



14th

International Donor Registry Conference
& WMDA Meetings

25 – 29 June, 2024 – Cape Town, South Africa

All patients & donors matter

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Donor selection in a resource constrained environment



ALBERTS CELLULAR THERAPY

Andrew McDonald



Disclosure

- DKMS -South Africa Board member

Case Study



25-Year-Old
Male
Newly Qualified Doctor

- Epistaxis early March 2024
 - Low Hb & platelets, previously normal FBC in January 2024
 - Treated as presumptive ITP with high dose Medrol (10mg/kg)
- Progressive pancytopenia – referred to us 25th March
 - (V) Severe aplastic anaemia : Neutrophils $0.1 \times 10^9/l$
 - Fanconi Anaemia mutations : Negative
- ATGAM (horse) + ciclosporin + eltrombopag approved
 - But horse ATG was not available, only the less effective rabbit ATG was available

Case Study – family typing

Donor Relation	Sister				Brother	
ABO & Rh	B Rh Positive				B Rh Positive	
DNA Based HLA Typing Postulated Haplotypes	a	b	c	d	a	e
HLA-A*	02:06:01	24:02:01	<u>02:01:01</u>	<u>26:01:01</u>	02:06:01	24:02:01
HLA-B*	35:03:01	07:02:01	07:02:01	<u>08:01:01</u>	35:03:01	<u>51:01:01</u>
HLA-C*	04:01:01	07:02:01	07:02:01	<u>07:02:01</u>	04:01:01	<u>14:02:01</u>
HLA-DRB1*	09:01:02	04:02:01	04:02:01	<u>15:06:01</u>	09:01:02	-
HLA-DQB1*	03:02:01	-	03:02:01	<u>05:02:01</u>	03:02:01	-
HLA-DRB4*	01:03:02	01:03:01	01:03:01		01:03:02	
HLA-DRB5*	-		01:01:01		-	
HLA-DPA1*	-	01:03:01	01:03:01	02:01:01	01:03:01	02:01:01
HLA-DPB1*	04:02:01	105:01:01	105:01:01	26:01:02	04:02:01	10:01:01
HLA-DQA1*	03:02:01	03:01:01	03:01:01	01:02:01	03:02:01	03:02:01
Ambiguity	-		-		-	

Brother - Haploidentical
CMV D-/R+
ABO match
No DSA (Luminex)

A Locus Specificity Grade MFI
No Class I HLA-A Antibodies detected

B Locus Specificity
B*15:16/B63 3467
B*46:01 2189

C Locus Specificity
C*03:02/Cw10 1514

HLA Class II Single Antigen Antibody Identification

Panel reactive antibody class II 1 %

DQB1 Locus Specificity Grade MFI
DQB1*04:01 1236

DRB1 Locus Specificity
No Class II HLA-DRB1 antibodies detected

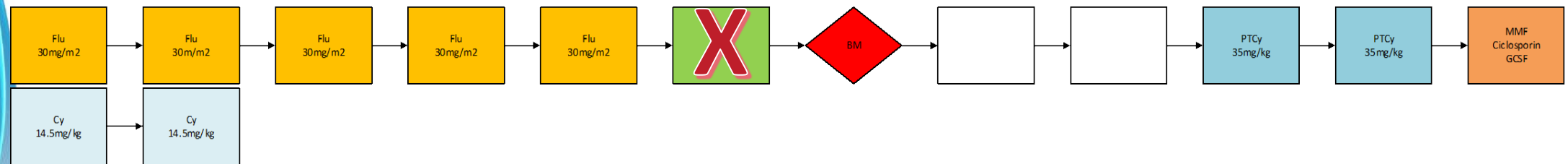
DPB1 Locus Specificity
No Class II HLA-DPB1 antibodies detected

Case Study – UD search

Probability of Mismatches ⓘ	A	B	C	DRB1	DQB1	DPB1	Registry	Sex	Age	Blood group	
Patient details											
	02:06:01 24:02:01	35:03:01 07:02:01	04:01:01 07:02:01	09:01:02 04:02:01		04:02:01 105:01:01					
7/8 (potential) allele matches											
# 5	GRID: 5285000000415997316 Status: RS CMV: G 2023-08-23 No. of donations: 0 Ethnicity:										Full report
0: 0%	A	A	A	L	P	Pe	5285 ✓ <u>SE-Tobias</u>	Female	22	O+	☆
1: 100%	-	-	-	-	-	-					
2: 0%	02:06:01G 24:02:01G	07:02:01G 35:03:01G	04:01:01G 07:02:01G	(04:04:01G) 09:01:02G	03:02:01G 03:03:02G	(02:01:02G) (04:01:01G)					
# 6	GRID: 6354000000316722725 Status: AV CMV: No. of donations: Ethnicity: ASSO										Full report
0: 0%	L	A	A	A	P	A	6354 ✓ <u>GB-ANT</u>	Female	26		☆
1: 100%	-	-	-	-	-	-					
2: 0%	(02:ANGA) 24:WYU	07:TDVB 35:03:01	04:BSUG 07:02:01	04:02:01 09:CTZ	03:YGKM	04:FNV5					
# 7	GRID: 3553000017372183815 Status: AV CMV: No. of donations: Ethnicity: AS										Full report
0: 0%	M	A	A	A	P	A	3553 ✓ <u>US-NMDP</u>	Male	26	B+	☆
1: 100%	-	-	-	-	-	-					
2: 0%	24:02:01:01 (24:02:01:02L)	07:02:01 35:03:01	04:01:01:01 07:02:01:03	04:02:01 09:CTZ	03:02:01 03:02:01	04:02:01:02 105:01					
# 8	GRID: 5285000000318349622 Status: AV CMV: O 2020-11-19 No. of donations: 0 Ethnicity:										Full report
0: 0%	A	A	A	M	P	Pe	5285 ✓ <u>SE-Tobias</u>	Male	29	B-	☆
1: 100%	-	-	-	-	-	-					
2: 0%	02:06:01G 24:02:01G	07:02:01G 35:03:01G	04:01:01G 07:02:01G	09:01:02G (15:01:01G)	03:03:02G 06:02:01G	(04:01:01G) (23:01:01G)					
# 9	GRID: 5081DKM000002241828 Status: AV CMV: No. of donations: Ethnicity: MX										Full report
0: 0%	M	P	A	A	P	Pe	3553 ✓ <u>US-NMDP</u>	Male	38		☆
1: 100%	-	-	-	-	-	-					
2: 0%	(03:BJZPD) 24:BZBB	07:ARUHS 35:BMD	04:KBG 07:02	04:02 09:01:02	03:YGKM 03:ABGFU	(02:AEMGJ) (02:AEMGJ)					

Case Study

- Decision to proceed with urgency : Haploidentical from brother
 - Pre-conditioning: Started within 8 weeks from presentation
 - Standard: Baltimore
 - BM harvest (GCSF stimulated)
 - $2.69 \times 10^6/\text{kg}$ CD34



- Micro-abscesses liver/spleen
 - Fungal biomarkers initially negative, later B-D-glucan >523 pg/ml
 - Started on liposomal amphotericin B 3 weeks prior to precondition start
 - 3 x granulocyte transfusions

Case Study

- Post Tx infectious complications
 - XDR *Ps. aeruginosa* pneumonia
 - Trichosporon fungaemia (on liposomal ampho-B)
- Died D+10 post transplant

Resource
Constrained : **YES**

Registry option for
donor choice

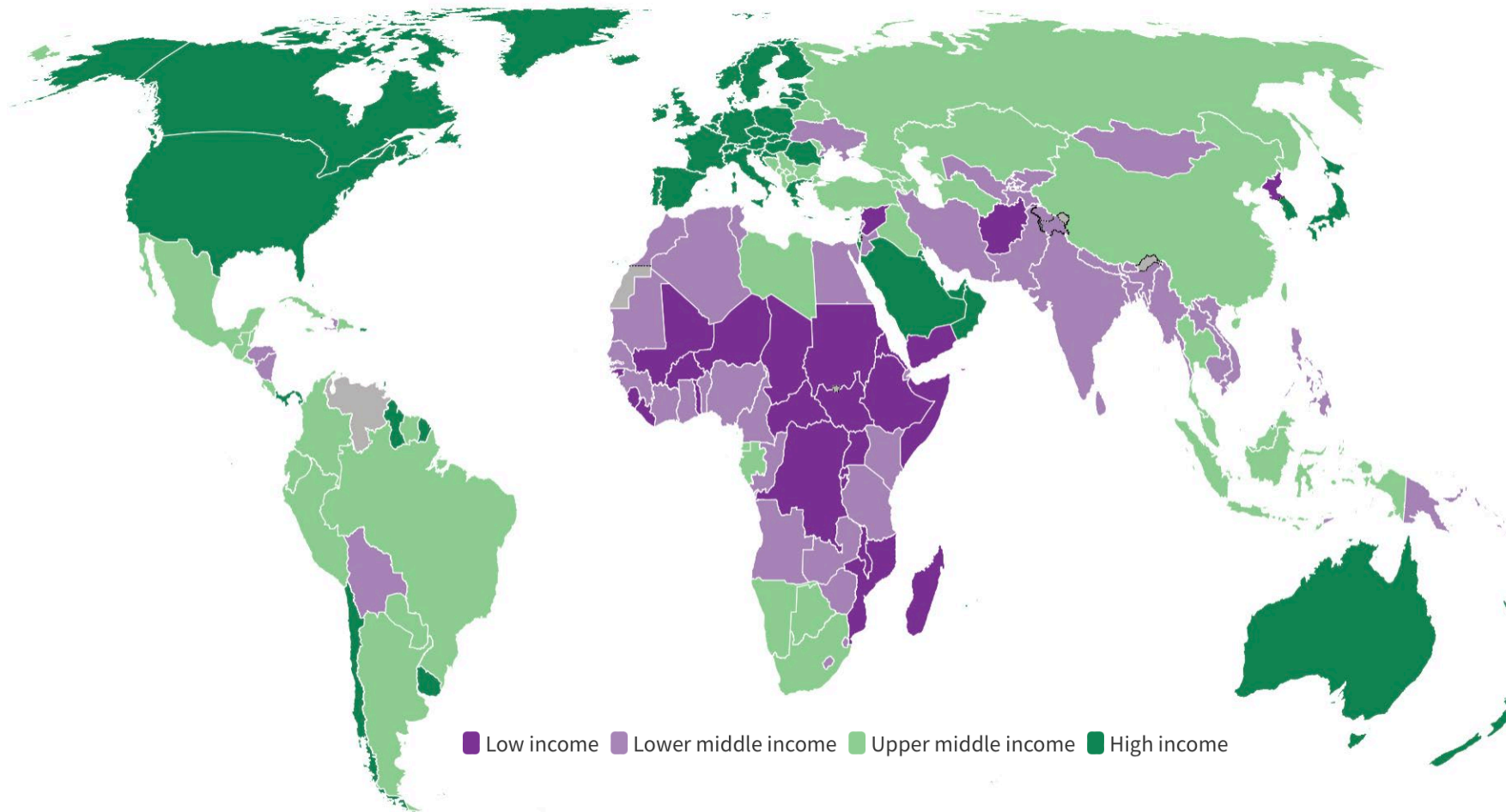
Resource
Constrained : **NO**

Liposomal Ampho-B

BM Stem cell source

Granulocyte
transfusions

Global Income

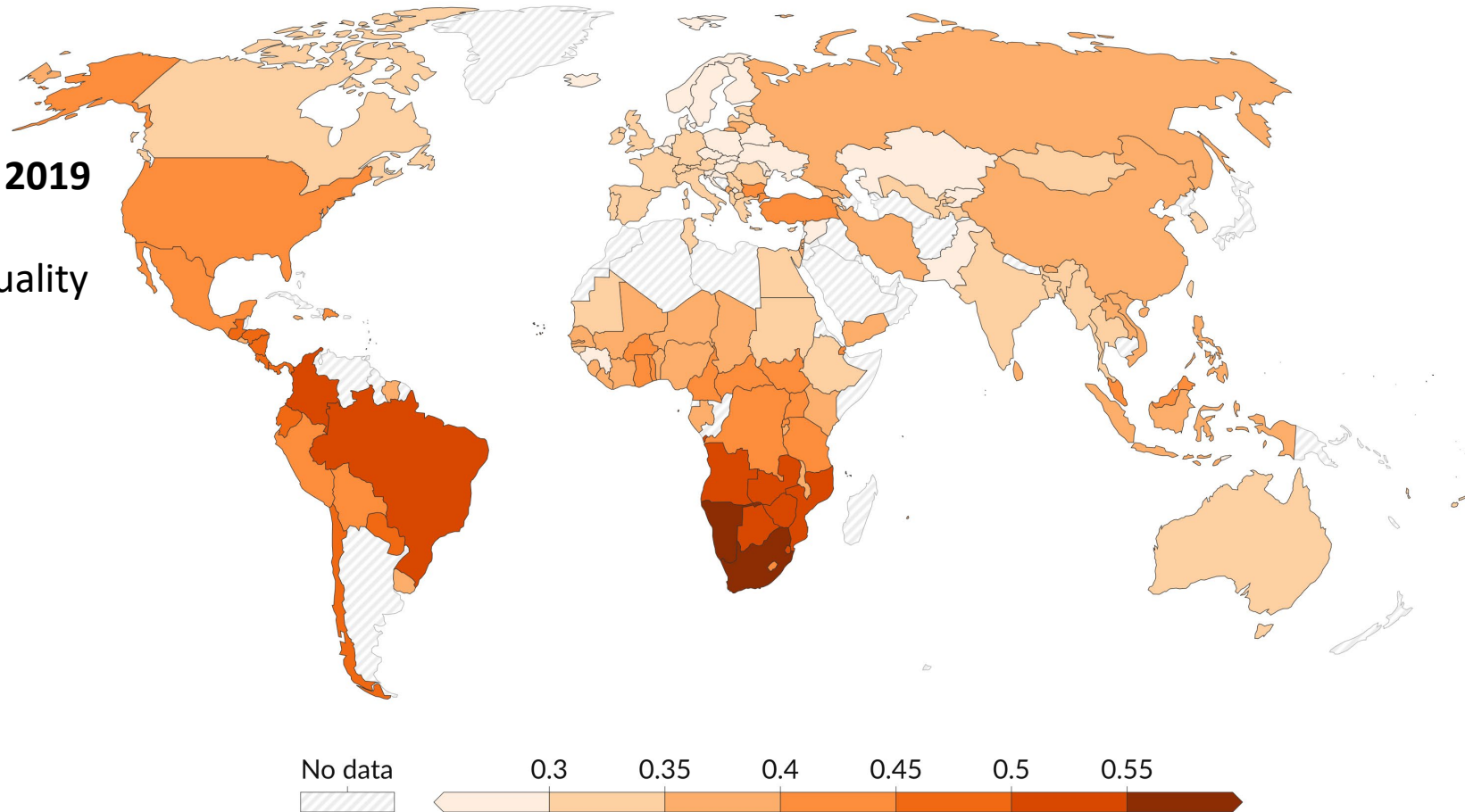


Zuhair M et al.. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. Rev Med Virol. 2019 May;29(3):e2034

Global Inequality

Income inequality: Gini coefficient 2019

The Gini Coefficient measures inequality on a scale of 0 to 1. Higher values indicate higher inequality.



Transplant Rates




2022
1668 transplants
890 allo
77/10 million population
Higher paediatric transplant
cf to SA

2022
386 (360 new) transplants
122 allo
64/10 million population

Passweg, J.R. et al. Hematopoietic cell transplantation and cellular therapies in Europe 2022. CAR-T activity continues to grow; transplant activity has slowed: a report from the EBMT. *Bone Marrow Transplant* 59, 803–812 (2024)

Simione, A. J et al. CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: BRAZILIAN SUMMARY SLIDES - 2023. *JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY*, 4(2), 200

Factors Influencing Outcome

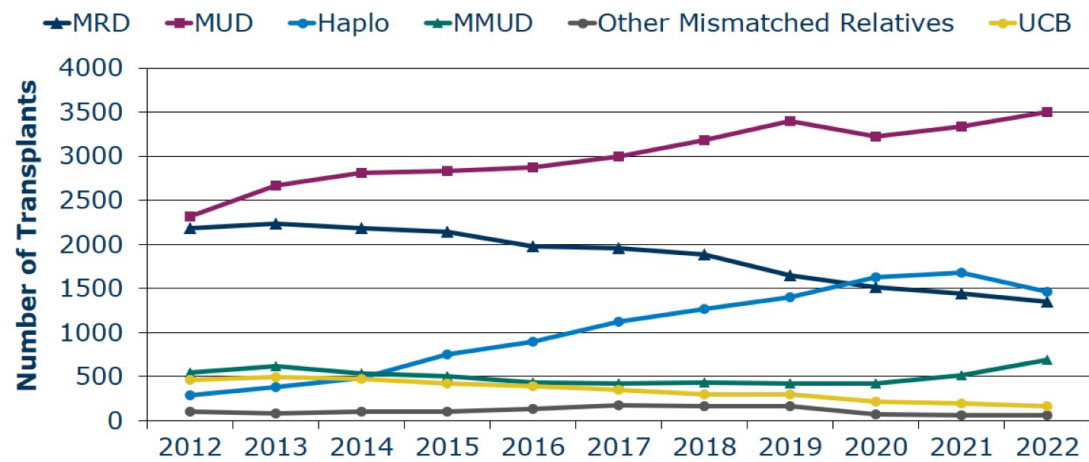
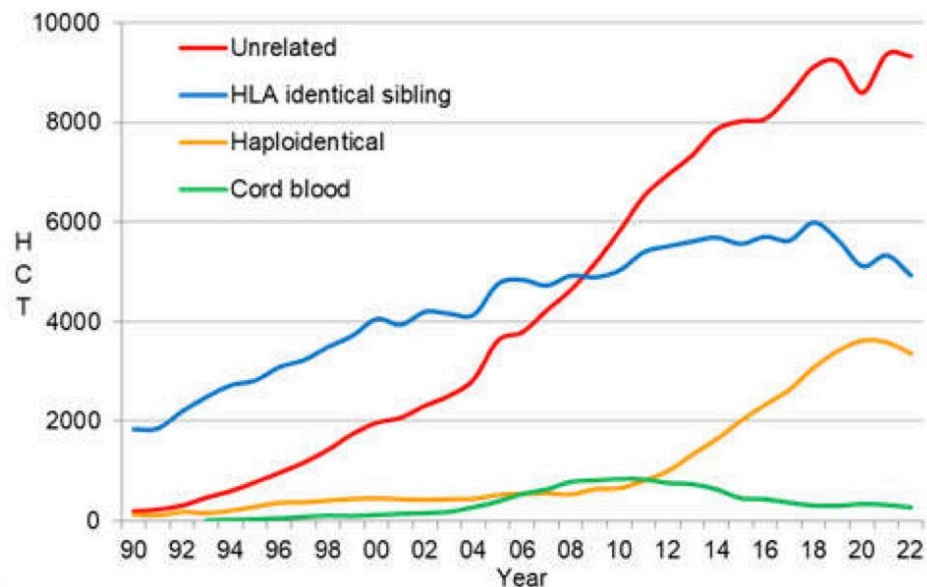


Patient	<ul style="list-style-type: none">• Age, Comorbid, CMV, ABO, PS• HLA antibodies• Disease / status
Preconditioning	<ul style="list-style-type: none">• RIC vs MAC• GVHD prevention
Supportive Care	<ul style="list-style-type: none">• CMV• Other
Donor	<ul style="list-style-type: none">• Age• HLA match, ABO match

EBMT Benchmark Statistics

INDICATOR		EBMT	ACT Pretoria
Patient CMV serostatus		66.3% +ve	76% +ve
Donor CMV serostatus		55.3% +ve	63.7% +ve
Donor age [median (Q1-Q3)]		31.4 (23.7-43.0)	36.5 (25.7-49.4)
Donor type	MRD	28.7%	38.1%
	MMRD	18.4%	35.8%
	UD	52.9%	26.1%
Stem cell source	BM	17.1%	1.1%
	PM	78.5%	98.9%
	CB	1.9%	0%

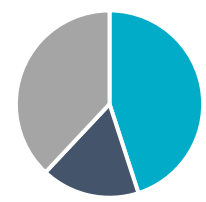
Transplant Activity



Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; Haplo, ≥ 2 HLA antigen mismatch; MMUD, mismatched unrelated donor $\leq 7/8$ HLA allele match; UCB, umbilical cord blood

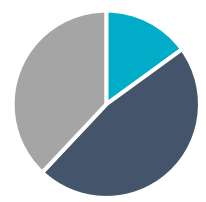
CIBMTR.org

Transplant% 2015



■ Haplo ■ UD ■ RD ■

Transplant% 2022



■ Haplo ■ UD ■ RD ■

ACT

Passweg, J.R. et al. Hematopoietic cell transplantation and cellular therapies in Europe 2022. CAR-T activity continues to grow; transplant activity has slowed: a report from the EBMT. Bone Marrow Transplant 59, 803–812 (2024)
 Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. CIBMTR Patient-Reported Outcomes Data
 ACT unpublished



Key Donor Challenges in a Resource Constrained Setting

- Funding:

- Insurance - Donor related
 - no donor funds
 - funding chosen donor only
 - fixed maximum fee / limit to international donor procurement
 - fully funded search and procurement
- Insurance – Patient related
 - Preconditioning / GVHD prophylaxis / supportive care may impact donor choice

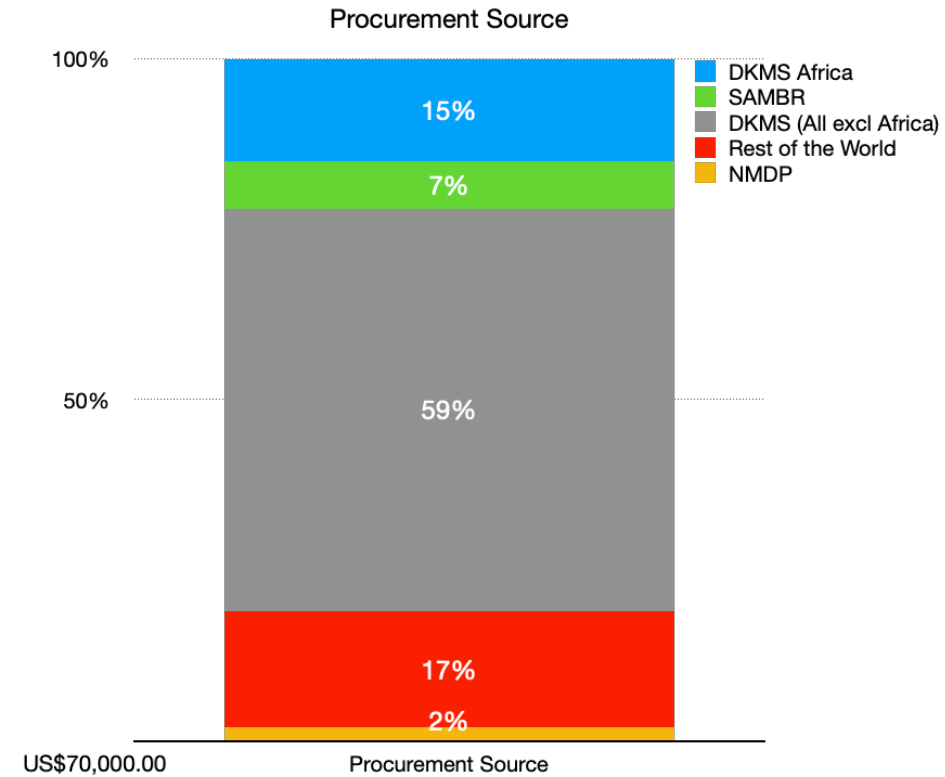
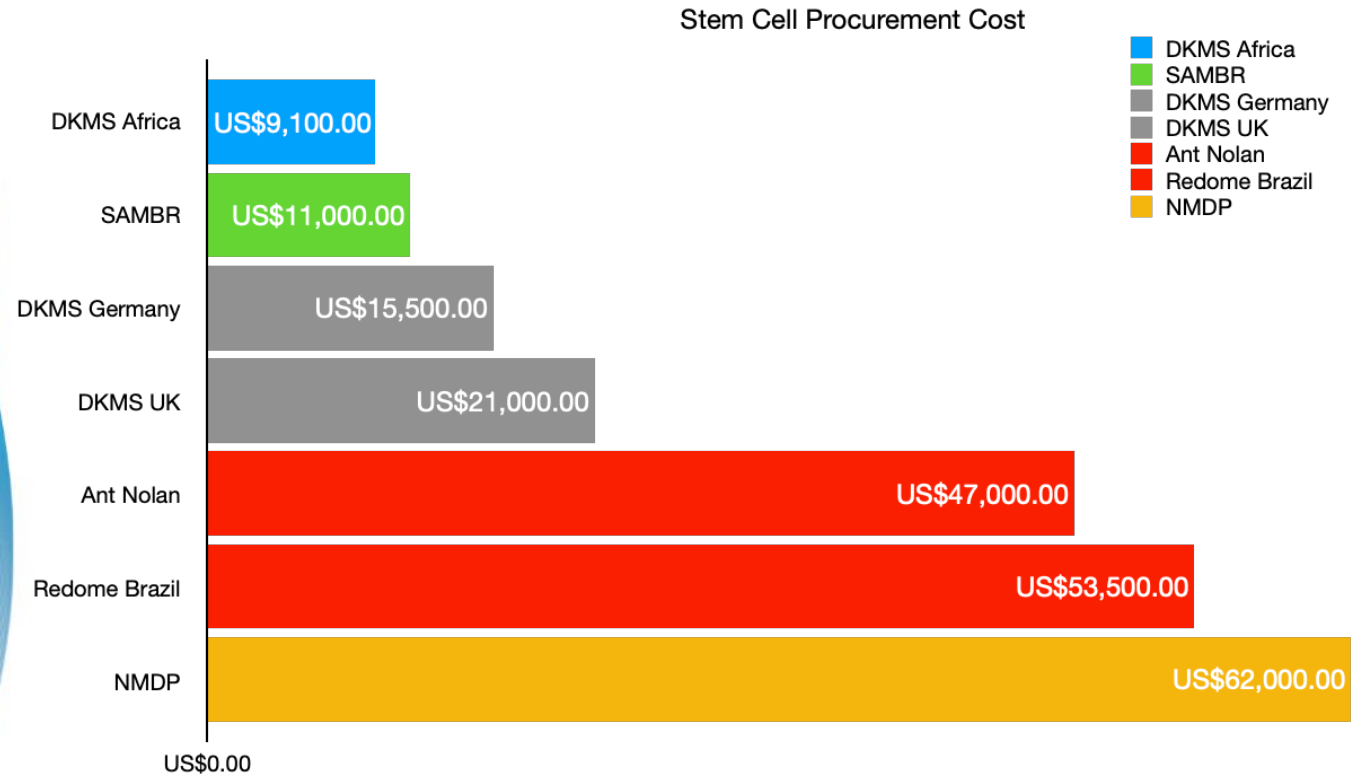
- Family Structure:

- One Child Policy
- Migrant Labour
- Polygamy

- CMV seropositivity rates

- Registry size, diversity & donor availability

Stem Cell Procurement Cost

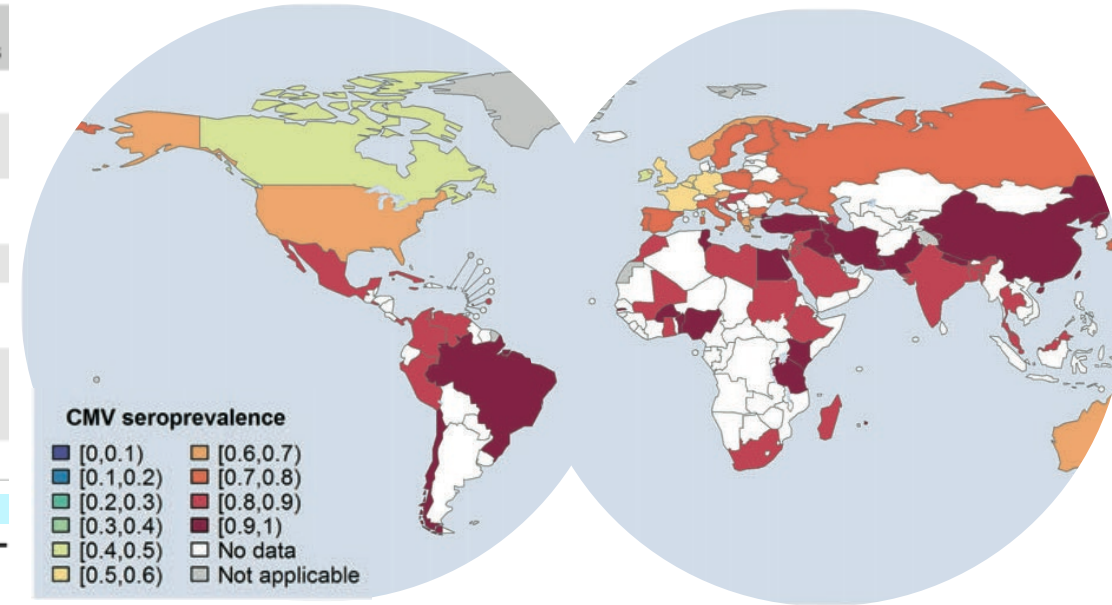


DKMS-Africa procurement invoices - unpublished

CMV Seroprevalence

Estimated cytomegalovirus means seroprevalence % and corresponding 95% uncertainty interval in the different WHO regions and global population group.

Regions	General Population	Women of Reproductive Age	Blood and Organ Donors
European region	66 (56-74)	70 (63-76)	69 (61-77)
Region of the Americas	75 (64-84)	79 (69-87)	78 (67-87)
South-east Asian region	86 (77-93)	89 (82-94)	88 (81-94)
African region	88 (80-93)	90 (85-94)	90 (84-94)
Western Pacific region	88 (81-93)	91 (86-94)	90 (85-94)
Eastern Mediterranean region	90 (85-94)	92 (88-95)	92 (87-95)
Global	83 (78-88)	86 (83-89)	86 (82-89)



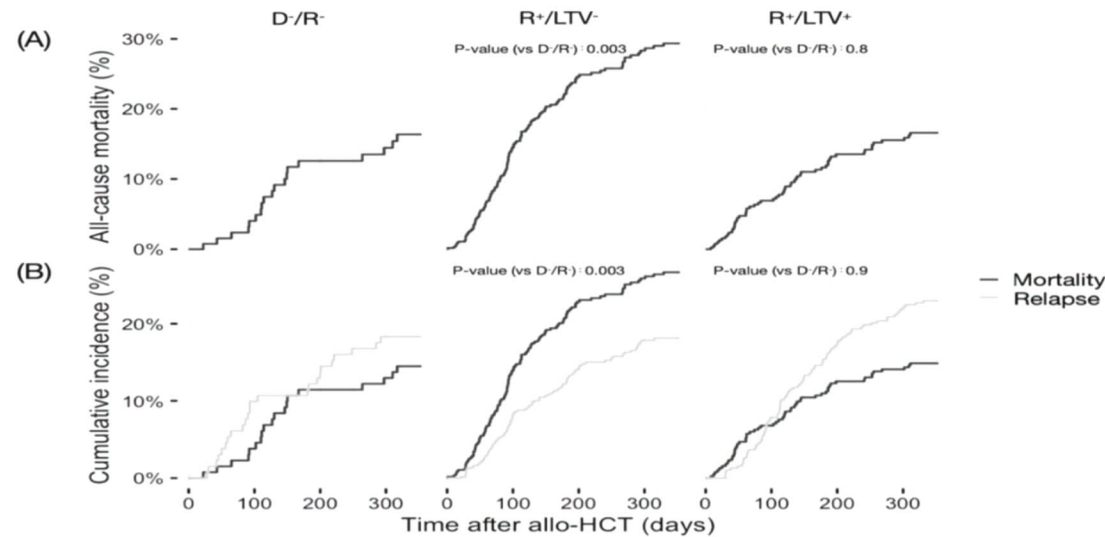
CMV serostatus	PFS	OS	NRM	RI	aGvHD	cGvHD
D-CMV ⁻ /R-CMV ⁻	52 (50-55)	65 (63-68)	21 (20-23)	26 (24-28)	30 (28-32)	47 (45-49)
D-CMV ⁺ /R-CMV ⁻	50 (47-54)	65 (61-68)	21 (18-24)	29 (26-32)	29 (26-32)	48 (44-51)
D-CMV ⁻ /R-CMV ⁺	48 (45-51)	59 (56-61)	26 (24-28)	26 (24-29)	31 (29-33)	44 (42-47)
D-CMV ⁺ /R-CMV ⁺	50 (48-52)	64 (62-66)	23 (21-24)	27 (25-29)	28 (26-30)	47 (45-49)
P	0.06	0.001	0.02	0.45	0.08	0.30
D-CMV ⁻ /R-CMV ⁻	52 (50-55)	65 (63-68)	21 (20-23)	26 (24-28)	30 (28-32)	47 (45-49)
Other combination	50 (48-51)	62 (61-64)	23 (22-25)	27 (26-29)	29 (28-30)	46 (45-48)
P	0.03	0.01	0.16	0.40	0.29	0.59

CMV cytomegalovirus, D-CMV donor CMV serostatus, R-CMV recipient CMV serostatus, - seronegativity, + seropositivity, PFS progression-free survival, OS overall survival, NRM non-relapse mortality, RI relapse incidence, aGvHD acute graft-vs.-host disease, cGvHD chronic graft-vs.-host disease

Zuhair M, Smit GSA, Wallis G, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. *Rev Med Virol.* 2019; 29:e2034
Cus

CMV Seroprevalence and impact

(A) All-cause mortality and (B) cumulative incidence of NRM with competing incidence of relapse are demonstrated.



allo-HCT, Allogeneic Hematopoietic Stem-Cell Transplantation; D-/R-: donor and recipient both cytomegalovirus (CMV) seronegative; NRM, Non-Relapse Mortality; R+/LTV-: CMV-seropositive recipient did not receive letermovir as primary prophylaxis after transplant; R+/LTV+: CMV-seropositive recipient received letermovir as primary prophylaxis after transplant.

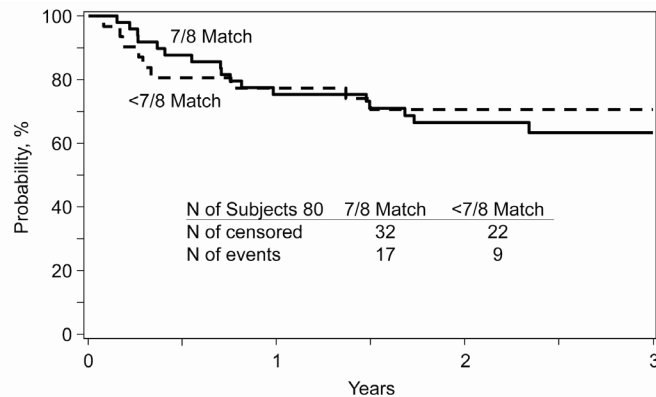
Adapted from *Febres-Aldana A, Chemaly R et al. Clin Microbiol Infect. 2024 Mar 7;51198-743X(24)00113-7*

- Letermovir:
 - Converts CMV R+ to effective CMV R- status
 - At cost 10x valacyclovir / ganciclovir prophylaxis

- Not feasible in low cost settings

PTCY – a leveller?

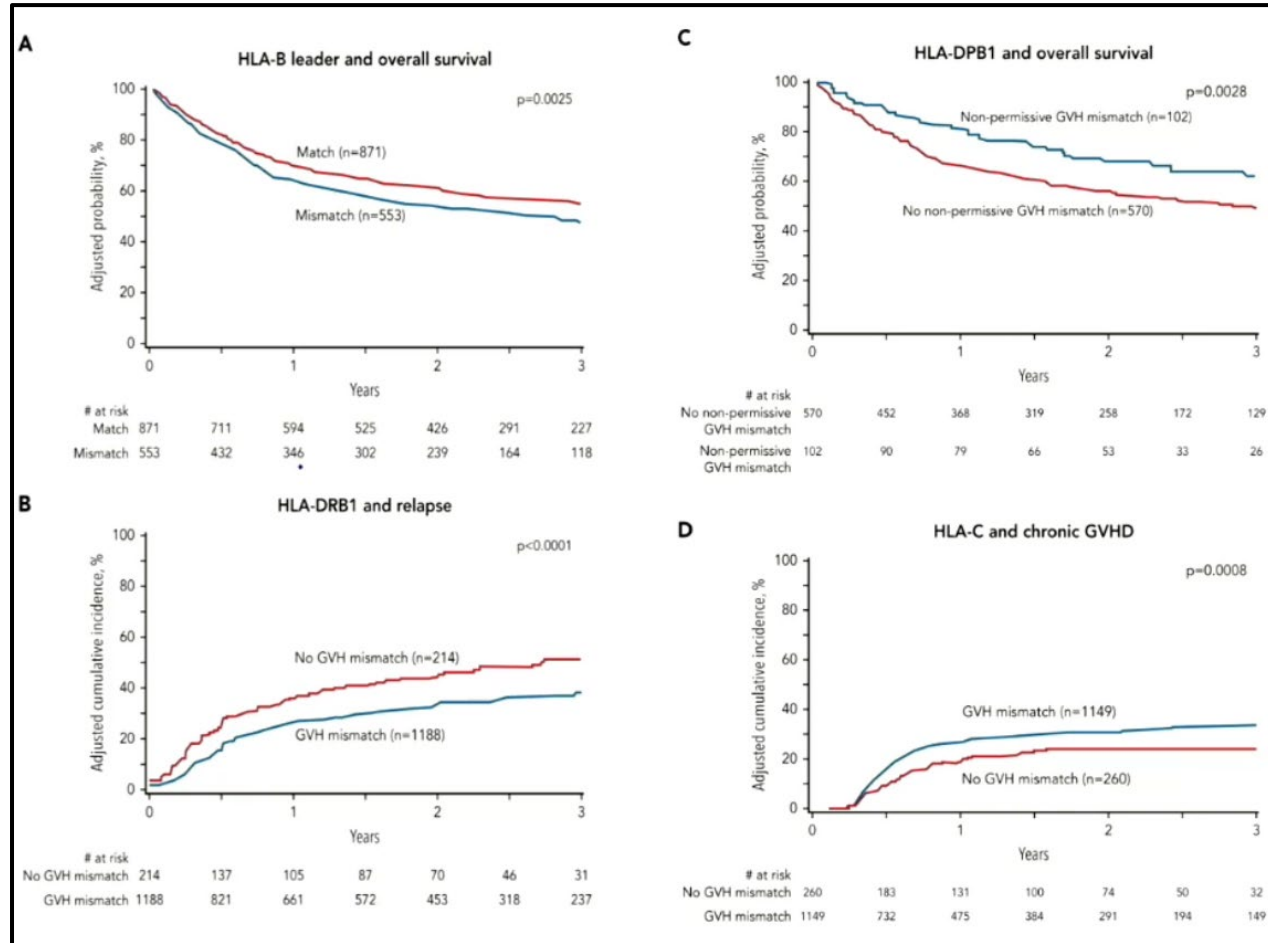
- Previous data indicates poorer outcomes with HLA mismatches
- African less like to find full matched unrelated donors
 - Higher use of haplo-identical donors
- Post transplant cyclophosphamide cheap and accessible



- Effective in mismatched HLA transplants
- Increase access for UD without OS loss
- CTN1703, ACCESS, MMUD studies

Shaw BE, et al. Three-Year Outcomes in Recipients of Mismatched Unrelated Bone Marrow Donor Transplants Using Post-Transplantation Cyclophosphamide: Follow-Up from a National Marrow Donor Program-Sponsored Prospective Clinical Trial. *Transplant Cell Ther.* 2023 Mar;29(3):208.e1-208.e6

PTCY – a leveller?



1453 AL/MDS transplants reported to CIBMTR
 Class I mismatches worsen outcome
 Class II mismatches improve outcome

PTCY issues

- Longer engraftment time = prolonged bed utilization
- Increased bacterial infections
- Haemorrhagic cystitis – BKV/adenovirus/acrolein
- Potential cardiac morbidity

- Decreased PTCY dose
 - 35-40mg/kg D3,4 vs 25mg/kg D3,4

Antigen and DS A

WHITE	
A*02:01g	26.31%
A*03:01g	15.61%
A*01:01g	15.07%
A*24:02g	8.90%
A*11:01g	5.89%
71.78%	

COLOURED	
A*02:01g	11.51%
A*24:02g	8.85%
A*01:01g	8.27%
A*03:01g	7.95%
A*11:01g	6.96%
43.54%	

INDIAN/ASIAN	
A*11:01g	15.57%
A*24:02g	14.59%
A*01:01g	14.09%
A*33:03g	9.86%
A*02:11g	8.25%
62.37%	

BLACK	
A*30:01g	10.08%
A*23:01g	9.49%
A*30:02g	8.45%
A*68:02g	7.98%
A*29:02g	6.81%
42.81%	

WHITE

~C*07:01g

(f=6.4%)

COLOURED

~C*07:01g

(f=1.9%)

INDIAN/ASIAN

(f=3.4%)

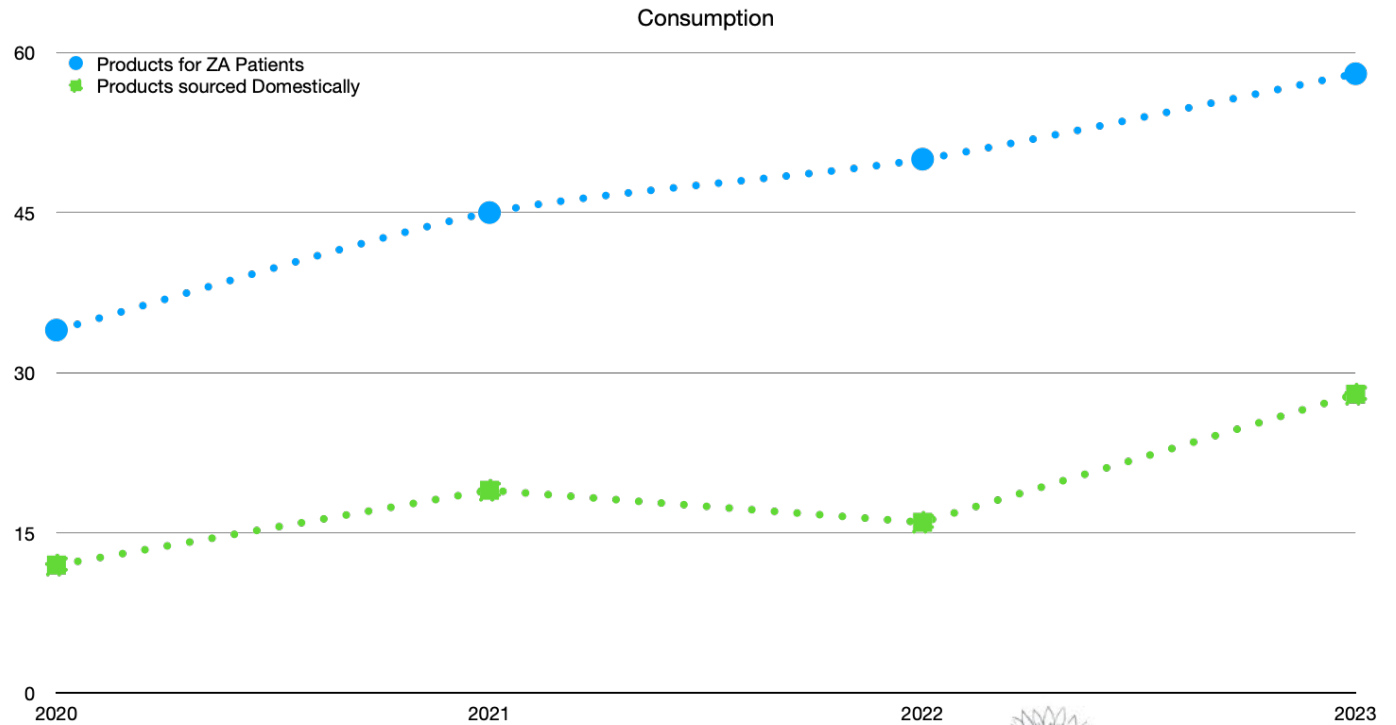
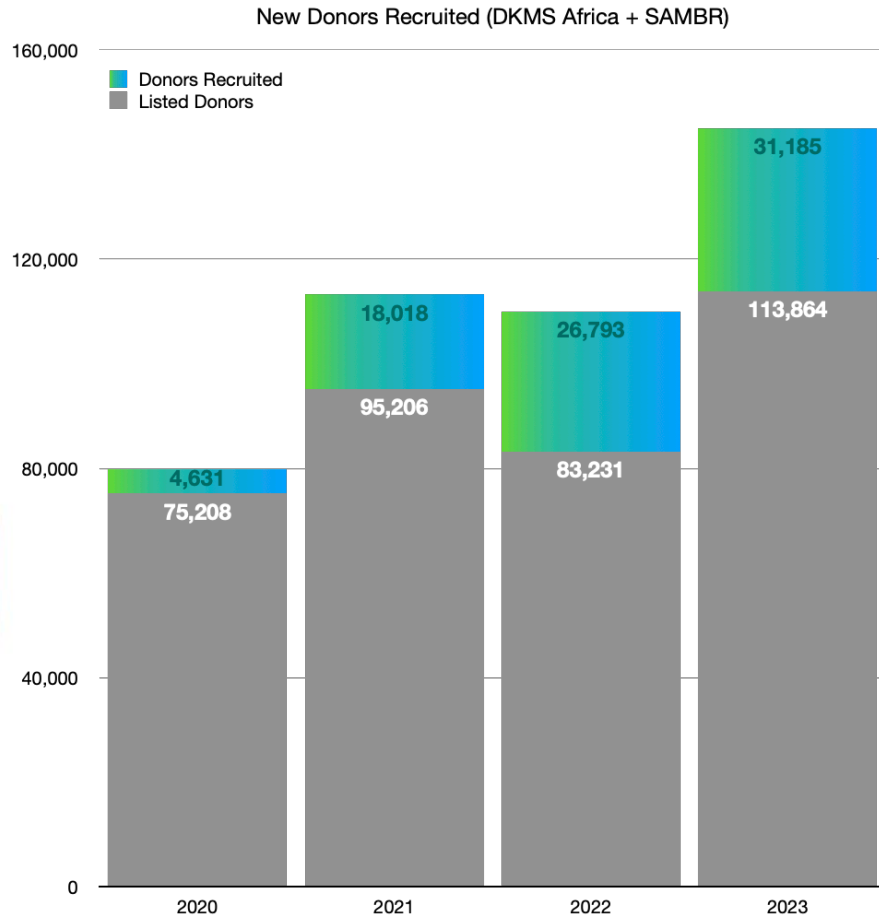
BLACK

(f=3.5%)

Alleles in red is not present in LABScreen™ Luminex Panel

South Africa:

donor recruitment and stem cell utilisation



Strategies to improve (allo) transplant rates

DONOR POOL:

- Increase donor numbers, diversity and availability
- Use of HIV positive donors?

FINANCIAL:

- Inclusive patient and (n) donor testing on one invoice
- Free donor and family testing
 - Including international based family members
- Procurement process starting prior to funding authorisation
- Foundation – funds for:
 - Stem cell procurement (part or full) for indigent patients
 - Transplant procedure

Conclusions

“give us the serenity to accept what cannot be changed,
the courage to change what can be changed,
and the wisdom to know the one from the other”

R Niebuhr 1930's

Thank you.



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All patients & donors matter
www.saphonewest.co.za