCT

- ATG has always been dosed using mg/kg according to total body weight (TBW)
  - Explicitly acknowledged in 2014 ASTCT obesity position statement as due to an **absence of data** rather than any evidence of efficacy in obesity[3]

1. *Health at a Glance 2025: OECD Indicators* 2025
2. Phelps et al., Lancet 2024
3. Bubalo et al., Biol Blood Marrow Transplant, 2014

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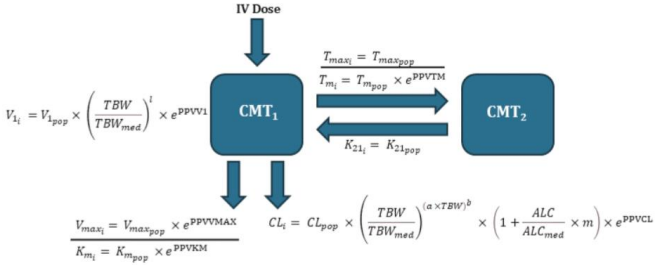
ATG Population Pharmacokinetics

- Active ATG binds to lymphocytes and cleared rapidly via Target Mediated Drug Disposition (TMDD)
- Total ATG cleared slowly via proteolytic degradation in absence of TMDD

- Active Thymoglobulin®:
  - Clearance **1.5–6 L/day** (5–40 times faster than endogenous IgG or total ATG)
  - Apparent volume of distribution usually reported between **12–16 L** (≈ extracellular fluid)



Biris, E et al., CPT: PSP 2026

Physiologically, as a large antibody cleared by TMDD:
- ATG is unlikely to distribute readily into adipose tissue
- ATG CL is unlikely to scale linearly with TBW

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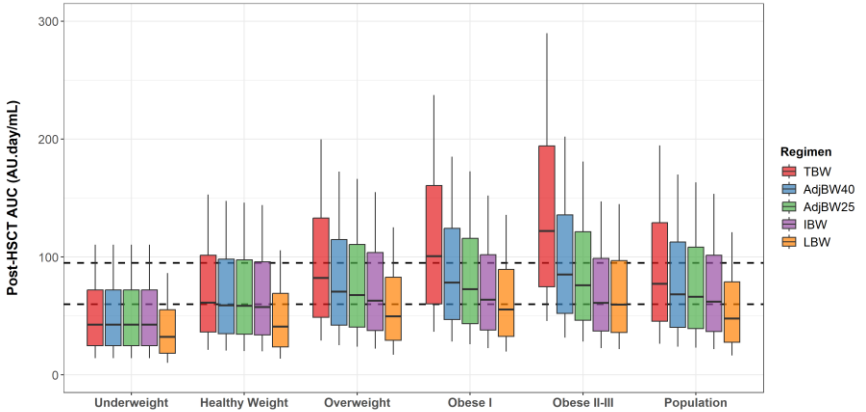
Hypothesis: Total body weight-based dosing of ATG produces systemic overexposure in patients with obesity, delaying immune reconstitution and leading to increased viral reactivation and relapse

Pre-implementation simulation study

- Conducted using a previously published pop pharmacokinetic model[1] of ATG
- 60,000 simulated patients distributed evenly among 5 BMI categories
  Therapeutic exposure window defined as 60-95 AU.day/mL
- Cumulative exposure predicted with 5 different bodyweight descriptors:
  - TBW
  - Adjusted Body Weight 25%, and 40% (AdjBW)
  - Ideal Body Weight (IBW)
  - Lean Body Weight (LBW)

- In obese patients, AdjBW25 provided the most consistent median target attainment



1. Admiraal et al., Lancet Haematol 2017

Biris E, et al. Manuscript under review (2026)

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Study design

- Single-centre, retrospective cohort study of obese individuals (BMI >30 kg/m^2) receiving ATG as part of MUD PBSC allo-HSCT at RAH

- N = 66: 47 TBW-dosed historical controls vs 19 AdjBW25-dosed patients following a statewide unit protocol change in Jan 2024
  - Historical cohort 2017-2023; Experimental cohort 2024-2026
  - No major changes to prophylactic supportive care over this period – CSA + MTX, UDCA, posaconazole, fam/valaciclovir, INH pentamidine/TMP-SMX, twice weekly CMV/EBV NATs

- Hypothesis generating and proof of concept given small sample size
  - Primary endpoints: ALC recovery, viral reactivation incidence (CMV/EBV)
  - Secondary endpoints: PTLD, aGVHD/ cGVHD, OS, RFS

Demographics

Reasonably matched for age, weight, BMI, conditioning intensity, CMV/EBV serostatus

Similar split of myeloid/ lymphoid, but more AML in TBW group, more MDS in AdjBW25 group

Median ATG dose 27% lower in experimental arm (450mg TBW vs 327mg AdjBW25)

Characteristic	TBW (n = 47)	AdjBW25 (n = 19)
ATG dose (mg)	450 (416–488)	327 (300–370)
Age (years)	58 (51–64)	57 (45–62)
Gender, male	24 (51%)	8 (42%)
Weight (kg)	100 (92–108)	103 (97–115)
BMI (kg/m^2)	34.2 (32.3–37.2)	35.5 (33.3–39.2)
ALC, pre-conditioning (×10^9/L)	1.14 (0.70–1.49)	0.95 (0.63–1.58)
HCT-CI	1 (0–3)	2 (1–3)
Conditioning, RIC	40 (85%)	14 (74%)
First allograft	44 (94%)	17 (89%)
CD34+ dose (x10^6/kg)	5.04 (5.00–6.56)	5.00 (5.00–5.01)
Malignancy		
Acute Leukaemia (ALL, AML, AUL)	29 (62%)	9 (47%)
Chronic Myeloid (MDS, MPN, CML)	11 (23%)	9 (47%)
Lymphoid (NHL, CLL)	7 (15%)	1 (5.3%)
CMV serostatus		
R-/D-	12 (26%)	3 (16%)
R-/D+	3 (6.4%)	0 (0%)
R+/D+	21 (45%)	9 (47%)
R+/D-	11 (23%)	7 (37%)
EBV serostatus		
R-/D-	2 (6.5%)	0 (0%)
R+/D-	2 (6.5%)	3 (16%)
R+/D+	25 (81%)	16 (84%)
R-/D+	2 (6.5%)	0 (0%)
Unknown	16	0

Categorical outcomes reported as count (%); continuous variables as median (IQR). *P* calculated using Fisher's exact test and Mann-Whitney U test.

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Clinical outcomes

Nil sig difference in primary endpoints (IR, viral)
- ? descriptive trend for EBV

Mortality and relapse favour AdjBW25 on unadjusted analysis
- However much shorter follow up noted using reverse KM method: median f/up is 1181 vs 518 days (p = 0.008)
- Addressed with 1 year sensitivity analysis

Outcome	TBW (n = 47)	AdjBW25 (n = 19)	p
Follow-up (days)	569 (77–1168)	408 (128–653)	0.2
Survival			
Mortality	27 (57%)	4 (21%)	0.013*
Relapse	17 (36%)	0 (0%)	0.001*
Viral complications			
EBV reactivation	16 (34%)	3 (16%)	0.23
PTLD	10 (21%)	2 (11%)	0.48
CMV reactivation	20 (43%)	9 (47%)	0.79
GVHD			
Any GVHD	20 (43%)	8 (42%)	>0.9
Acute GVHD	13 (28%)	6 (32%)	0.77
Chronic GVHD	9 (19%)	5 (26%)	>0.9
Severe GVHD (III-IV)	4 (9%)	2 (11%)	>0.9
Immune reconstitution			
Time to ALC recovery (days)	76 (51–131)	86 (47–160)	0.80
Time to IS cessation (days)	167 (136–215)	166 (125–215)	>0.9

Categorical outcomes reported as count (%); continuous variables as median (IQR). *P* calculated using Fisher's exact test and Mann-Whitney U test. * indicates $p < 0.05$.

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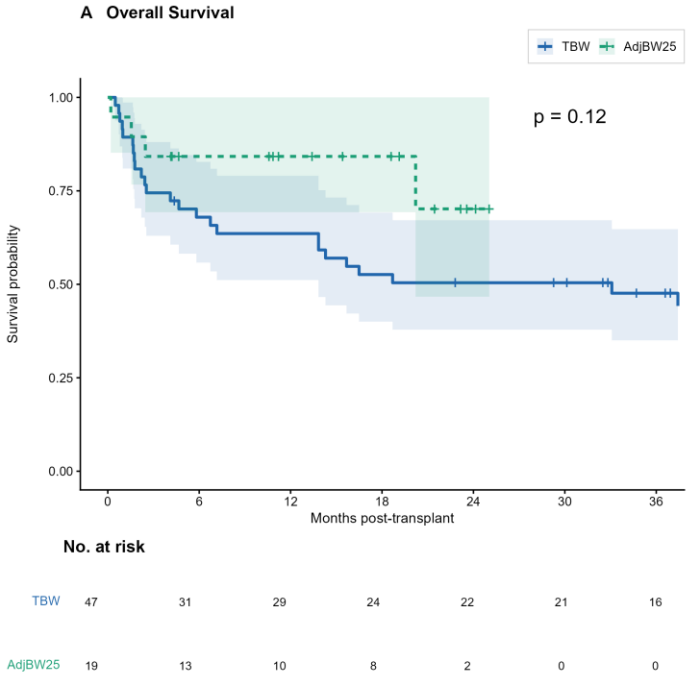
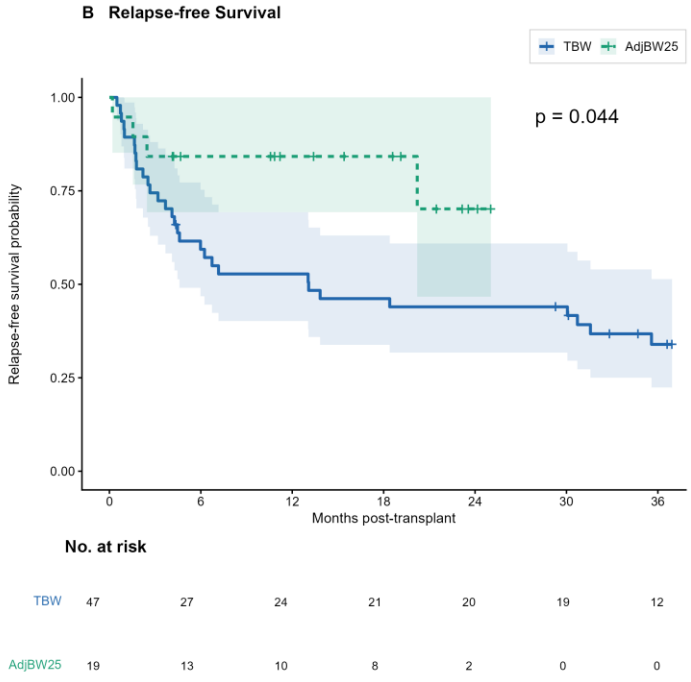
Survival





OS: median OS not reached vs 34 months, log rank *p* = 0.12

RFS: median RFS not reached vs 13 months, log rank *p* = 0.044

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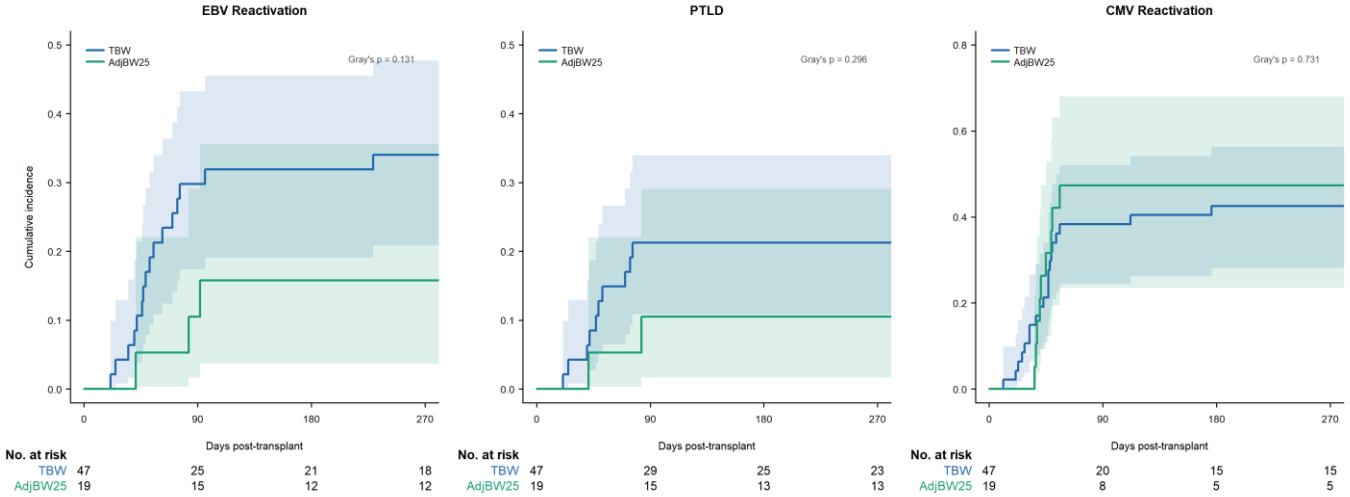
Viral reactivation



Fine-Gray subdistribution hazard ratios adjusted for age and R/D serostatus:

EBV: 0.34 (0.1–1.16, p = 0.085)

CMV: 0.85 (0.4–1.82, p = 0.67)

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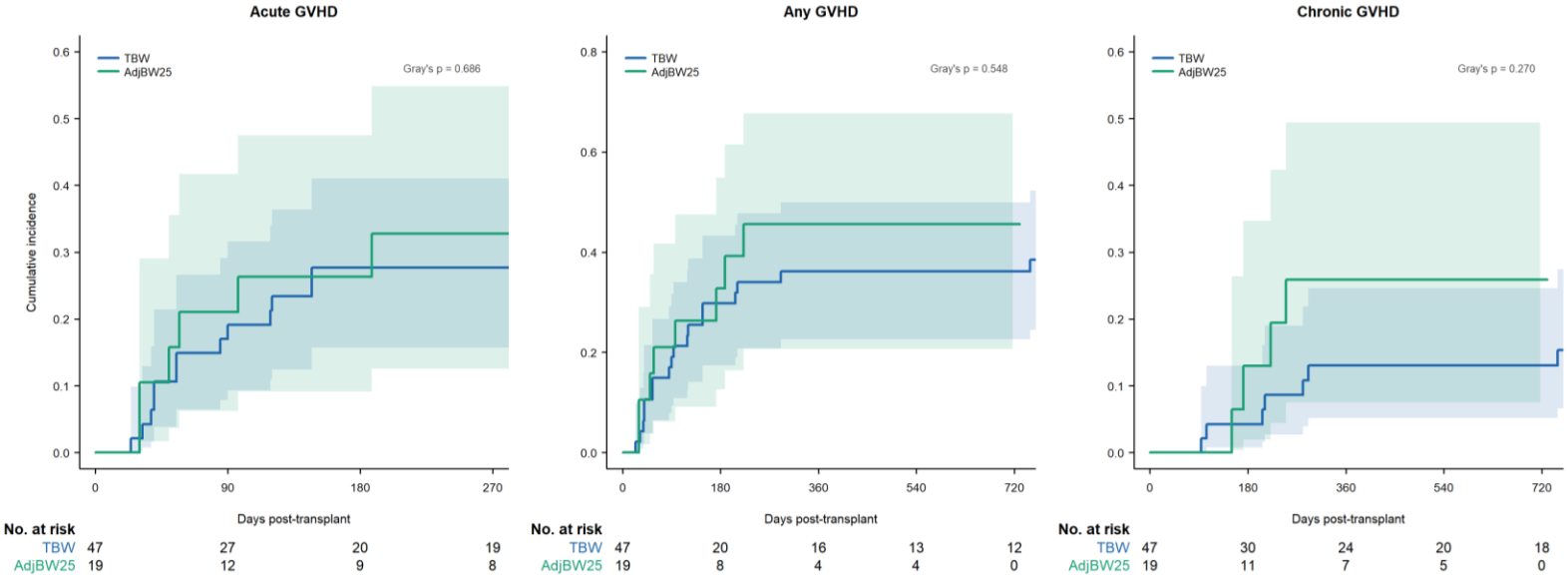
GVHD



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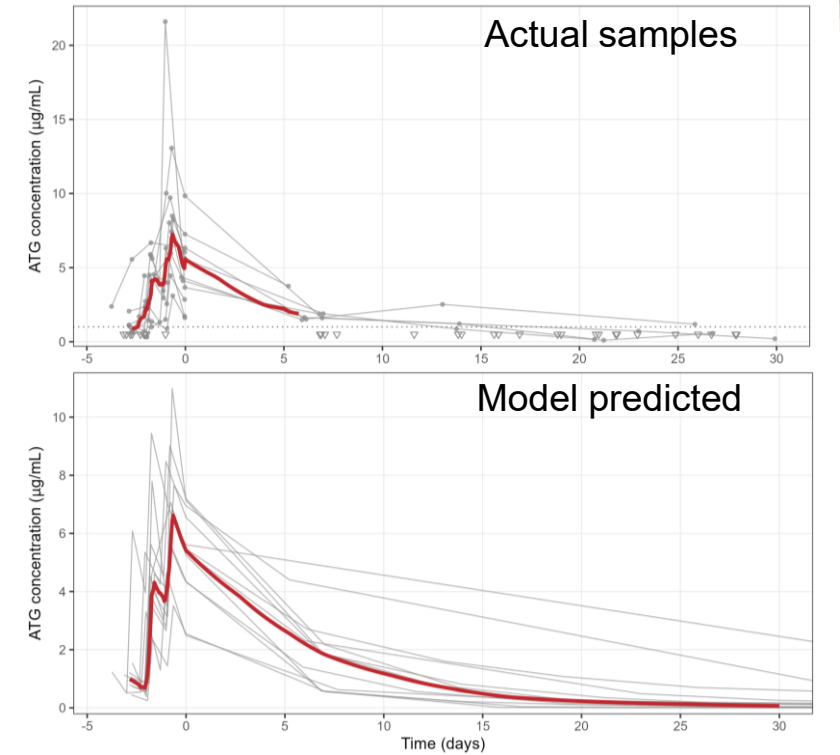
ATG sampling sub-analysis



- 12/19 AdjBW25-dosed patients had plasma samples collected for ATG concentration analysis
  - Median 10 samples per individual (6–12)
- Active ATG measured using a novel liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay
- Median model-fitted post-HSCT exposure (AUC) was 35.6 µg.mL/day (12–89)
  - Substantially lower than therapeutic window
  - 4/11 patients had cleared to <1 µg/mL by D+7
  - All had cleared by D+28

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Cost minimisation

- Median saving of 133mg (6 vials) of Thymoglobulin per dose-adjusted patient ≈ $2500 per patient
- Total cost saving of $50,000 in drug utilisation alone since implementation

Conclusions

- Dose adjustment of ATG in obese individuals may be associated with improved RFS
  - Supports mechanistic framework of ATG PK and simulated findings
  - Present retrospective study limited by small sample size, historical comparators
  - Further studies required -> prospective, multi-centre?

- ATG dosing in allo-HSCT will need to adapt for it to survive in the PTCy era
  - Individualised dosing of ATG utilising drug monitoring, nomogram-based dosing, or dose attenuation in vulnerable cohorts has the potential to substantially improve outcomes

- Future directions
  - Validation of LC-MS/MS active ATG assay – extrapolation with ATGAM, ATLG?
  - Refinement of population pharmacokinetic models to further improve ATG target attainment

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