Quality of Life and Associated factors in HIV positive transplant patients

Access, Equity and Outcomes

Prof Elmi Muller,
Professor in Surgery and Dean of the Faculty of Medicine and Health Sciences
Stellenbosch University,
South Africa

WMDA congress, 27 June 2024

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Inequality in the South African context

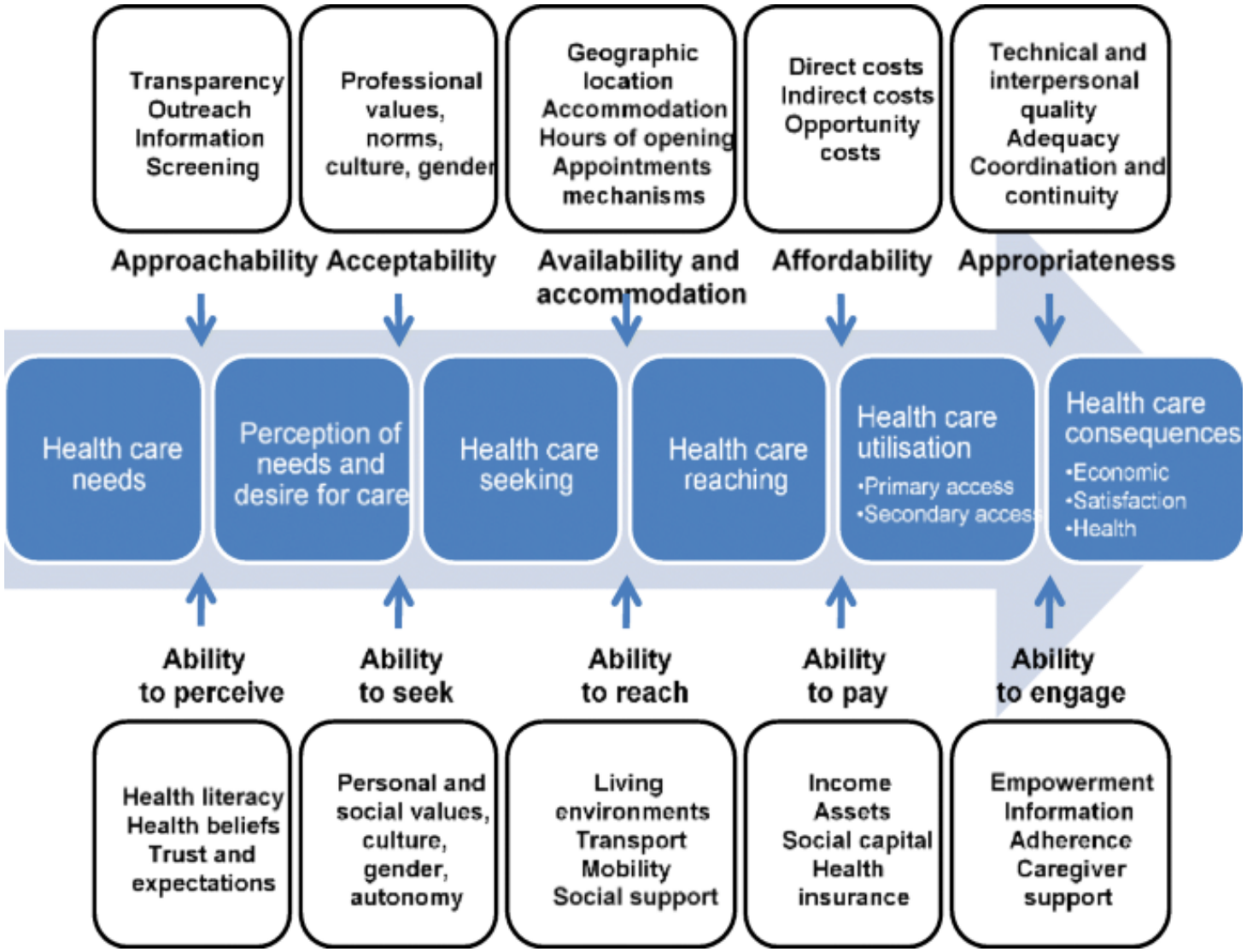
People between 15 and 64 years	40,7	million
At school/ill	13,2	million
	27,5	million
Currently working	16,4	million
Percentage employed	40	%

Drivers for inequlaity

- Unemployment (current unemployment rate is 32%-44% depending on the definition we use)
- Low wages in informal sector

A highly unequal healthcare system

- People exceeds capacity
- People don't know their health status
- The way the system is funded perpetuates inequality



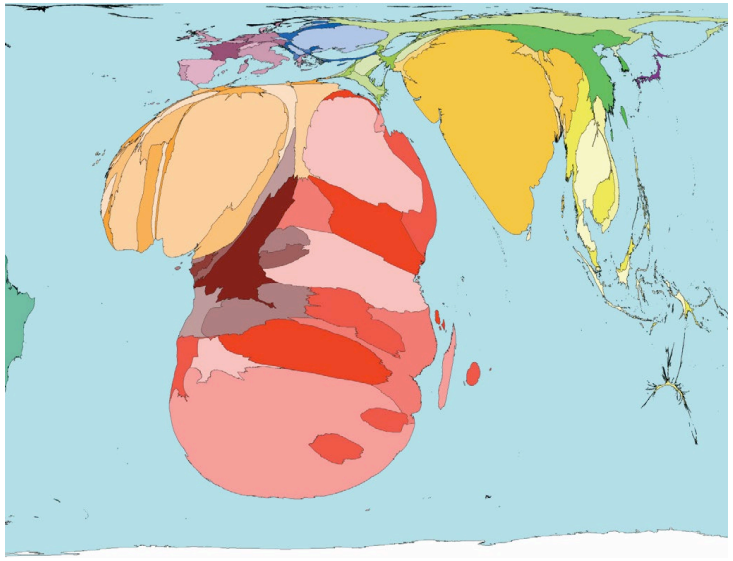
Opportunities for improvement in South Africa

- A strong primary health care network with competent well trained community health workers
- The efficiencies of hospitals
- Explicit priority setting in determining who accesses key services: people with the least coverage need to be prioritised before expanding access to others already experiencing better care
- The high cost of private care has detrimental effects on public health care

An example to improve access to care by utilizing HIV positive deceased donors

South Africa

- ART only became available in South Africa in 2004 with a slow uptake between 2004 and 2008
- Political denial
- Funding



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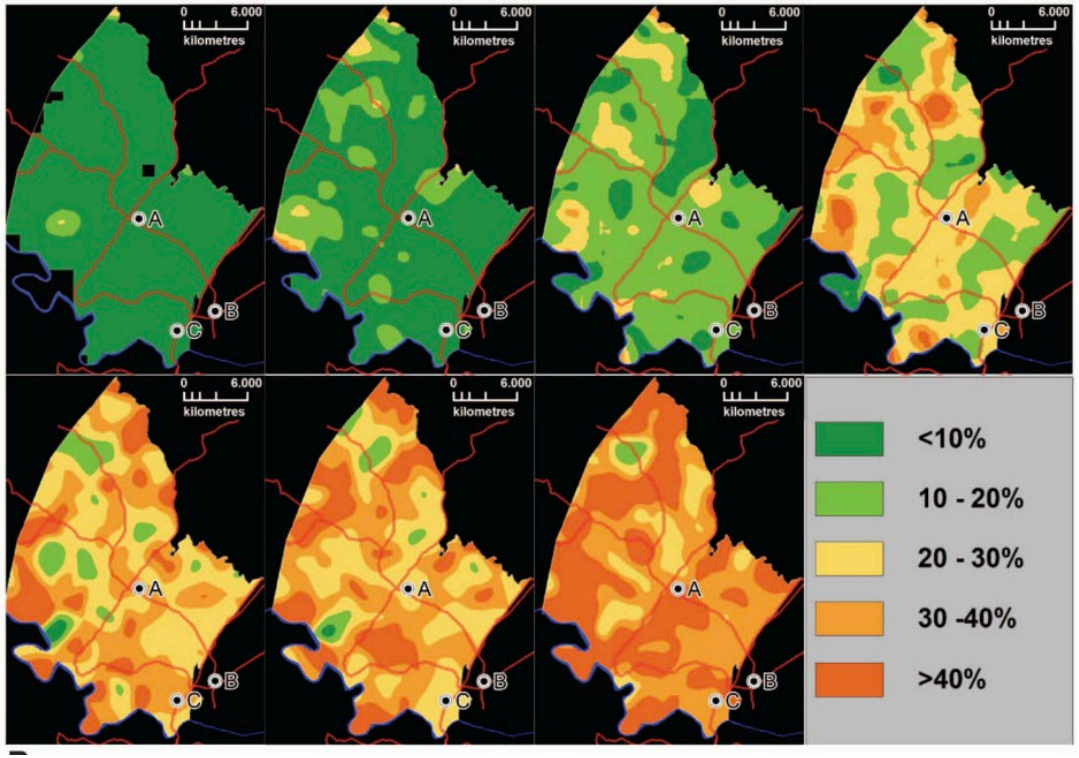
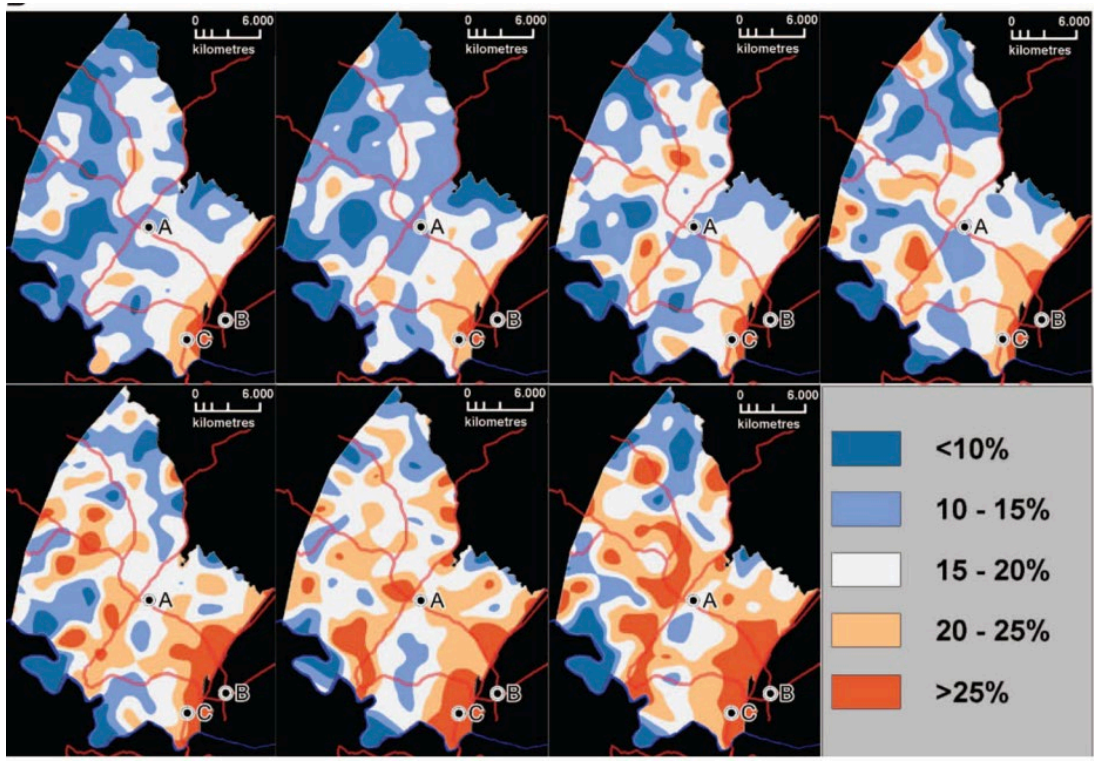
High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser[1,*], **Till Bärnighausen**[1,2], **Erofili Grapsa**[1], **Jaffer Zaidi**[1], and **Marie-Louise Newell**[1,3]

[1]Africa Centre for Health and Population Studies, University of KwaZulu-Natal, South Africa



The proportion of the HIV-infected adults (≥15 years of age) receiving ART

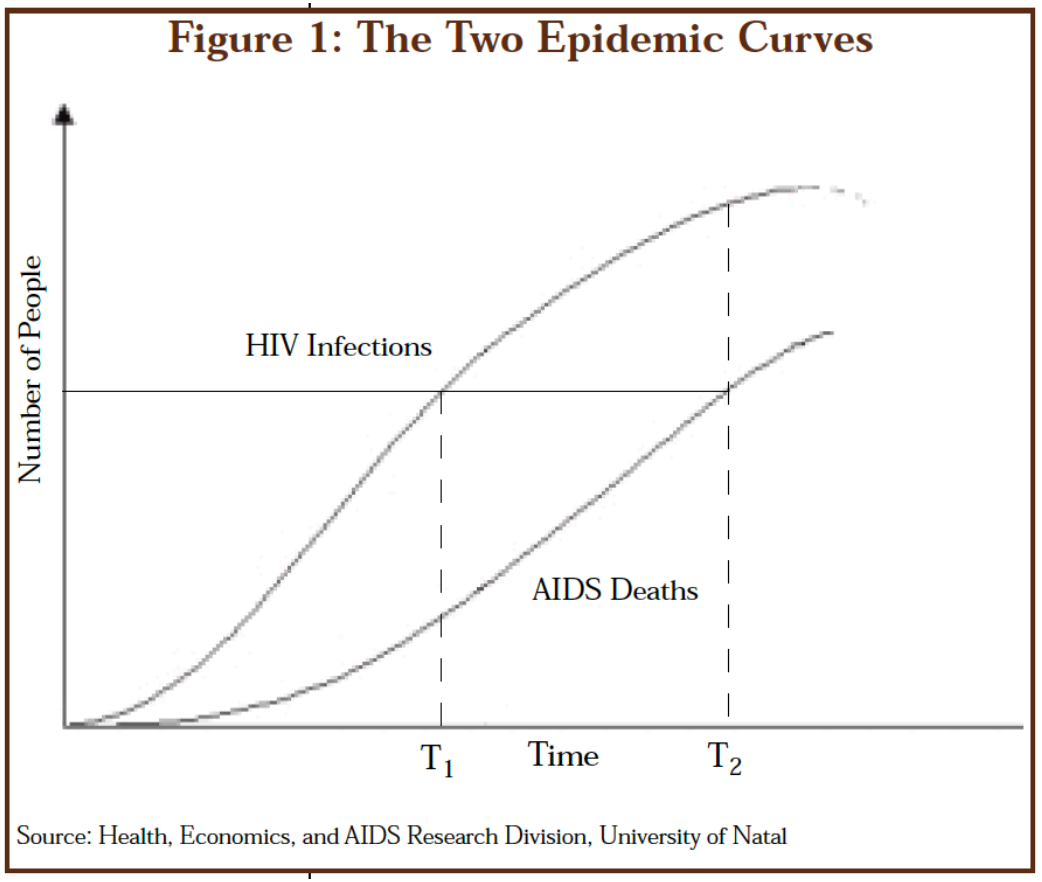


HIV prevalence

Science. 2013 February 22; 339(6122): 966–971

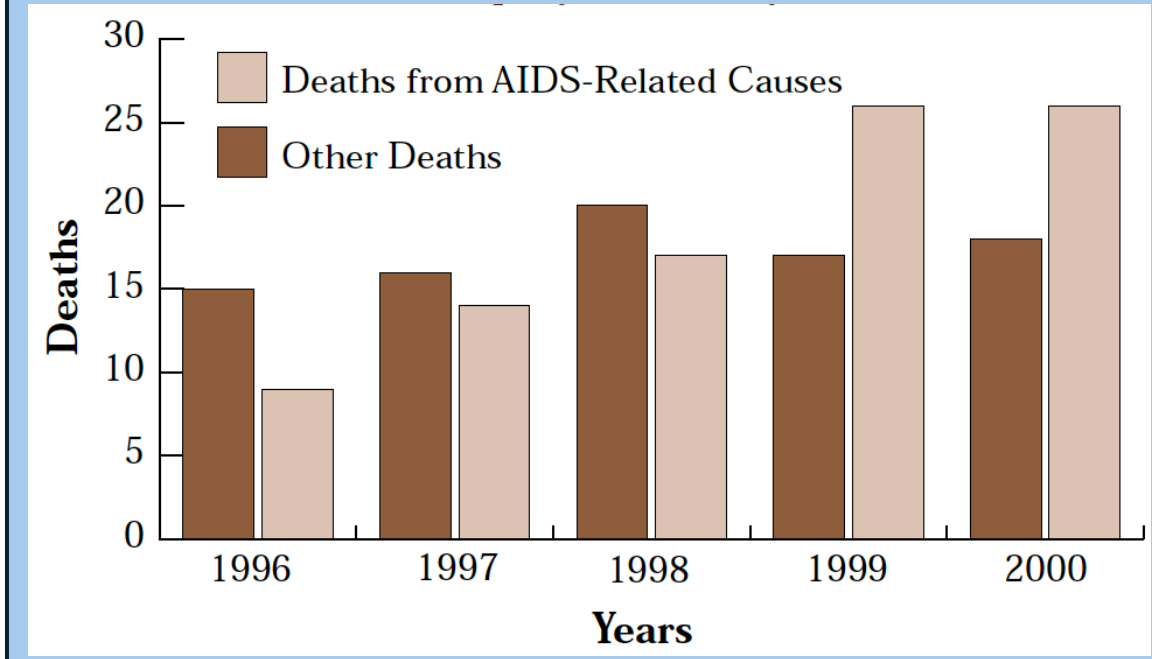
Economics of HIV

- South Africa has a disproportionate spend on health infrastructure in large metropolitan areas. This has led to an under investment in primary health care where the 80% of people access services.
- Many patients are unaware that they are HIV positive
- HIV/AIDS reduces productivity, disrupts organizations, and unravels institutions. The implication is that the epidemic's effects are non-linear.



The Economic impact of HIV on South African Business

Debswana Diamond Company: Summary of Deaths in Service

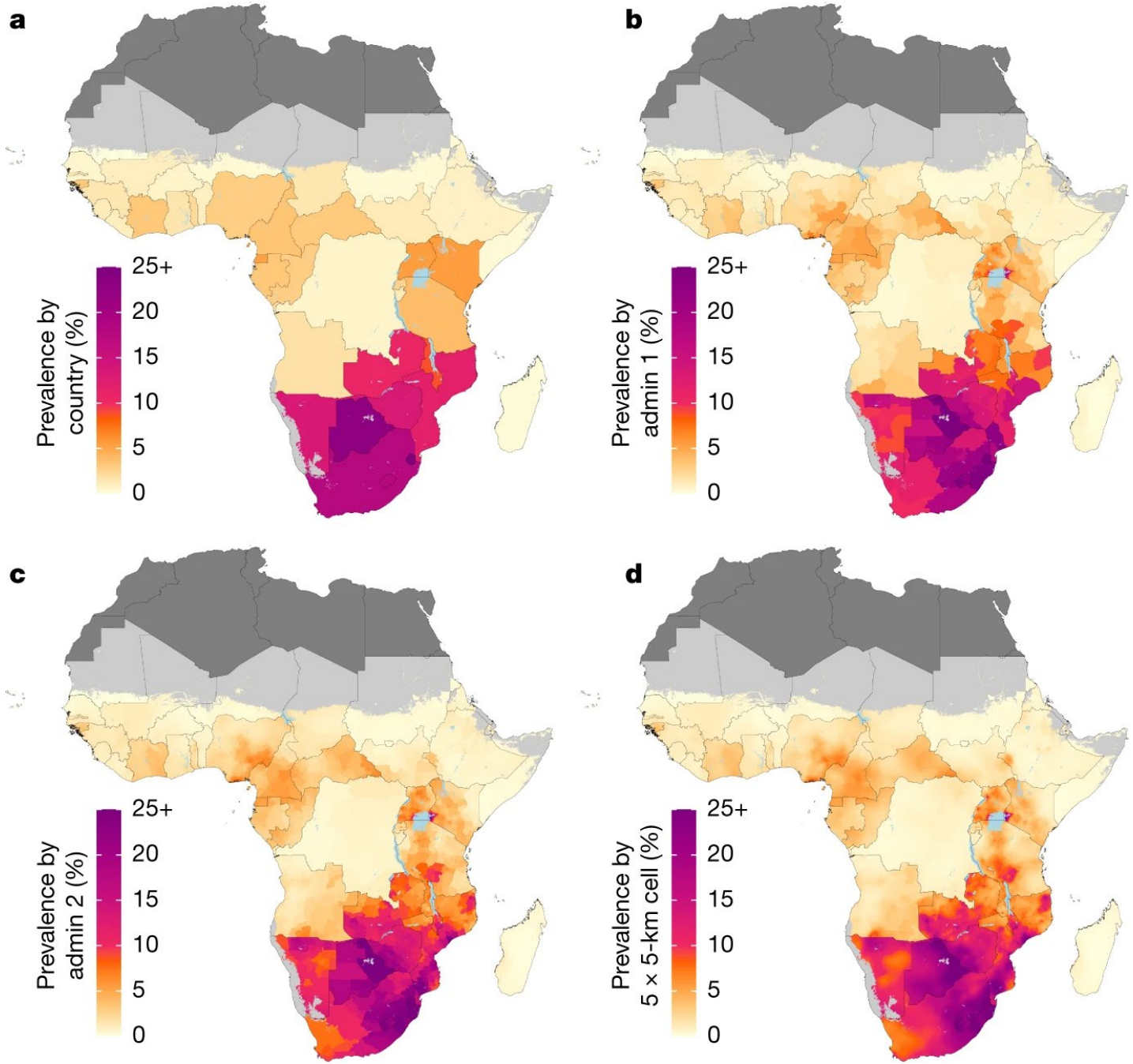


Cost of HIV/AIDS to Firms in South Africa

Company	A	B	C
Location	South Africa (national)	South Africa (KwaZulu Natal)	Botswana
Sector processing	Heavy industry	Agriculture	Mineral
Workforce size	>20,000	5,000-10,000	<1,000
Company's discount rate (real)	6%	10%	4.50%
HIV prevalence	8.8% (1999)	22.9% (1999)	28.8% (2000)
Present value per infection as a multiple of average salary—technicians[a]	5.4	1.3	5.1
Share of indirect costs (productivity) in total cost	24%	93%	26%
Share of retirement and disability benefits in total cost	65%	0%	65%

(a) Technicians are skilled machine operators, drivers, craftsmen, engineering assistants, etc. They typically have both formal and informal technical training but no university-level education. The costs for this job level are provided as an example.

Research of the AIDS Economic Team, Centre for International Health, Boston University, 2001

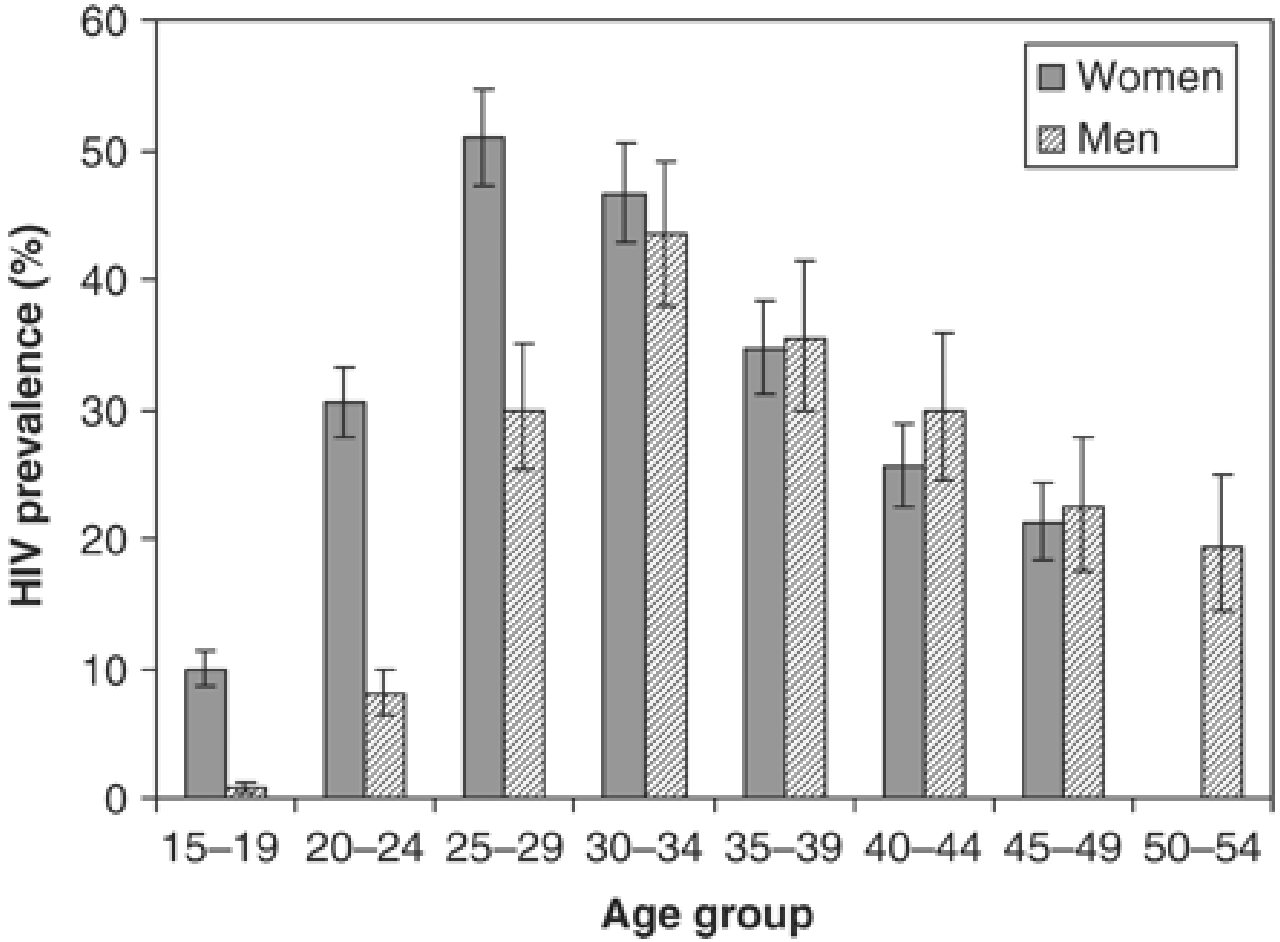


Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017

L. Dwyer-Lindgren, M. A. Cork, A. Sligar, K. M. Steuben, K. F. Wilson, N. R. Provost, et al.

Nature 2019 Vol. 570 Issue 7760
Pages 189-193

HIV sero-prevalence by age and sex (95% CI) among residents (2003–2004) in Kwa Zulu Natal

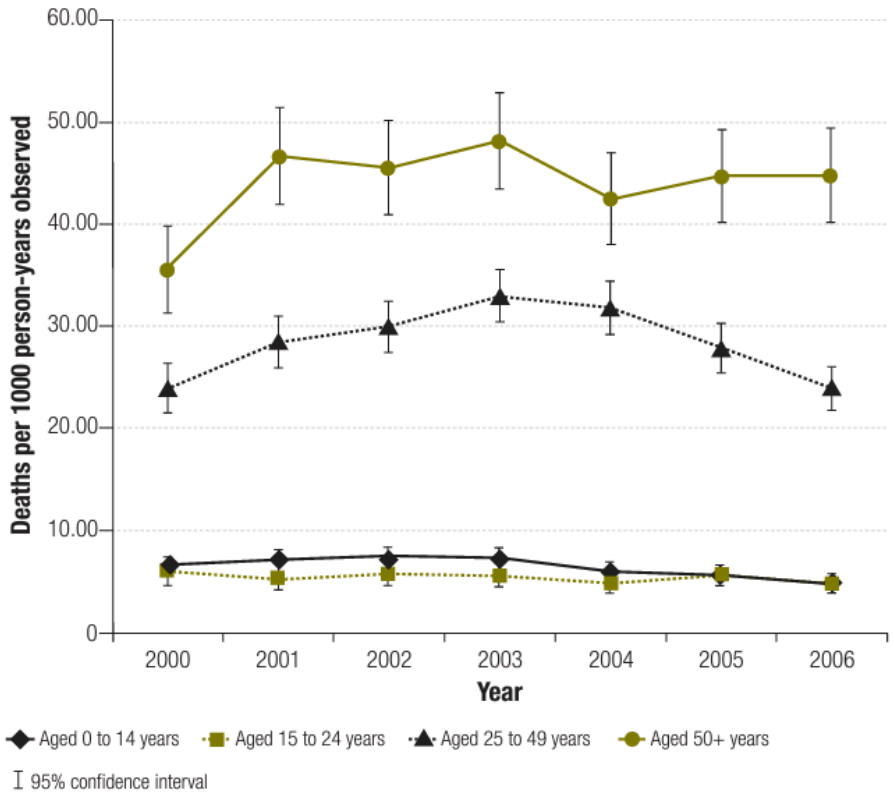


Int J Epidemiol, Volume 37, Issue 5, October 2008, Pages 956–962, https://doi.org/10.1093/ije/dym211

Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa

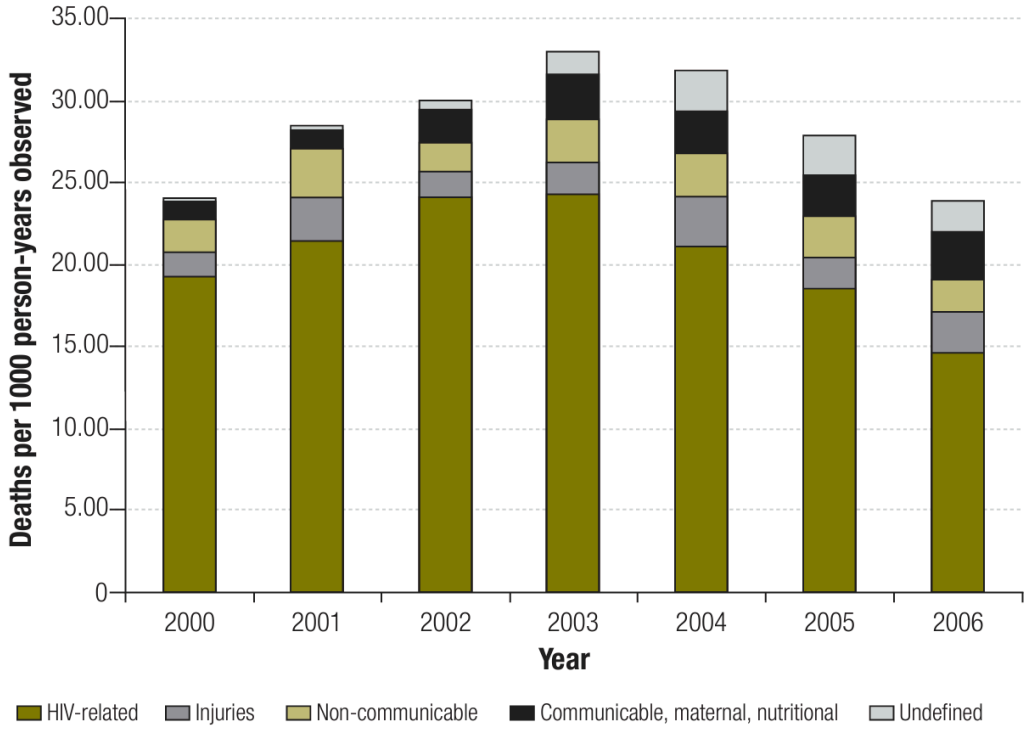
Abraham J Herbst,[a] Graham S Cooke,[a] Till Bärnighausen,[a] Angelique KanyKany,[a] Frank Tanser[a] & Marie-Louise Newell[a]

Fig. 1. **All-cause SMRs by age group, for males and females, KwaZulu-Natal, South Africa, 2000–2006**



SMR, age-standardized mortality rate.

Fig. 2. **Cause-specific SMRs for adults aged 25–49 years, KwaZulu-Natal, South Africa, 2000–2006**



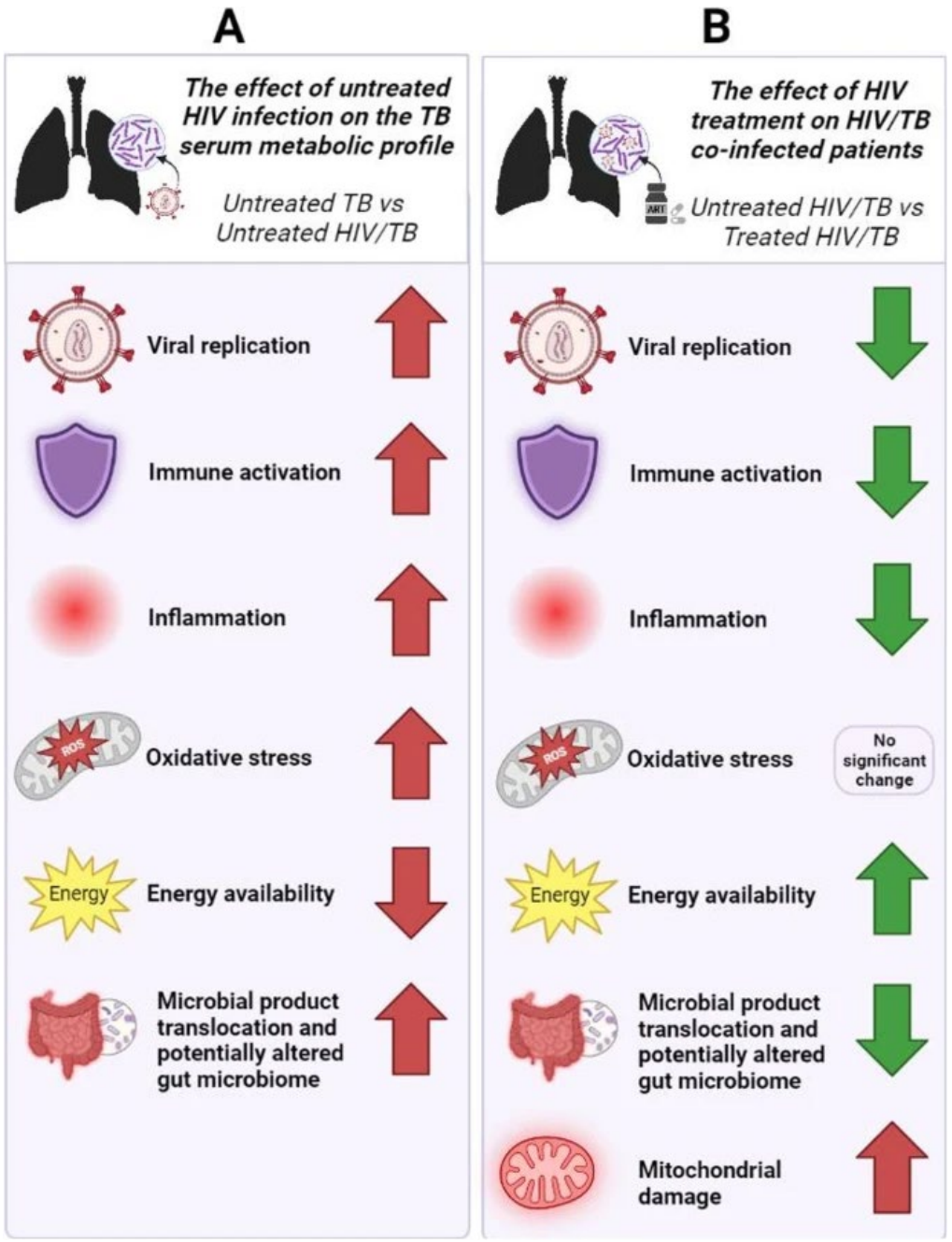
SMR, age-standardized mortality rate.

Bull World Health Organ 2009;87:754–762

Primary causes of end-stage kidney disease in sub-Saharan Africa

Primary Cause	Average Proportion of adults with disease	High-range estimate	Low-range estimate
Glomerular disease	35%	52%	16%
Hypertension	46%	69%	21%
Diabetes	13%	24%	3%
HIV	22%	48.5%	5.5%

Problem: High Mortality Rates due to a lack of available treatment options



The metabolic consequences of HIV/TB co-infection

C. Herbert, L. Luies, D. T. Loots and A. A. Williams
BMC Infectious Diseases 2023 Vol. 23 Issue 1 Pages 536
DOI: 10.1186/s12879-023-08505-4

Common Opportunistic Infections

- **Candidiasis**
- Invasive cervical cancer
- **Coccidioidomycosis**
- **Cryptococcosis**
- Cryptosporidiosis
- Cystoisosporiasis
- **Cytomegalovirus (CMV)**
- **Encephalopathy, HIV-related**
- Herpes simplex virus (HSV)
- Histoplasmosis
- **Kaposi's sarcoma**
- **Lymphoma**
- *Mycobacterium avium* complex (MAC)
- ***Pneumocystis* pneumonia (PCP)**
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicaemia
- Toxoplasmosis

https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html

Ethical considerations

- The role of physicians in the allocation of healthcare: is some justice better than none?
- Cost conscious medical decisions: the conflicting demands of ethics and economics
- Administrative gatekeeping: the role of physicians

Kennedy Inst Ethics J. 2019;29(1):1-31. doi: 10.1353/ken.2019.0008.

SELECTION OF PATIENTS FOR DIALYSIS

CATEGORY 1

- The ideal candidate
- No other medical or social issues
- Patient ONLY has ESRF

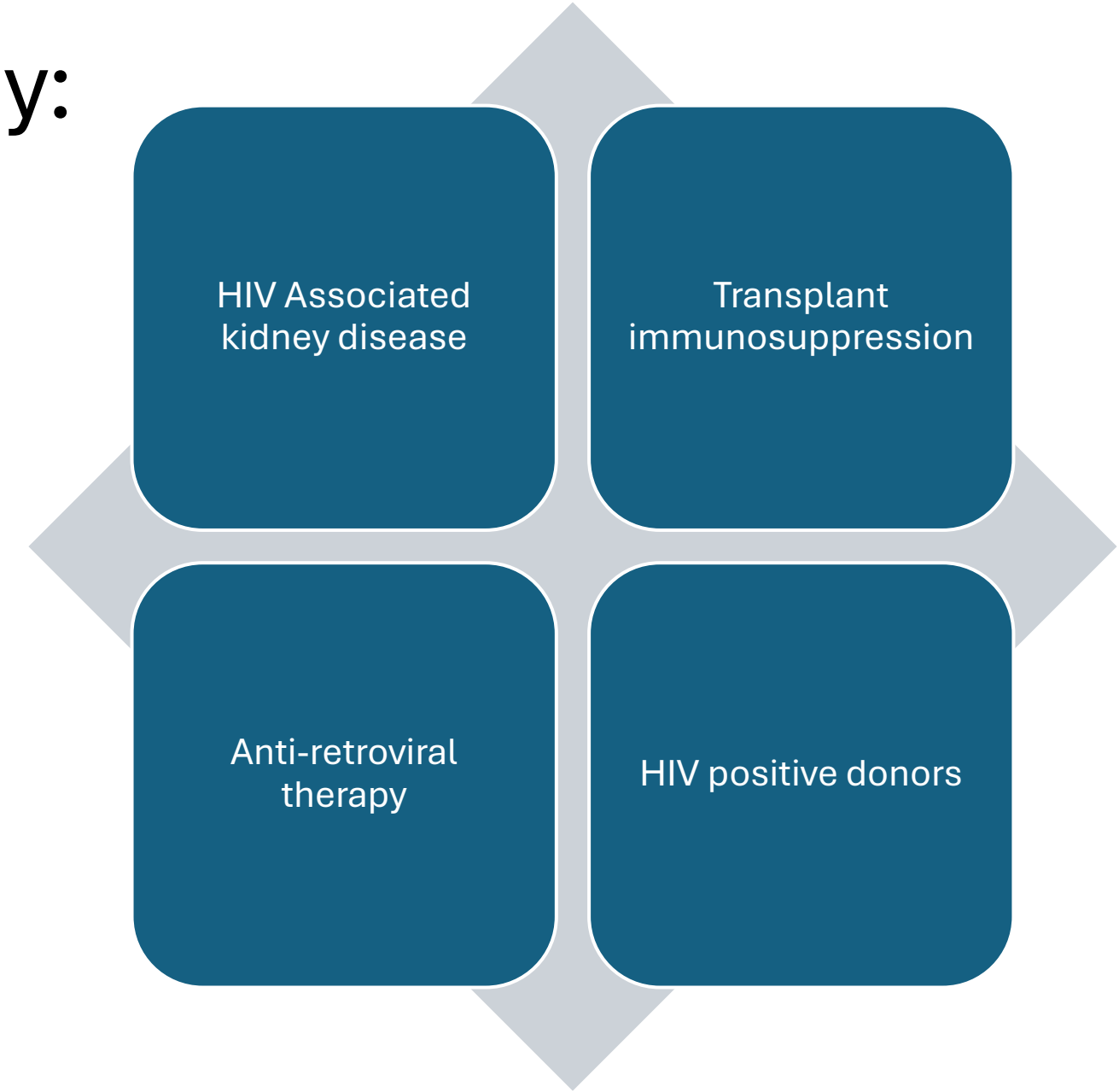
CATEGORY 2

- Patient might have some other organ disease but well controlled for instance hypertension and controlled or asthma

CATEGORY 3

- Patient has social issues to come to hospital/do not attend regularly
- Patient has serious heart disease
- Patient has diabetes with other end-organ involvement
- HIV

Interplay:


HIV Associated kidney disease
Transplant immunosuppression
Anti-retroviral therapy
HIV positive donors

Patient Quality of Life

> Qual Life Res. 2022 Jan;31(1):171-184. doi: 10.1007/s11136-021-02898-y. Epub 2021 Jun 22.

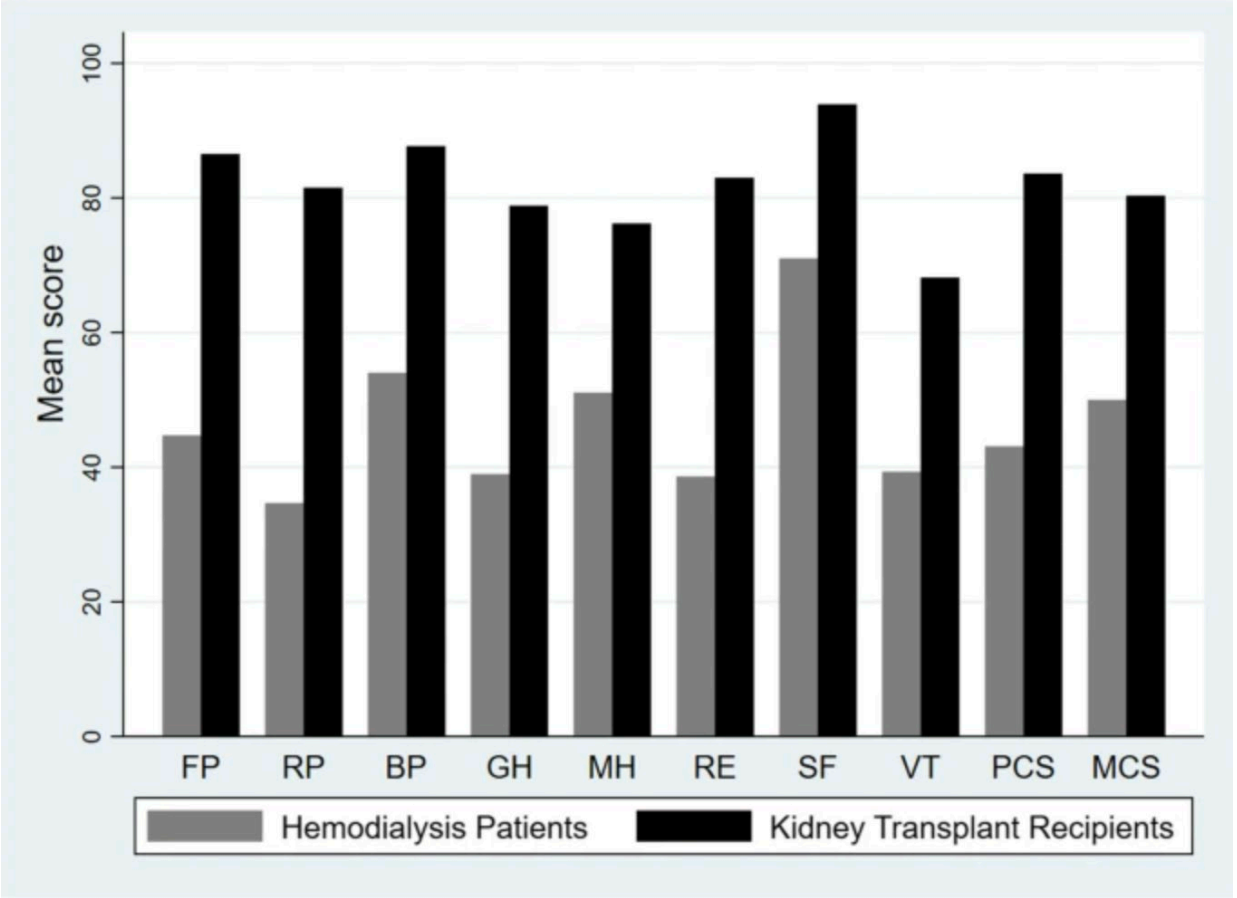
Health-related quality of life and associated factors in HIV-positive transplant candidates and recipients from a HIV-positive donor

Claire Juliet Martin [1] [2], Elmi Muller [3], Demetre Labadarios [4], Frederick Johannes Veldman [5], Susanna Maria Kassier [6]

Affiliations + expand

PMID: 34156597 DOI: 10.1007/s11136-021-02898-y

- Transplant recipients had high HRQOL scores in all domains.
- Patients on dialysis had lower QOL than transplant recipients. The main mental stressors were income, employment and waiting for a donor.
- Physical health complaints for dialysis patients were body pain and fatigue.
- Pre-albumin and BMI was positively correlated with general health.
- Albumin correlated positively with physical composite score (p = 0.034) and emotional score (p = 0.024). Higher pre-albumin was associated with better emotional and physical abilities



31 Deceased donors

Deceased donors: 2008-2022

Donor	n=31
Age* - year, med (IQR)	31 (IQR 26-36)
Male sex - no. (%)	23 (74%)
Race - no. (%)	
Black African	19 (61%)
Mixed Ancestry	8 (26%)
Caucasian	4 (13%)
On ART (MASS-SPEC)	3/11 (13%)
Hepatitis B–virus coinfection, no. (%)	1 (3%)
Donor histology (implantation biopsy)	
No specific histological findings	12 (39%)
Acute tubular injury (ATI)	14 (45%)
Donor disease with hypertensive features	4 (13%)
Suspected HIVAN	1 (3%)

HIV-Positive Kidney Donor Selection for HIV-Positive Transplant Recipients.

Muller E, Barday Z.

J Am Soc Nephrol. 2018 Apr;29(4):1090-1095. doi: 10.1681/ASN.2017080853. Epub 2018 Jan 12.

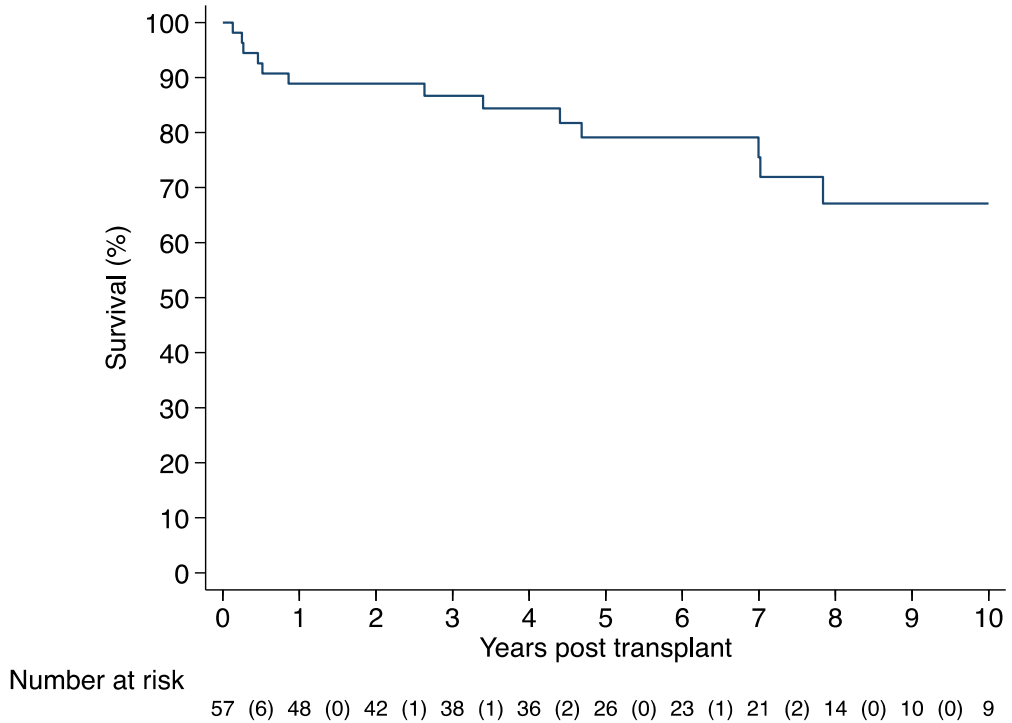
PMID: 29330339 Free PMC article. Review.

57 HIV-positive recipients received kidneys from 31 HIV-positive deceased donors

Recipients

	N=57
Age	40 (33-47)
Sex	
M	32/57 (56%)
Race	
Black African	53/57 (93%)
Mixed ancestry	4/57 (7%)
ARTs	
N/NRTi	49/57 (86%)
PI-based at transplant	8/57 (14%)
CD4 (n=55)	436 (291-578)
Cause of Renal Failure	
HIVAN + HPT	24/57 (42%)
HIVAN	17/57 (30%)
HIVAN + GN	1/57 (2%)
HPT	7/57 (12%)
HPT + GN	1/57 (2%)
GN	4/57 (7%)
ADPCKD	1/57 (2%)
REFLUX NEPHROPATHY	1/57 (2%)
SEVERE IFTA	1/57 (2%)
Non-communicable comorbidities	
HPT	50/57 (88%)
DM	2/57 (4%)
Overweight/Obese (BMI > 25)	27/57 (47%)
Communicable comorbidities/prior infections	
Prior TB	17/57 (30%)
Hep B positive	3/57 (5%)

Patient survival

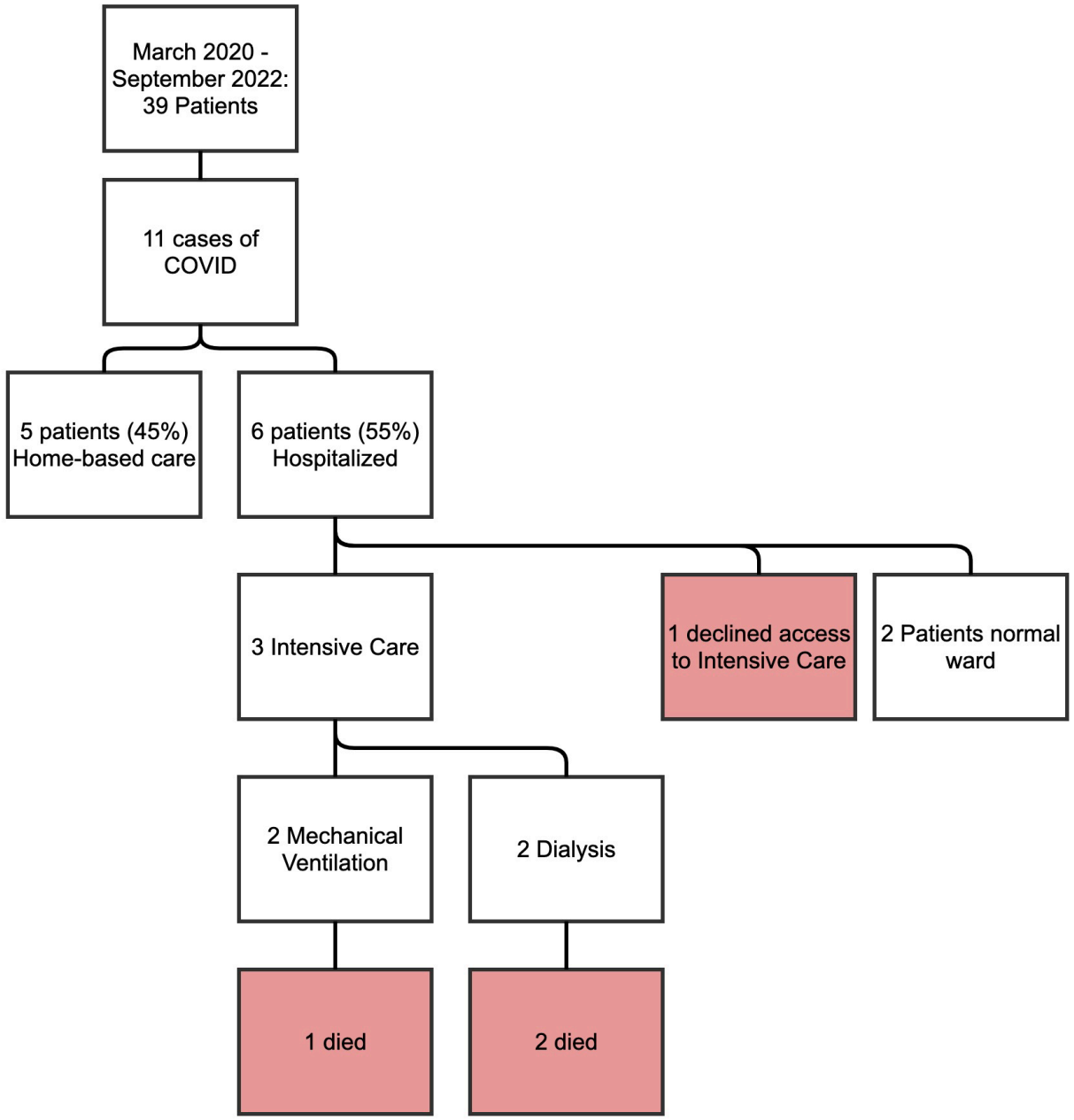


	Patient survival
1-Year	88.89% (95% CI 76.93-94.85)
2-Year	88.89% (95% CI 76.93-94.85)
3-Year	86.67% (95% CI 73.98-93.43)
4-Year	84.39% (95% CI 71.07-91.91)
5-Year	79.11% (95% CI 64.28-88.32)

Cause of death (n=13)	
COVID-19 Pneumonia –	4 (31%)
Sepsis –	3 (23%)
Respiratory failure	2 (15%)
From TB – n=1 & Aspergillus – n=1	
Cardiac failure	2 (15%)
CVA	1 (8%)
Malignancy	1 (8%)

COVID

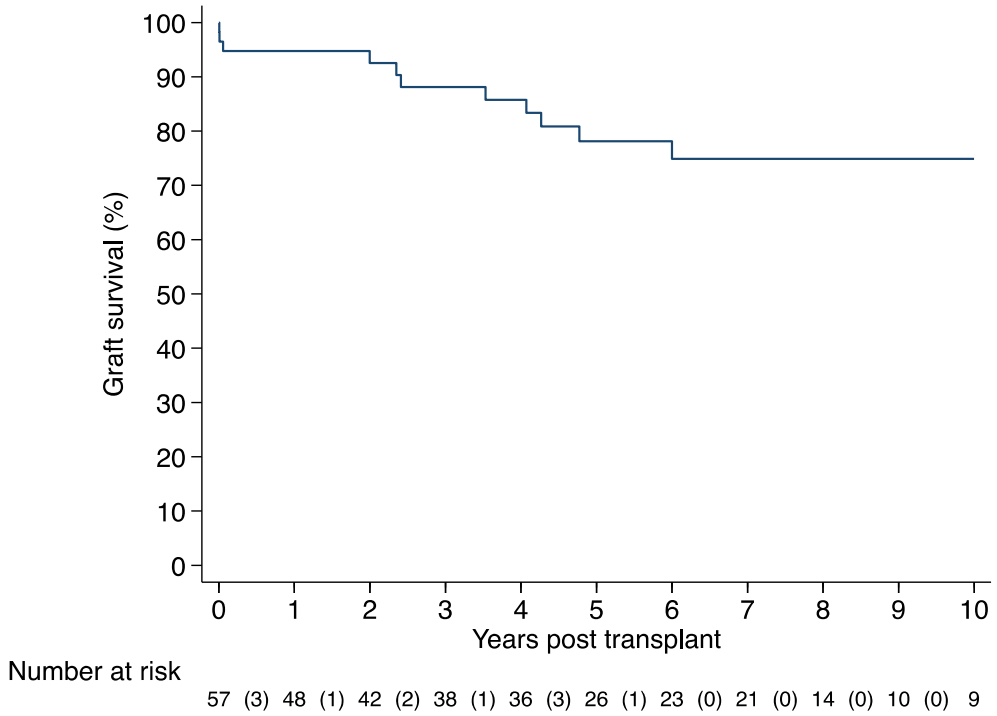
Nineteen (79%) patients were vaccinated, and the remaining 5 (21%) patients declined vaccination.
Of the vaccinated patients, 16 (67%) received 2 doses of the Pfizer vaccine, and 3 (13%) received a single dose Johnson & Johnson vaccine.



In our cohort there was a 10% mortality rate from COVID (in press Bertels et al)

Patients who died all had a background of hypertension and underlying comorbidities such as obesity (n=3), cancer (n=1) and diabetes (n=1)

Graft Survival



	Death-censored Graft survival
1-Year	94.74% (95% CI 84.56 –98.27)
2-Year	92.53% (95% CI 81.20 – 97.15)
3-Year	88.13% (95% CI 75.30 – 94.53)
4-Year	85.75% (95% CI 72.20 – 93.00)
5-Year	78.14% (95% CI 62.83 – 87.73)

Cause of Graft failure (n=11)	
Rejection	5 (45%)
HIVAN	2 (18%)
Renal vein thrombosis	2 (18%)
BK Virus	1 (9%)
Severe IFTA	1 (9%)

Rejection

- Induction therapy included rabbit anti-thymocyte globulin (rATG)
- Maintenance immunosuppression included mycophenolate mofetil and tacrolimus

From our current cohort (n=57):

- 24 (42%) have experience at least one episode of suspicious or confirmed (ABMR/TCMR) rejection

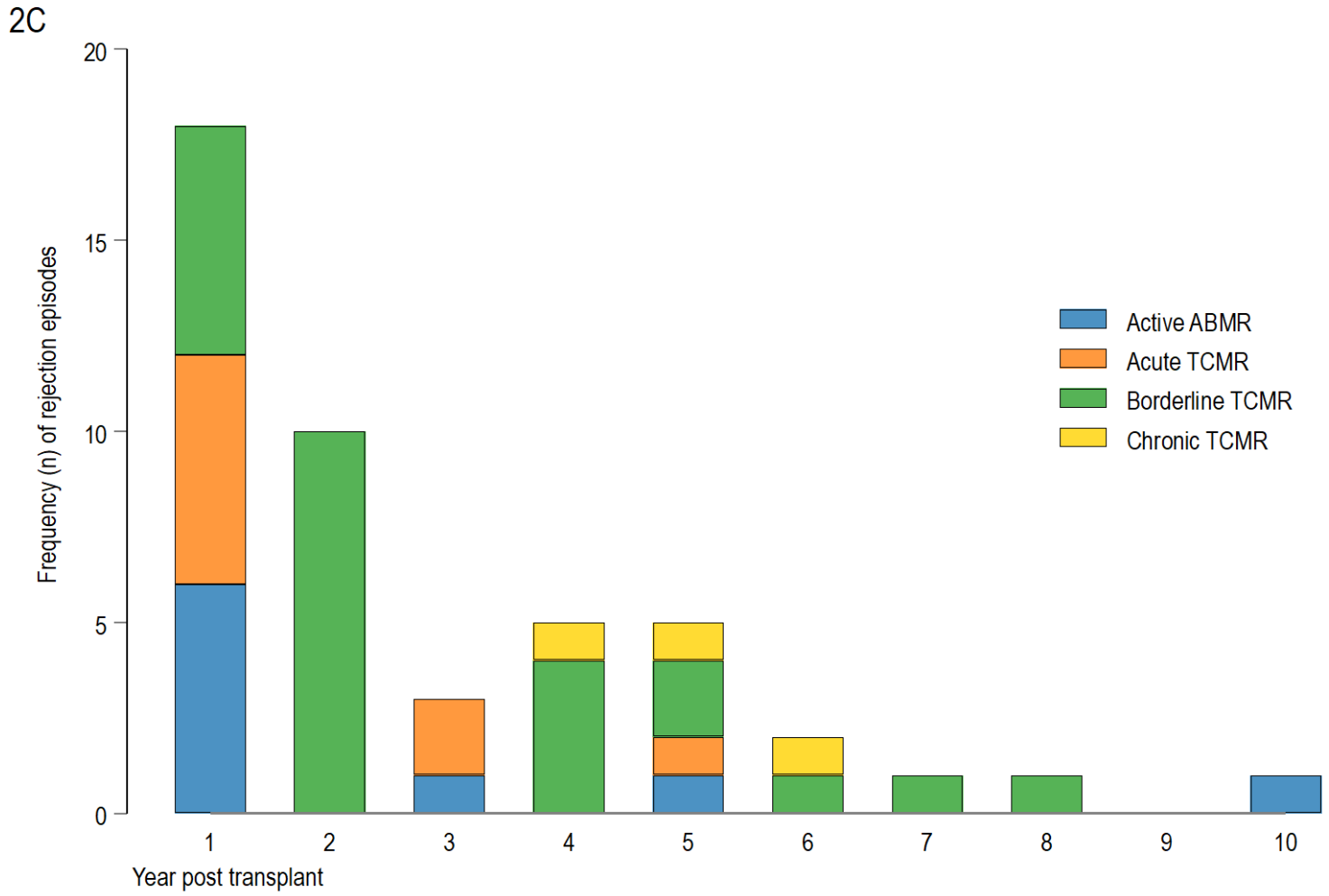
Kidney Transplantation in HIV-positive Patients: Current Practice and Management Strategies.

Muller E, Botha FCJ, Barday ZA, Manning K, Chin-Hong P, Stock P.

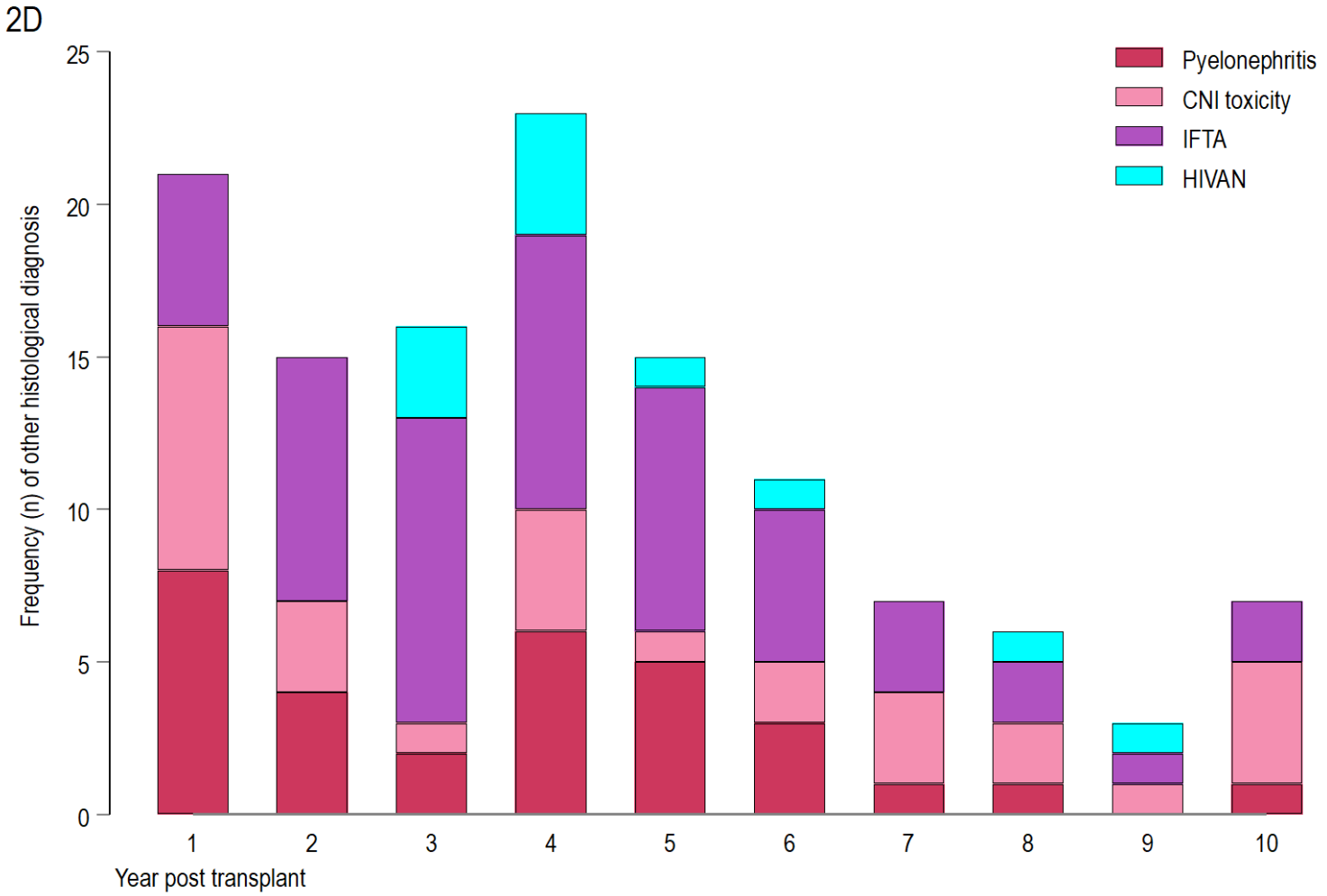
Transplantation. 2021 Jul 1;105(7):1492-1501. doi: 10.1097/TP.0000000000003485.

PMID: 33044431 **Free PMC article.** Review.

Distribution of rejection episodes over time



Distribution of other histological diagnoses over time



Lessons learned

Surgical outcomes were good

Minimal infectious complications

Minimal intra-abdominal complications

Selected group of patients: VL undetectable and CD4 count >200 with strong adherence to ART

Ultra deep sequencing of HIV

15 donors and 26 recipients:
Samples of plasma and peripheral-blood mononuclear cells (PBMCs) were collected and tested for:

1. The presence of antiretroviral drugs in donors
2. HIV drug–resistant mutations present
3. Evidence of viral inoculum from the donor
4. Sustained donor-derived HIV superinfection in the recipient
5. Viral Load Blips

Longer-Term Outcomes of HIV-Positive-to-HIV-Positive Renal Transplantation.
Selhorst P, Combrinck CE, Manning K, Botha FCJ, Labuschagne JPL, Anthony C, Matten DL, Breaud A, Clarke W, Quinn TC, Redd AD, Williamson C, Muller E.
N Engl J Med. 2019 Oct 3;381(14):1387-1389. doi: 10.1056/NEJMc1903013.
PMID: 31577883 Free PMC article. No abstract available.

1. Presence of antiretroviral drugs in donors

- South African donors are viremic & mostly ART naive
- ART reported in 1 donor and detected with Mass Spectrometry in 2 additional donors

Sequencing results confirmed all donors to be infected with subtype C virus and revealed a dual infection in one patient

Viral Load

Donor	Date of transplant	Copies /ml	ARVs in plasma
KID-5007	05-Aug-11	221 180	×
KID-5008	14-Oct-11	82 040	×
KID-5011	21-Nov-12	60 000	×
KID-5012	25-Feb-12	<100	×
KID-5013	27-May-13	<960	EFV + FTC + TFV
KID-5014	11-Nov-13	7 805 044	×
KID-5015	16-Jan-14	23 316	×

Donor	Date of transplant	Copies /ml	ARVs in plasma
KID-5016	26-Jun-14	100 000	
KID-5018	10-Mar-15	129 732	×
KID-5020	19-Jun-15	116 316	×
KID-5022	21-Sep-16	112 360	
KID-5023	29-Nov-16	54 365	
KID-5024	04-Mar-17	590 085	

Recipients from very high VIRAL LOAD donor (7.8 million copies/mL)

Patient 1

- **21 May 2018**
  - Creatinine 96
  - GFR > 60
- **11 Dec 2017**
  - CD4 296
  - VL LDL

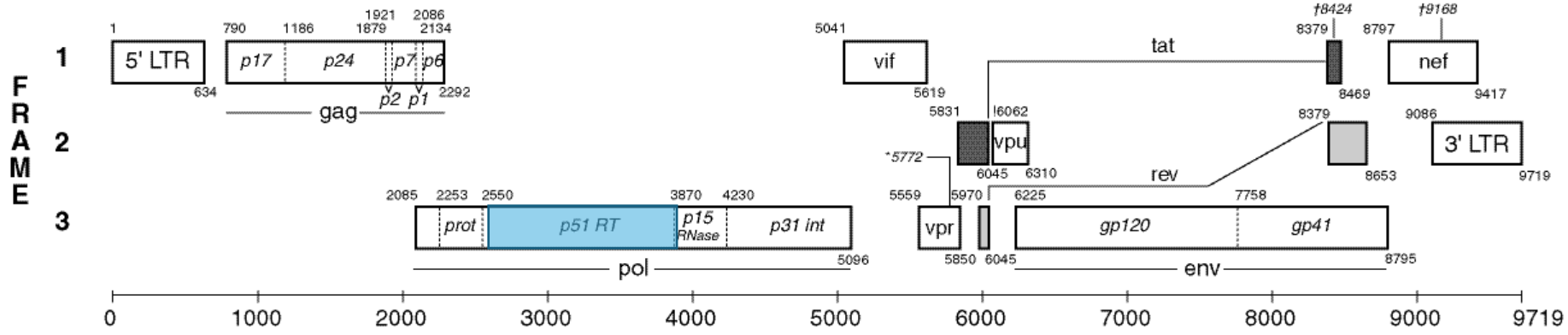
Patient 2

- **7 May 2018**
  - Creatinine 111
  - GFR = 50
- **11 Dec 2017**
  - CD4 612
  - VL LDL

Biopsy reports: No HIVAN, No Rejection

2. HIV drug–resistant mutations

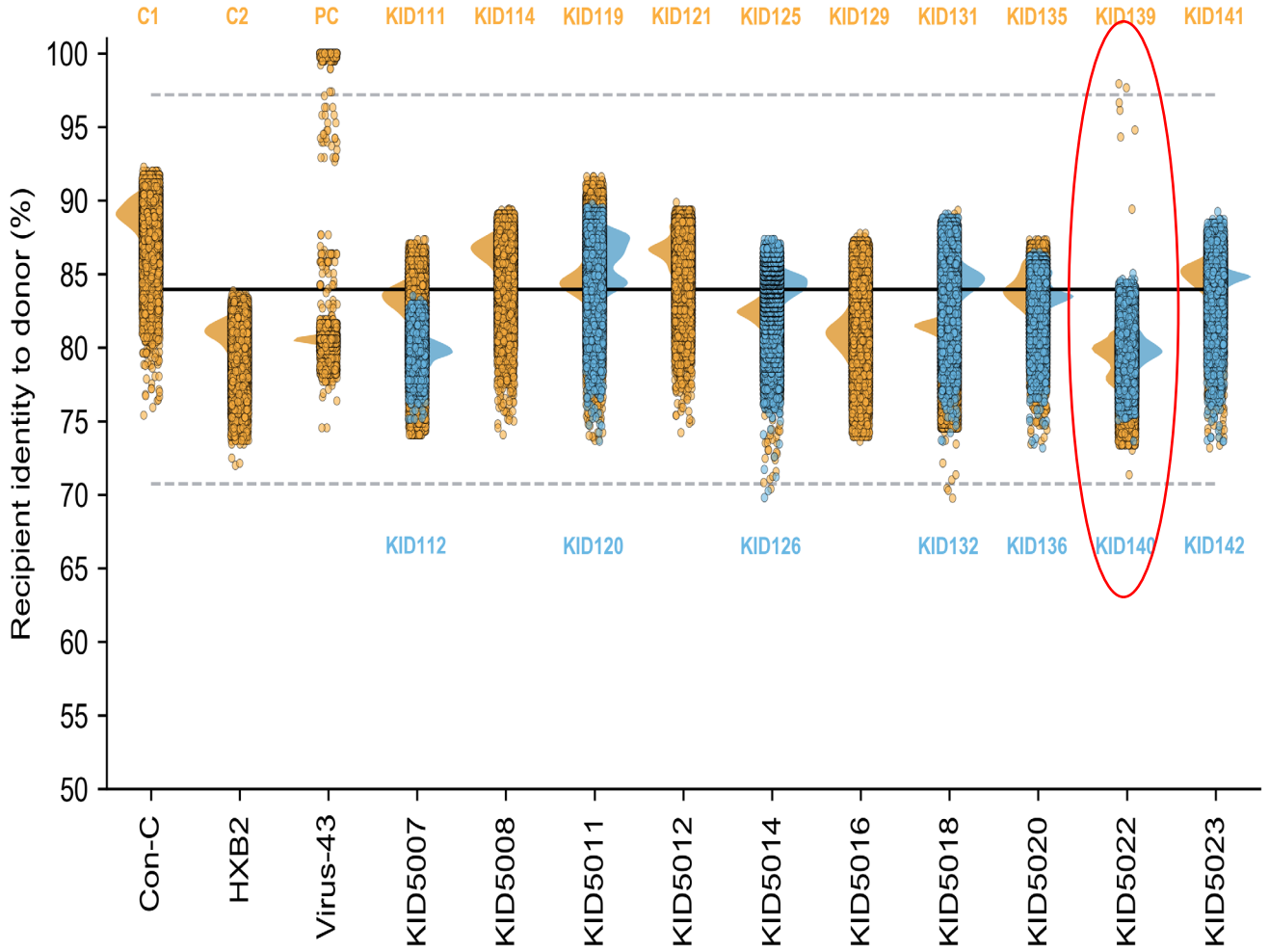
- Evaluated PBMC samples for drug-resistant mutations before transplantation and after transplantation
- Although drug-resistant mutations were found in the samples from 6 recipients, none were donor derived

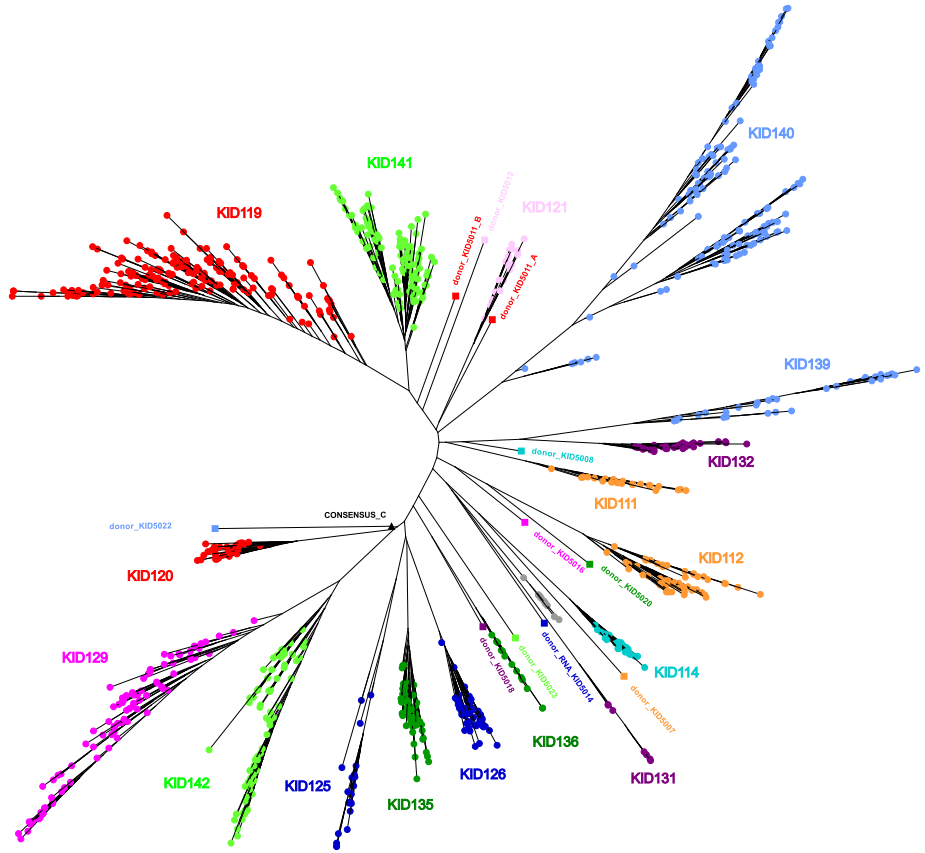


3. Evidence of viral inoculum from the donor

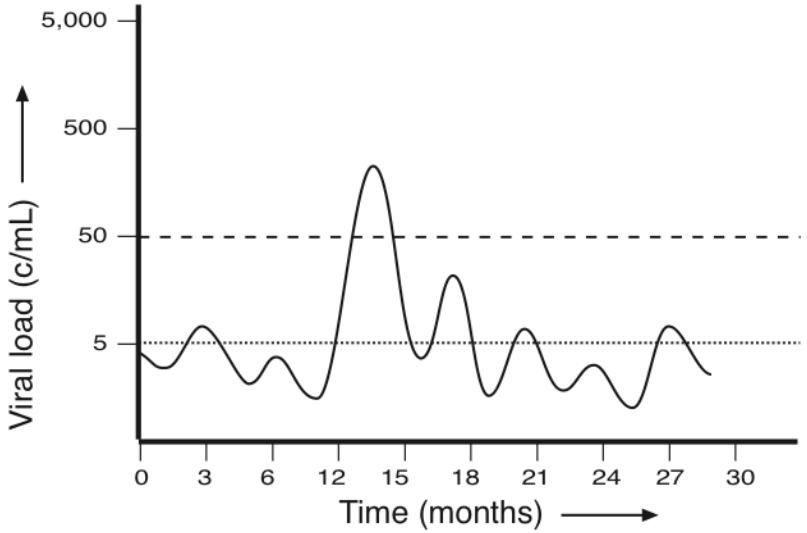
- Detected viral inoculum from the donor in the plasma samples from 8 recipients (32%) that were obtained at the earliest available time point after transplantation

4. Sustained donor-derived HIV superinfection





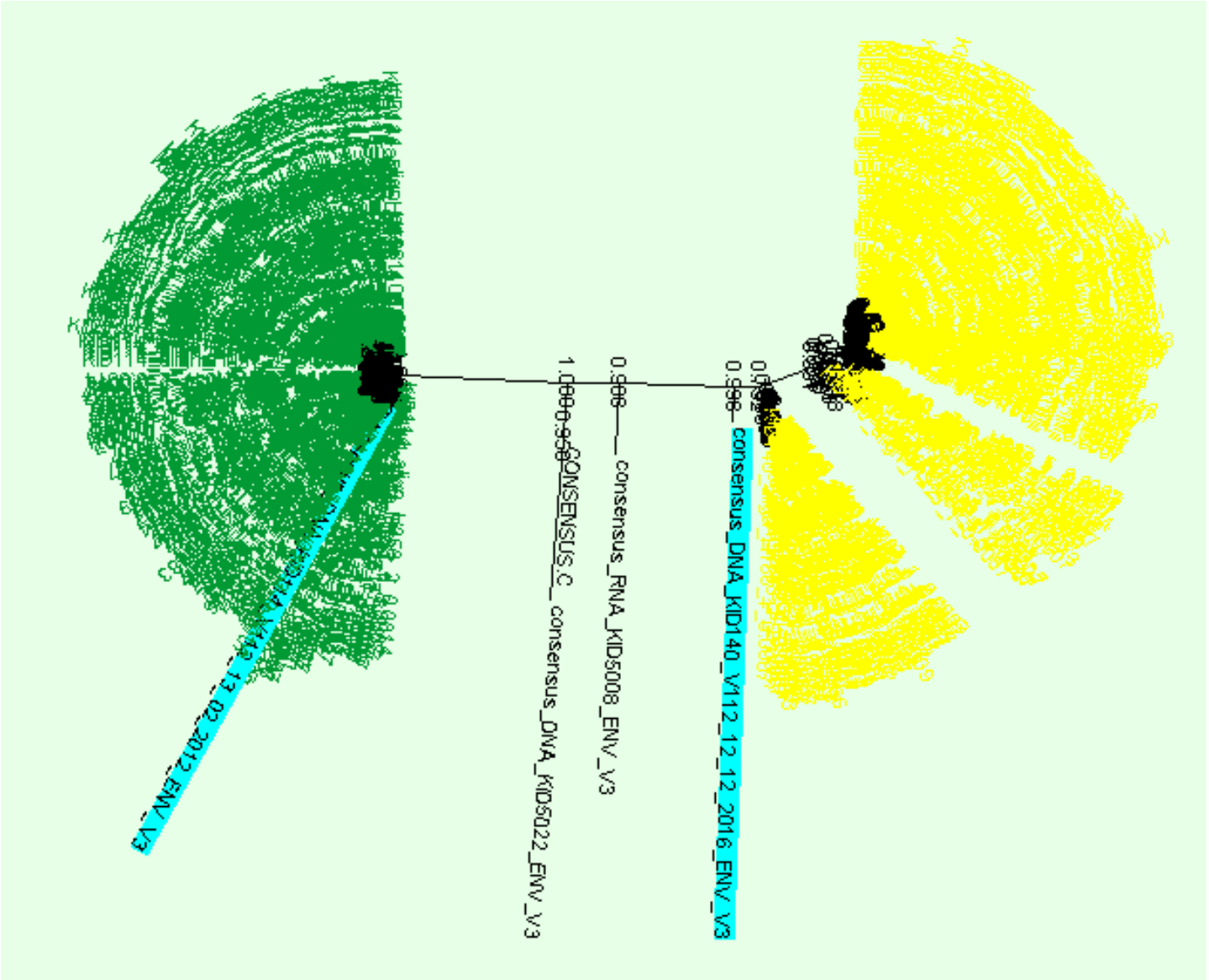
Viral Load Blips



Viral load blips in 6 patients, one patient experienced several recurrent blips

If you remove therapy, will the donor virus emerge?

No donor virus identified in this recipient with viral load blip



SUMMARY

- HIV positive donors provided an expansion of the donor pool
- The second viral strain is not a problem in controlled circumstances and with adherence to ART
- The landscape for HIV positive patients with elective surgery has changed dramatically and generally patients do well despite some underlying immunological issues
- Prognosis is good and outcomes are excellent in treated and stable HIV patients as long as there is strict adherence to ART

THANK YOU

- Andrew Redd, Tom Quinn (Hopkins NIH)
- Laurie Bertels, Kath Manning, Zunaid Barday, Nicci Wearne, Brendon Price (UCT)
- Francois Botha (Pathcare)
- Peter Stock (UCSF)