Liver transplantation from HIV positive donors to HIV negative recipients: A World First

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MEDICLINIC

Introduction

Solid organ transplantation is the best therapeutic option for those in end stage liver disease

The pool of human donors fails to meet the requirements of an increasing demand for organs

Efforts to increase the donor pool include donation after cardiac death, use of extended or marginal organs, living donor programs and split liver transplantation

Global activity in organ transplantation

Estimations 2020

Kidney	Liver	Heart	Lung	Pancreas	S. bowel
80 926	32 586	8 101	5 940	1 970	158

≈ 129 681 solid organ transplants

≈ 17.6% decrease vs 2019

≤ 10% of global needs

32 % living kidney transplants

20% living liver transplants

36 100 deceased donors (27 934 DBD and 8 166 DCD donors)

-17.6%
In 2020

Information of 93 Member States on organ transplantation activities (80.4 % of the global population)

Table 2 **Criteria and rates of split liver transplantation in different transplant programs according to the transplant programs homepages.**

Program	Rate of SLT	Donor age	Weight/BMI	Transaminases	Other criteria
UNOS	1%-4% (but according to UNOS criteria > 10% eligible)	< 40	< 28 kg/m^2	< 3 × ULN	Single vasopressor
ET	6%	< 50	> 50 kg		
United Kingdom	10.6%	< 40	> 50 kg		< 5 d ICU
Argentina/Brazil	10%	< 47	umbilical perimeter < 92 cm	AST < 42 U/L ALT < 29 U/L	
Oceania	6%				
Scandia-transplant	?	< 51	< 26 kg/m^2	ALT/AST < 3 × normal	< 4 d ICU
Saudi-Arabia	5.6%				
South Africa	3%				
Japan	1.8%				
Italy	8% (Northern Italy: 20%)	< 60		Near-normal liver function tests	< 5 d ICU Low inotropic support

ALT: Alanine transaminase; AST: Aspartate aminotransferase; ET: Eurotransplant; ICU: Intensive care unit; SLT: Split liver transplantation.

Efforts to increase the donor pool include donation after cardiac death, use of extended or marginal organs, **living donor programs** and split liver transplantation

Living donor program commenced at WDGMC in 2013: only program in sub-Saharan Africa

Our RLD statistics

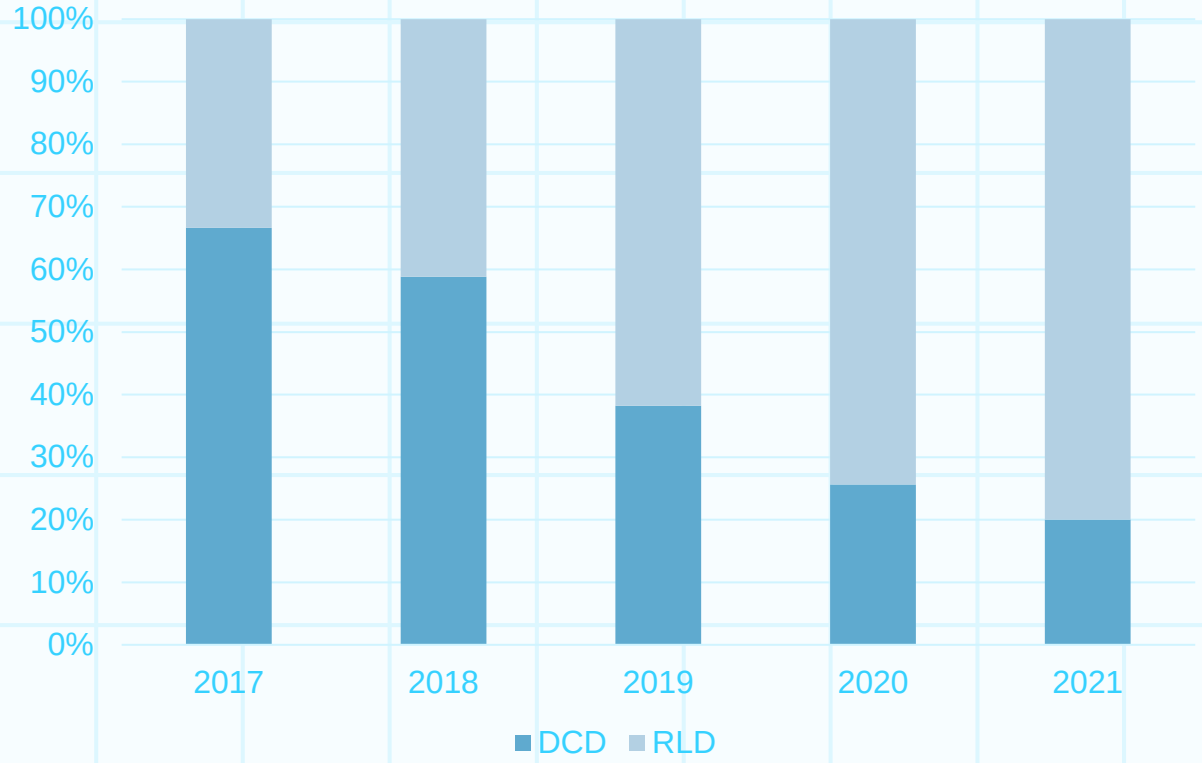


Table 7: Paediatric Liver Transplant Candidates on the Waiting List

	2017
Patients at start of year	18
Patients added during year	44
Patients removed during year	41
Patients at end of year	21
Reason for removal from waiting list	
Transferred to another centre	
Moved into adult transplant category	
Deceased donor transplant	14
Living donor transplant	8
Patient died	14
Transplanted at another centre	
Too sick for transplant	
Improved, transplant not needed	
Nutritional failure	2
Other	3

Waitlist Mortality

15-20%

Limited Donor pool

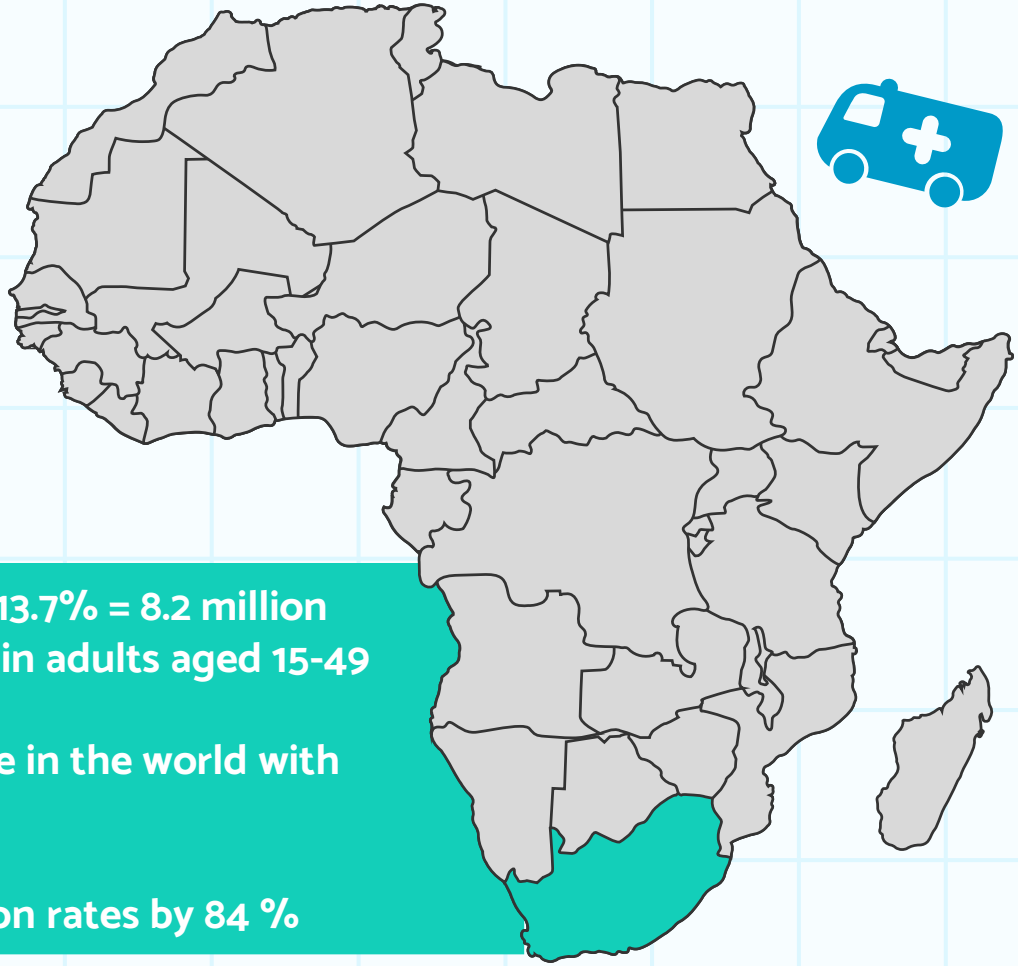
Size match discrepancy

HIV negative children born to HIV + mothers with RLD being the best chance of success

“Why does being HIV positive mean I cant be a donor?”

—**Worried Mother**

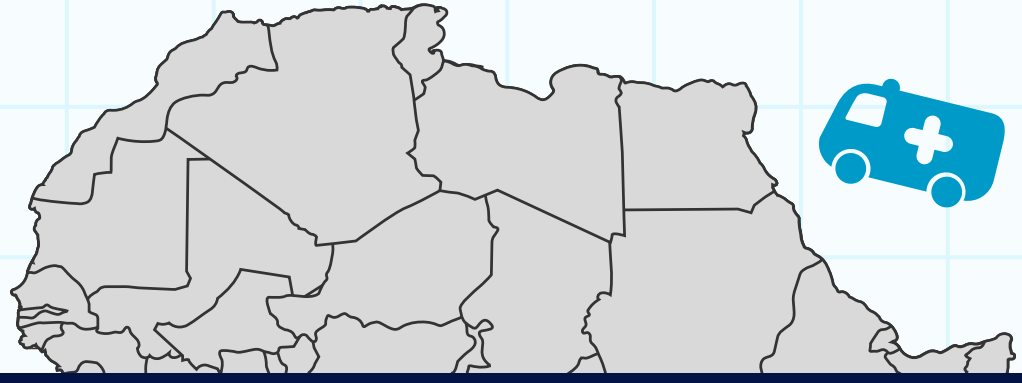
HIV IN SOUTH AFRICA



Highest prevalence of HIV of 13.7% = 8.2 million people living with HIV ; 19.5% in adults aged 15-49

Largest treatment programme in the world with 4.4 million people on ART

PMTC has reduced transmission rates by 84 %



POOL OF HEALTHY YOUNG PARENTS LIVING WITH WELL CONTROLLED HIV WITH HIV NEGATIVE CHILDREN

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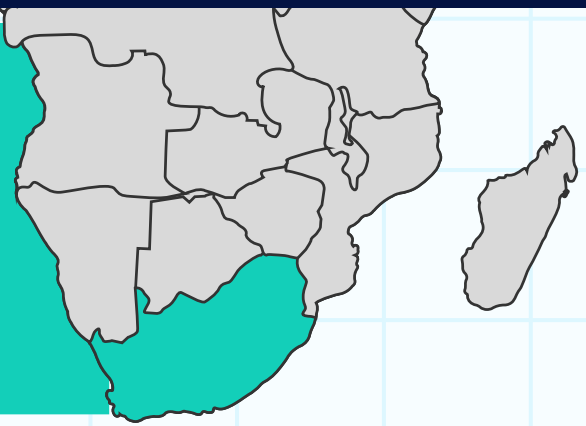
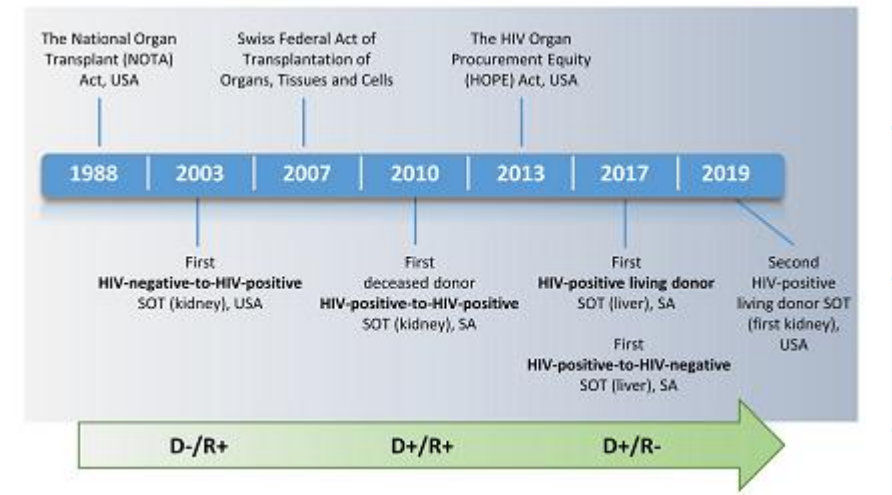


History of HIV in transplant



1988
Organ transplantation to HIV infected individuals banned

2010
First HIV + to HIV + kidney transplant in SA

2013
HOPE act reverses NOTA Act based on work done in Cape Town since 2008

What changed?

- Prior to ART, survival in HIV + patients was inferior to HIV negative counterparts
- Widespread access to ART changed this pattern to similar survival rates
- Early initiation of ART and long term retention mitigated
    - HIV infection of the organ
    - Opportunistic infections
    - Consequence's of ART
- Concerns regarding increased risk of surgical complications not supported by a substantial body of evidence showing equivocal outcomes to HIV negative counterparts
- US and European studies have demonstrated favourable outcomes in HIV infected individuals receiving HIV uninfected solid organs
- Poorer outcomes in liver patients related to HCV which has is expected to be annulled with the advent of DAA's

Experience in HIV + to -

- Few reports of inadvertent HIV transmission
- ART commenced within 48 hours post-transplant
- Patient survival of 100%
- Transmission secondary to uncontrolled circumstances

INTENTIONAL HIV + TO - ?

Controlled
Potential to prevent transmission with prophylaxis

Effective control with ART

HIV not accelerated by immunosuppressive therapy

Similar quality of life to HIV uninfected patients

HIV infected organ and transmission

Our process

Donor

CD4 count > 200cells/uL
HIV viral suppression for minimum of 6 months
No HIV associated malignancy or opportunistic infections
No active TB

Consent

Fully informed donor and partner especially regarding risk of contracting HIV
Assisted by multilingual independent donor advocate

Recipient

ART prophylaxis (raltagrivir; lamivudine and abacavir)
Standard immunosuppression: methylprednisone, prednisone and tacrolimus
Testing: HIV 1-2 Ag/Ab serological combo assay + HIV-1 virological testing – DNA and RNA

The Recipients

2017

Case 1

2019

Case 2

Patient 1

- 7 month old female
- Biliary Atresia
- Kasai portoenterostomy at 12 weeks of age : bile flow not established
- Wait listed with a PELD of 15
- Two family members evaluated and found to be unsuitable
- Both parents are HIV +

- Pregnancy and infancy
    - Mother diagnosed at 27 and commenced on ART 4 months after: Efavirenz, Lamivudine and Tenofavir
    - Conceived 6 weeks later with an uncomplicated pregnancy
    - Patient received 6 weeks of Nivirapine prophylaxis for PMTCT + exclusive formula feeding

181 DAYS (Av = 49)

07/2016
Kasai

11/2016
Sclerotherapy

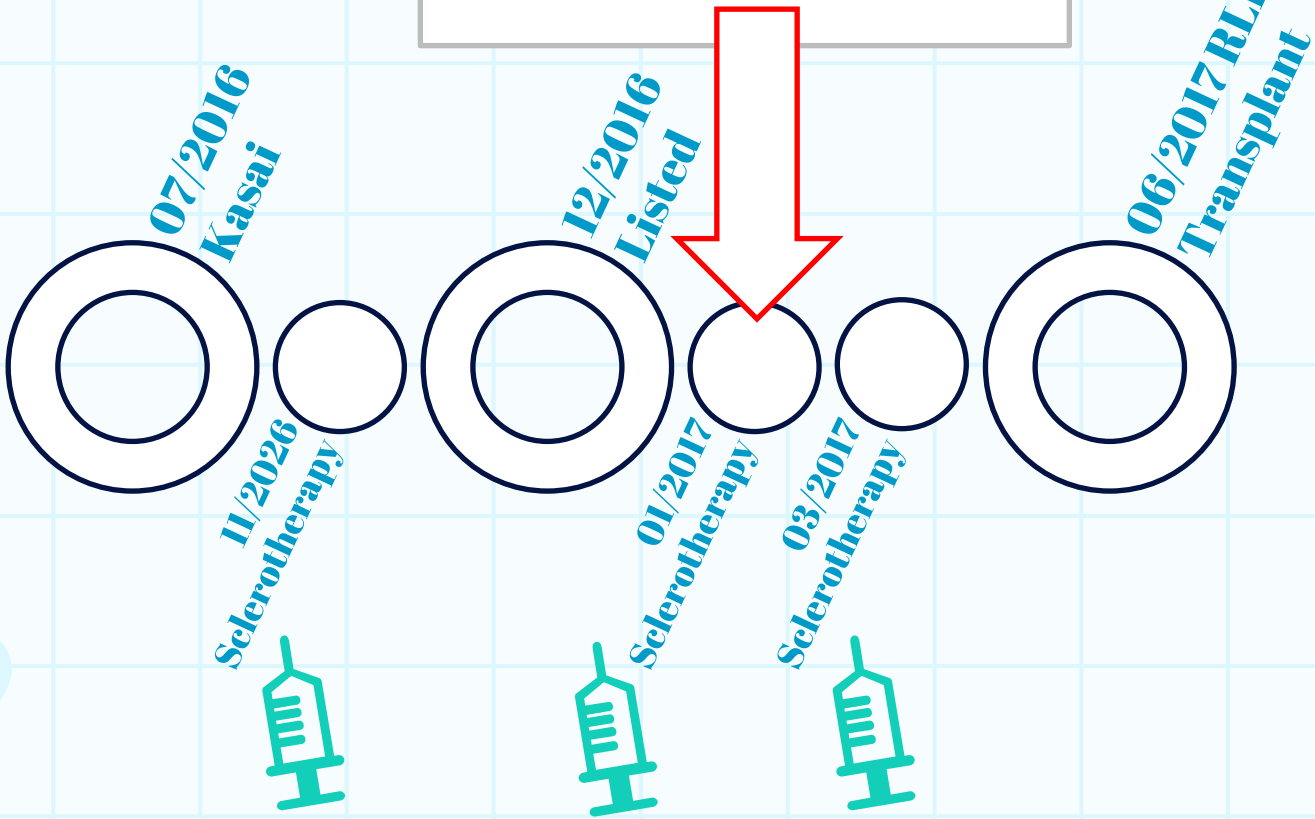
12/2016
Listed

01/2017
Sclerotherapy

03/2017
Sclerotherapy

06/2017 RLD
Transplant

LIFE THREATENING UPPER GASTROINTESTINAL BLEED



POST STRANSPLANT FOLLOW UP

2017

JAN	FEB	MARCH	**APRIL** **Pneumonia** **Pigtail drainage of epigastric collection**	MAY	JUNE
JULY	AUGUST	**SEPT** **Pneumonia**	OCT	NOV	DEC

2018

JAN	FEB	MARCH	APRIL	**MAY** **Salmonella acute gastroenteritis**	JUNE
JULY **PTLD suspected** **Work up negative**	AUGUST	**SEPT** **Crytosporidium** **ACR: steroid pulse**	OCT	NOV	DEC

2019

JAN	FEB	MARCH	**APRIL** **Pneumonia**	MAY	JUNE
JULY	AUGUST	SEPT	OCT	**NOV** **Sternal fracture in an accidental injury**	DEC

Course of HIV testing

June 2017

Pretransplant HIV ELISA - : Maternal Ab absent

1

September 2017

D43 Seroconversion HIV ELISA +

2

Febuary 2018

D225 Western Blot Indeterminant with Ab vs HIV 1 Gag detected

3

June 2018

D349 HIV Ab undetectable

4

2022

ELISA remains indetermiannt

5

HIV DNA undetectable including via ultra-sensitive qualitative nested PCR assay

Course of HIV testing

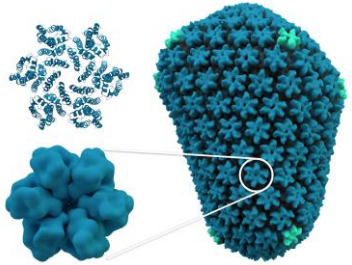
Febuary 2018

D225 Western Blot Indeterminant
with Ab vs HIV 1 Gag detected

1 — 2 — 3 — 4 — 5

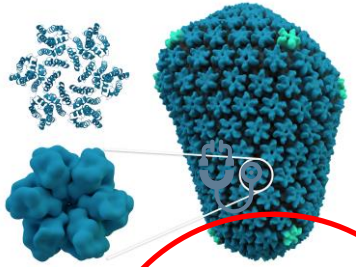
No HIV prodromal DNA detected in peripheral blood mononuclear cells , CD4+ or CD4 depleted leukocytes when readily detected in all 16 replicated of the maternal PBMC's

Acute infection with high antigen levels



Development of antibodies and low level viral replication

Acute infection with high antigen levels



Development of antibodies [but not low level viral replication]

Early initiation of ART

Hypothesised explanations

Small but measurable reservoir in the periphery that is below detection limits

Seroconversion event is generated by maternal liver immune cells, resident or transferred with the graft

Detectable reservoir is limited to the infected donor. No new infection of the recipient

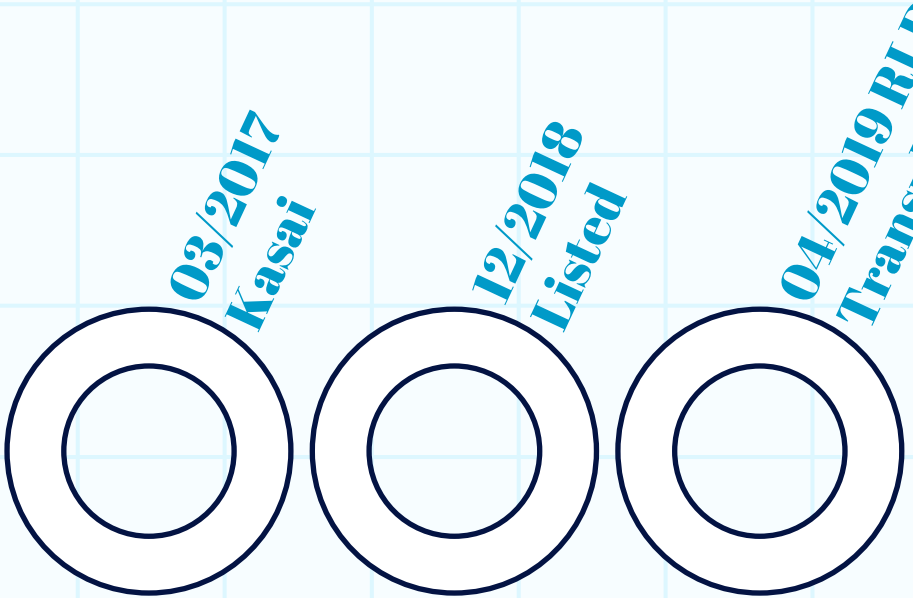
HIV antibodies are produced by the recipient B cells on presentation of HIV antigens by donor liver antigen presenting cells

Patient 2

- 2 year 8 month old female
- Biliary Atresia : syndromic with interrupted IVC and polysplenia
- Kasai portenterostomy at 6 months of age : bile flow not established
- Wait listed with a PELD of 16
- Blood group B +
- Both parents are HIV + on ARVs

- Pregnancy and infancy
    - Mother on ART: Efavirenz, Lamivudine and Tenofavir
    - Uncomplicated pregnancy; Caesarian Section
    - Patient received 6 weeks of Nivirapine prophylaxis for PMTCT + exclusive formula feeding

126 DAYS (Av = 49)



APRIL			
WEEK 1 **Rt sided pleural effusion**	**WEEK 2** **Fungal sepsis**	WEEK 3	**WEEK 4** **Supraventricular tachycardia responded to adenosine** **RSV pneumonia**
MAY			
WEEK 1 **ACR: steroid pulse**	**WEEK 2** **ACR: steroid pulse** **ATG deferred**	WEEK 3	WEEK 4
JUNE			
WEEK 1	**WEEK 2** **URTI: Tamiflu**	WEEK 3	WEEK 4
JULY			
WEEK 1	WEEK 2	**WEEK 3** **Demised following admission for Influenza ARDS**	WEEK 4

Course of HIV testing

April 2019

Pretransplant HIV ELISA - : Maternal Ab absent

1

April 2019

D13 Seroconversion HIV ELISA +CD4 449

2

May 2019

D 37 Western Blot Negative ; Ab vs HIV 1 and 2 detected CD4 1071

3

HIV DNA undetectable

The Unknowns

HIV Ab

Unlikely to develop a response with early ART

Studies support the transfer of antibody response from donor to recipient

I. Peanut allergy
II. HCV negative patients with undetectable VLs but + Ab from an HCV + donor

HIV DNA/RNA

Cannot gaurantee an absence of infection as small reservoirs of latent infected cells may exist below the detection of assays

Drugs

Effect of immmunosuppression on possible viral rebound on discontinuation of ART

The Future

- Status is equivocal
- Planned interruption of ART following 5 years of uninterrupted ART

I. Improve on progress addressing needle phobia

II. Support from mother's employment for additional time required to conduct additional testing and follow up

III. Assist in disclosure efforts in the family

IV. Exploring options of disclosure to the patient

- Intended protocol submitted to the Institutional review board for ethics consideration

Future of the protocol

Efforts to increase the donor pool include **donation after cardiac death**, use of extended or marginal organs, living donor programs and **split liver tranplantation**

In the face of the extreme organ scarcity faced in South African, the protocol is unlikely to become redundant until all avenues of increasing the pool have been exhausted

Resources

AIDS. 2018 Oct 23;32(16):F13-F19. doi: 0.1097/QAD.0000000000002000.

Living donor liver transplant from an HIV-positive mother to her HIV-negative child: opening up new therapeutic options

Jean Botha 1, Francesca Conradie 2 3, Harriet Etheredge 1 3, June Fabian 1 3, Mary Duncan 1, Ahmad Haeri Mazanderani 4 5, Maria Paximadis 4 6, Heather Maher 1, Russell Britz 1, Jerome Loveland 1 7, Bernd Ströbele 1, Sharan Rambarran 1, Adam Mahomed 1 3, Alta Terblanche 1, Marisa Beretta 1, Liam Brannigan 1, Michael Pienaar 1, Lindsay Archibald-Durham 1, Allison Lang 1, Caroline T Tiemessen 4 6

Curr HIV/AIDS Rep. 2019; 16(5): 404–413. PMCID: PMC6813753

HIV and Solid Organ Transplantation: Where Are we Now

Jean Botha,1 June Fabian,1 Harriet Etheredge,1 Francesca Conradie,2 and Caroline T. Tiemessencorresponding author3,4

With permission from mom

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Thank you

Do you have any questions?

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