Donor infection and the impact on transplantation

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THE INSTITUTE OF TRANSPLANTATION

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Donor derived infection

Organ transplant is a low risk but an important route of transmission of infection from donor to recipient.

The most important resource for microbiology guidance in transplantation in the UK

SaBTO

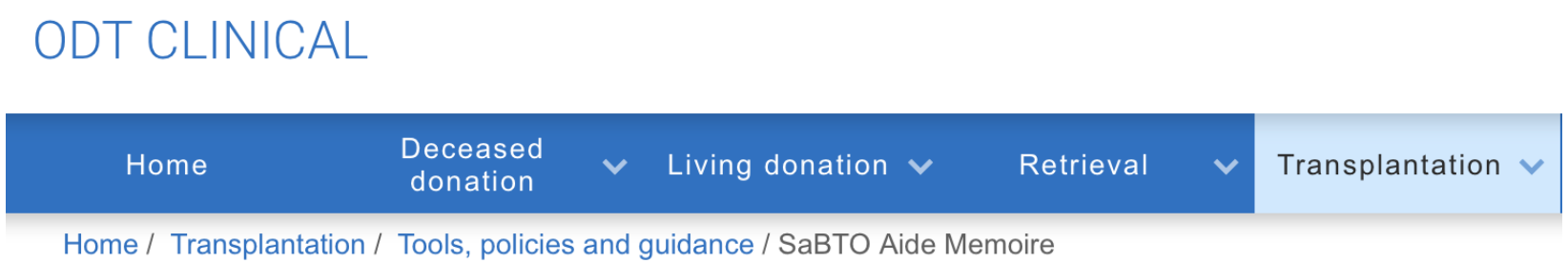
Advisory Committee on the Safety of Blood, Tissues and Organs

MICROBIOLOGICAL SAFETY GUIDELINES

PREVIOUSLY KNOWN AS

GUIDANCE ON THE MICROBIOLOGICAL SAFETY OF HUMAN ORGANS, TISSUES AND CELLS USED IN TRANSPLANTATION

Aide Memoire



Aide Memoi

Disease Type

Infection

Category

Viral infection

Specific Infection/Disease Type

Dengue virus (DENV)

Specific Infection/Disease Subtype

Donor with acute illness

Results: Infection, Viral infection, Dengue virus (DENV), Donor with acute illness

Recipient
Urgency:

Exceptional: DO NOT USE

Urgent: DO NOT USE

What are we dealing with ?

The degree of risk for transmission of infection carried with grafts, notably of viruses, is largely unknown and, for a specific organ, difficult to assess.

Days from Transplant to Recognition of Infection					
	0-30 days	31-90 days	91-180 days	>181 days	TOTAL
Viral	11	7	4	8	30
Bacterial	23	1	0	0	24
Fungal	20	5	2	1	27
Mycobacterial	2	2	2	0	6
Parasitic	7	4	6	1	18
TOTAL	63	19	14	10	106
	59%	18%	13%	9%	

Table 3– Mandatory and recommended screening of organ, tissue and cell donors

Infection	Serological Test	Organs*	Tissues**	Haematopoietic progenitor cells (HSPC), therapeutic cells (TC) and human embryonic stem cells**	Gametes and embryos***
HIV1/2	Anti-HIV1/2Ab/HIV Ag combo	**M**	**M**	**M**	**M**
HBV	HBsAg	**M**	**M**	**M**	**M**
	Anti-HBc	**M**	**M**	**M**	**M**
HCV	Anti-HCV IgG	**M**	**M**	**M**	**M**
HTLV1/2	Anti-HTLV1/2****	**R**	**M**	**M**	**M**
Syphilis	Anti-*T. pallidum* antibody	**R**	**M**	**M**	**R**
Toxoplasma gondii	Anti-*T. gondii* IgG	**R**	**NR**	**R*****	**NR**
CMV	Anti-CMV IgG	**R**	**NR**	**R**	**R**
EBV	Anti-EBV IgG	**R**	**NR**	**R**	**NR**
HEV	HEV RNA	**R**	**R**	**R**	**NR**
Chlamydia trachomatis	n/a	**NR**	**NR**	**NR**	**M**
Neisseria gonorrhoea	n/a	**NR**	**NR**	**NR**	**M**

M = Mandatory Tests as required by EUODD and EUTCD
R = Recommended tests
NR· = not required; n/a = not applicable;

ndatory
creening

Required Donor Information

- Treatment received in the illness before donation (including duration and dose of antimicrobial and other drug therapy)
- Vaccination history and immunisation status
- History of receipt of blood, blood components, blood products, tissue or organ graft.
- Previous or current immunosuppression (by disease or drugs) as this may affect the interpretation of test results or the donor's suitability.
- Travel History

Required Donor Information

- History of contact with animals and other vectors. Transplantation may transmit zoonotic infections.
- History that may have put the donor at increased risk of transmissible spongiform encephalopathies (TSEs).
- History of malignancy, recent infectious disease or exposure to an infectious disease.
- Behavioural history that could have put the donor at risk of transmissible pathogens This will include questions about risk behaviours such as recreational drug use, men who have sex with men (MSM), sex with commercial sex workers, sex with a partner know to have a sexually transmissible disease, acupuncture, tattooing and body piercing.
- Results of any recent microbiological tests should be reviewed.

What do you think are the risks?

Donor :

a 33-year-old male, had a known history of polysubstance abuse and other high risk forensic history. The cause of death was a cardiac arrest and subsequent hypoxic brain injury shortly preceded by elicit IV substance abuse.

OOHCA – Overdose – Cocktail of methadone, cocaine ? Others.

Recent release from HMP – Overdosed in HMP (Scotland)

Sofa surfing

Known active IVDU user since 2022.

Bitten from another human.

Infection – aspiration only .

Virology – EBV positive remaining virology negative at time of donation.

Had IVDU overdose earlier in the day – taken to ED , given Naloxone, self discharged and further IVDU overdose, found with needle in his arm

Transmission of Blood born virus

- Human immunodeficiency virus (HIV)
- Hepatitis C virus (HCV)
- Hepatitis B virus (HBV)
- CMV and EBV

Transmission rates

Hepatitis B 100 more transmissible than HIV

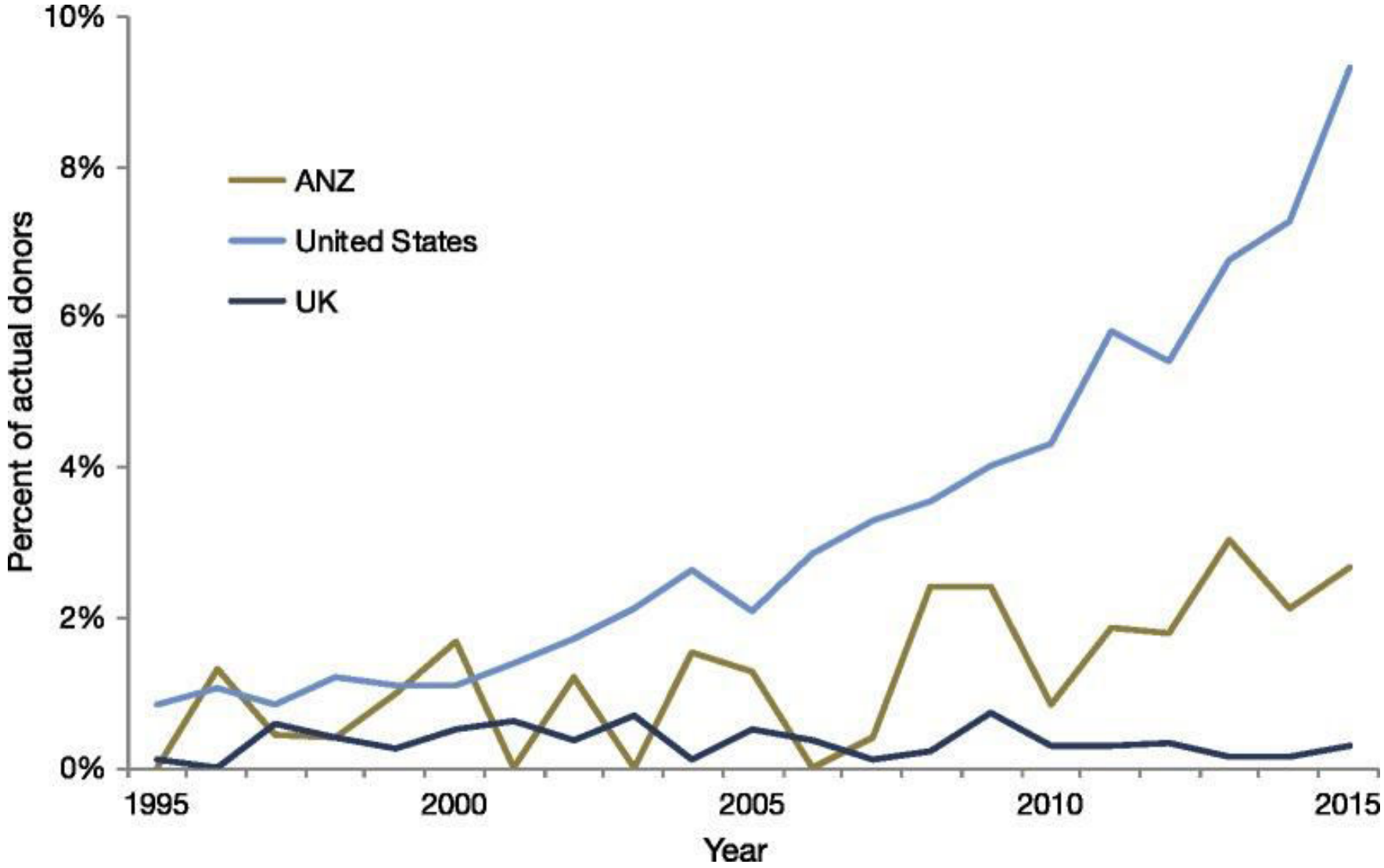
Hepatitis C 10 times more transmissible than HIV

HIV - often has the largest Stigma attached

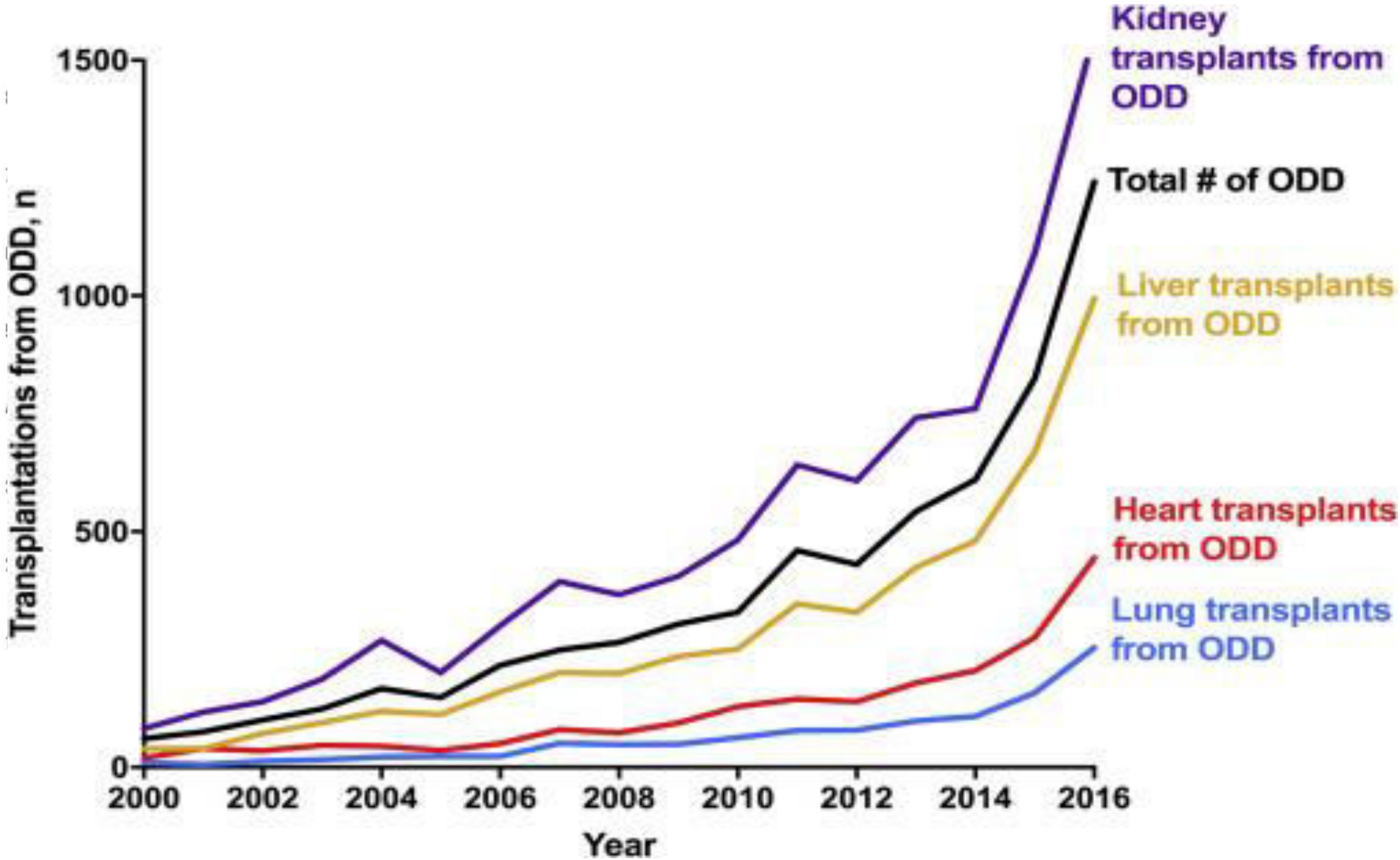
High Risk activity

Pathogens	Behavioral characteristics	Nonbehavioral characteristics
HIV	• MSM • IVDU • Noninjection illicit drug use • Multiple sex partners • Sex with partner known to be HIV-infected • Age ≤ 18 at first sexual intercourse	• STI • Marital status
HCV	• IVDU • Noninjection illicit drug use • Multiple sex partners • Sex worker • Inmates • Age ≤ 18 at first sexual intercourse • Sex with partner known to be HCV-infected • Sex with an injection drug user • Tattooing performed by a nonprofessional	• Hemodialysis • Receipt of blood transfusion • Signs and symptoms (eg, jaundice, elevated ALT) • STI • Marital status
HBV	• MSM • IVDU • Multiple sex partners	• Hemodialysis • STI • Marital status

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; MSM, men who have sex



Twenty-year trends in the percentage of donors with drug overdose (intended or unintended) as a cause of death in Australia and New Zealand (ANZ) compared with the United Kingdom (UK) and United States (data sources: Australia and New Zealand Organ Donation Registry [ANZOD], Organ Procurement and Transplantation Network [OPTN], National Health Service Blood and Transplant [NHSBT]).

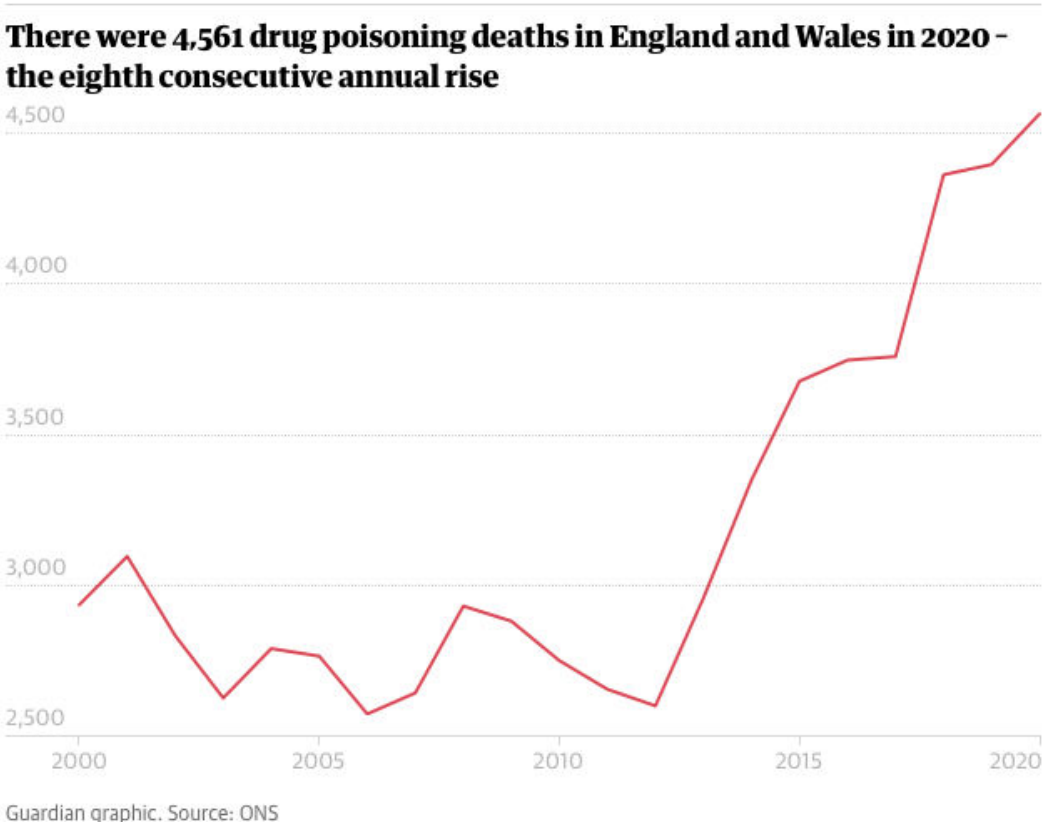

Kidney transplants from ODD
Total # of ODD
Liver transplants from ODD
Heart transplants from ODD
Lung transplants from ODD
Transplantations from ODD, n
1500
1000
500
0
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year

Drug poisonings in England and Wales

The rate of drug poisonings continues to increase

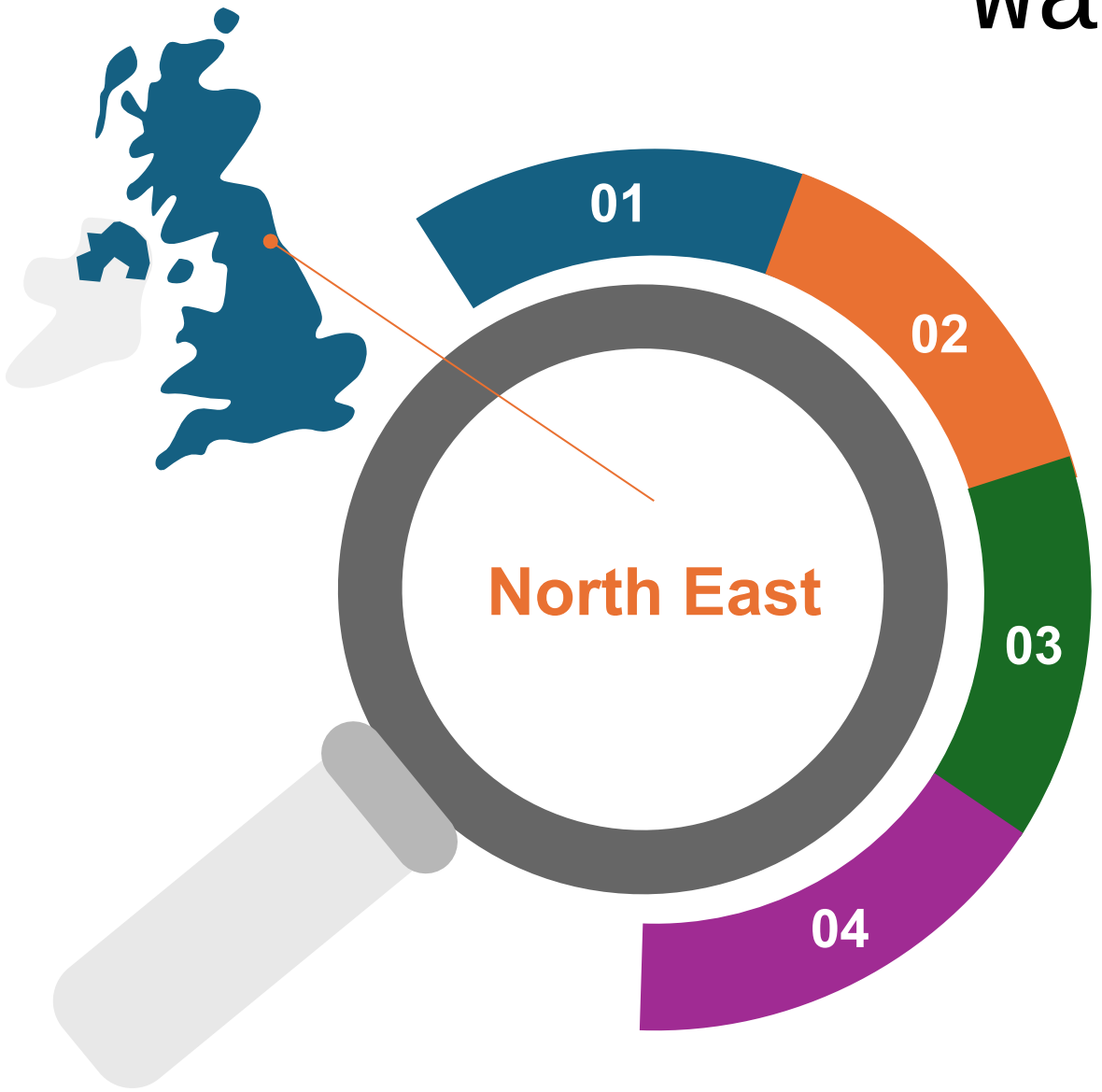
Rates of drug-related poisoning were 60.9% higher in 2020 (79.5 deaths per million) than they were in 2010 (49.4 per million).

The rate has increased every year since 2012



ONS:Deaths related to drug poisoning in England and Wales: 2020 registrations

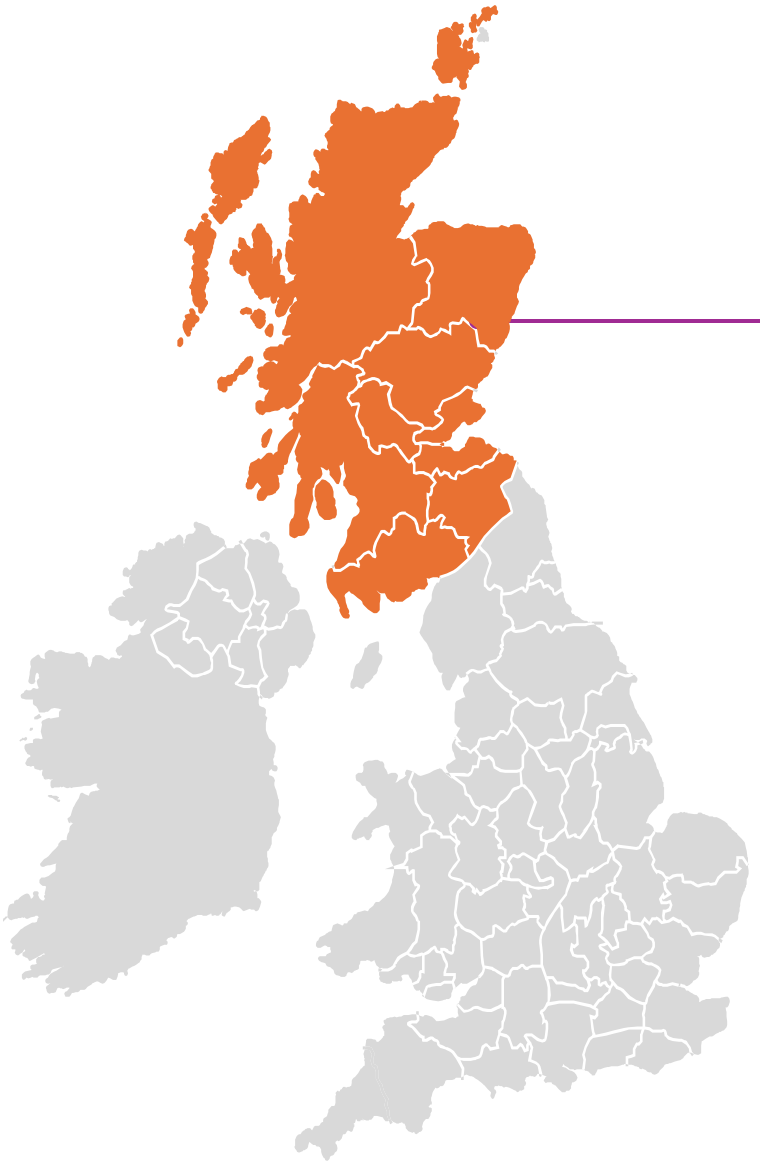
Regional Variation (England and Wales)

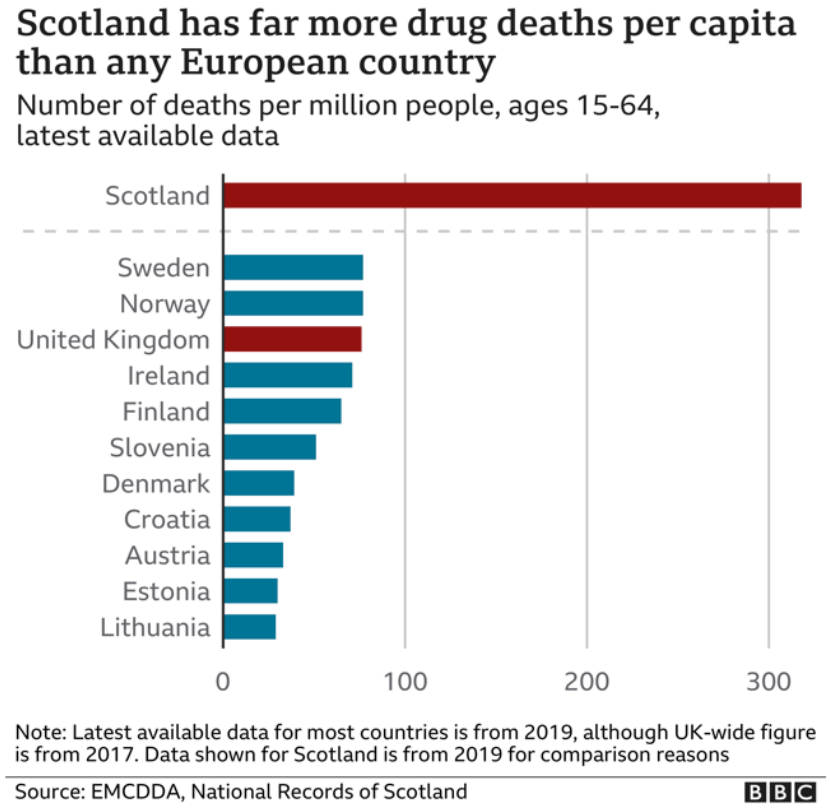


North - South Divide

In 2020, the highest rate of drug misuse deaths was observed in the North East (104.6 deaths per million; 258 registered deaths), while the lowest rate was in London (33.1 deaths per million; 256 deaths).

The North East has had the highest rate of drug misuse for the past eight years and has a statistically

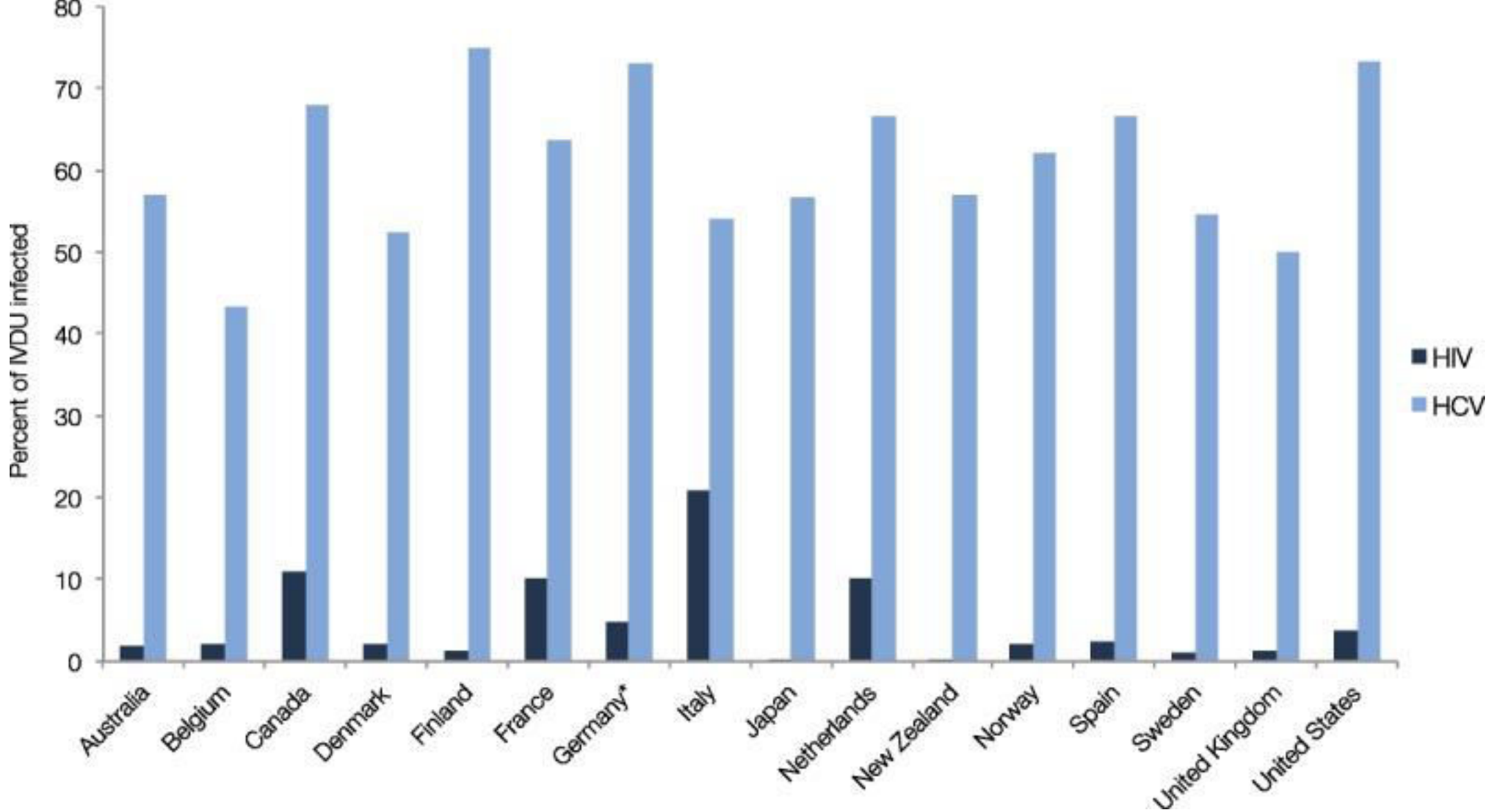




Scotland

It means Scotland continues to have by far the highest drug death rate recorded by any country in Europe.

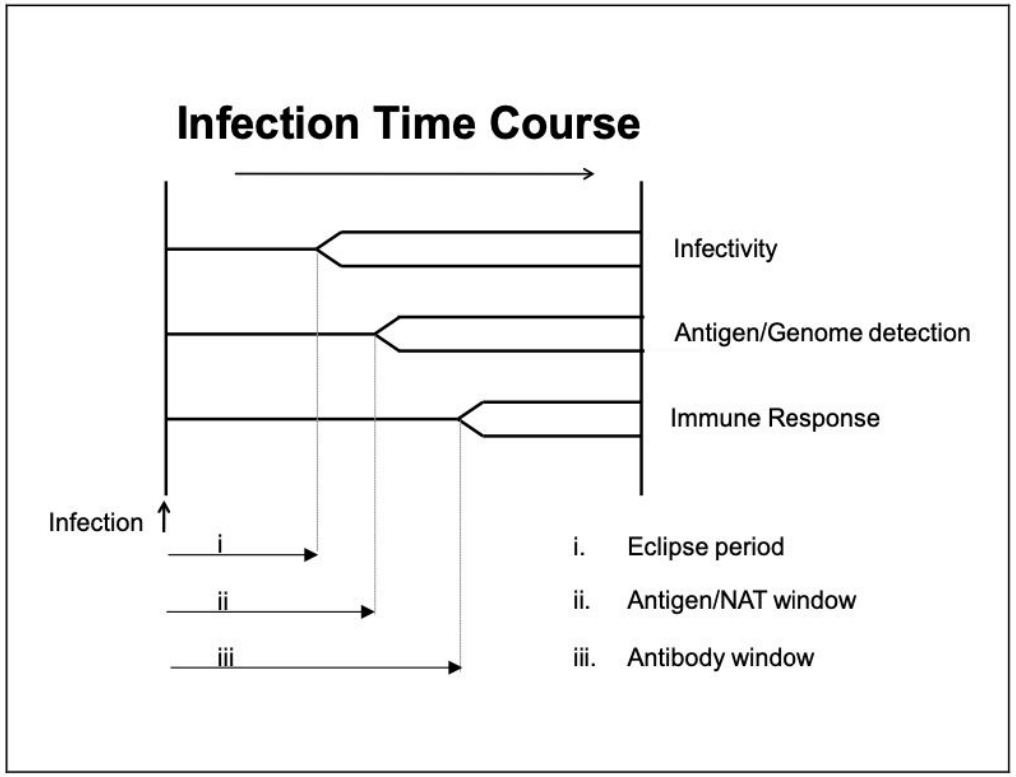
And its rate is more than three-and-a-half times that of England and Wales.



Estimated prevalence of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) among people who inject drugs in selected high-income countries. HCV prevalence estimates represent mid-range estimates (source of HCV data: United Nations Office on Drugs and Crime http://unodc.org; source of HIV data: UNAIDS aidsinfo. unaids.org). *HCV estimate for Germany represents high range estimate for the year 2011. IVDU, intravenous drug users.

Interpreting donor test results

- Following exposure to, and infection by, a microbiological agent there is a period of time during which no microbe can be readily recovered from the host; this is classically called the eclipse period.
- Donations taken during this period are unlikely to be infectious but in practice this would not be safe and should be avoided.



** Not always correct

Infection Time Course

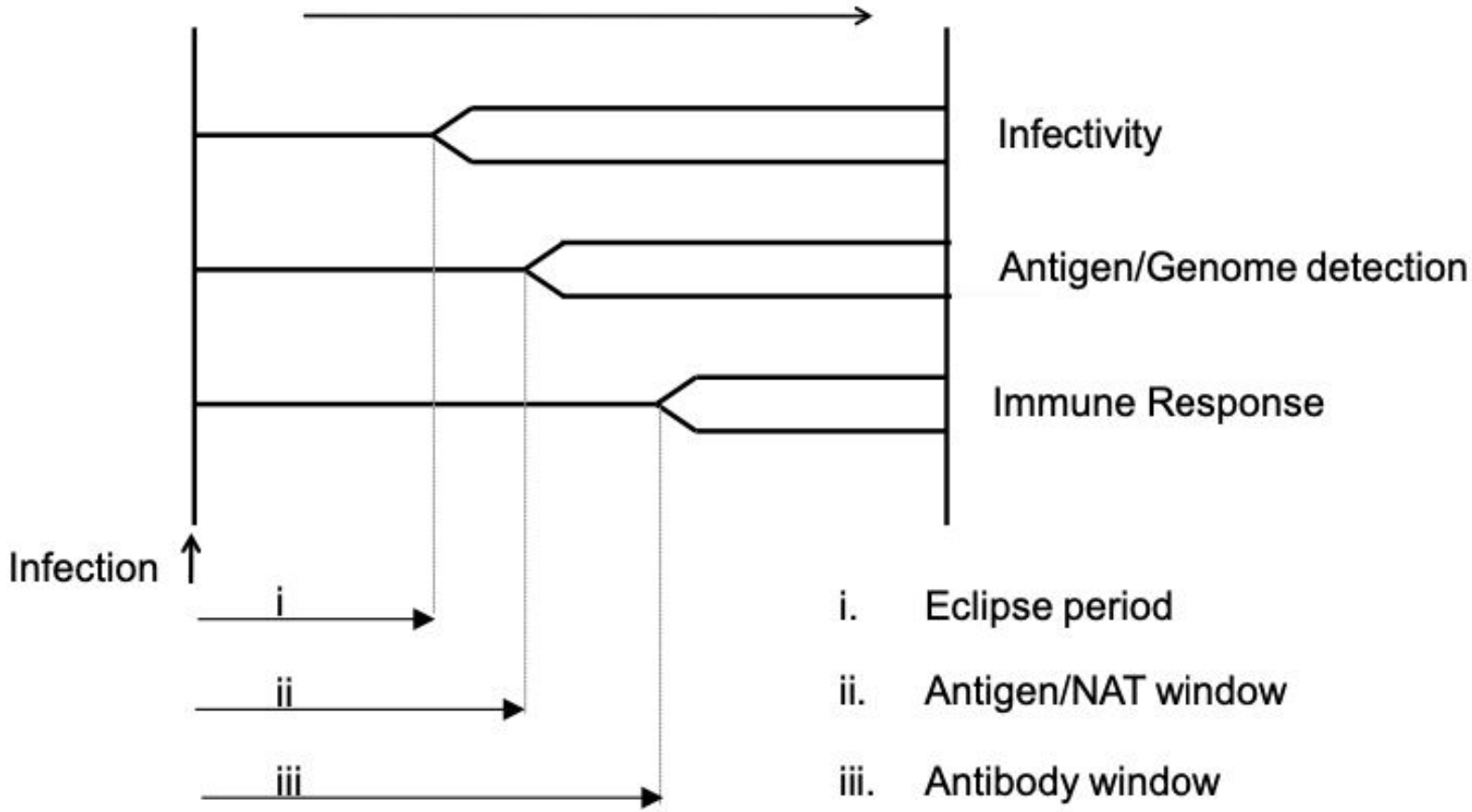


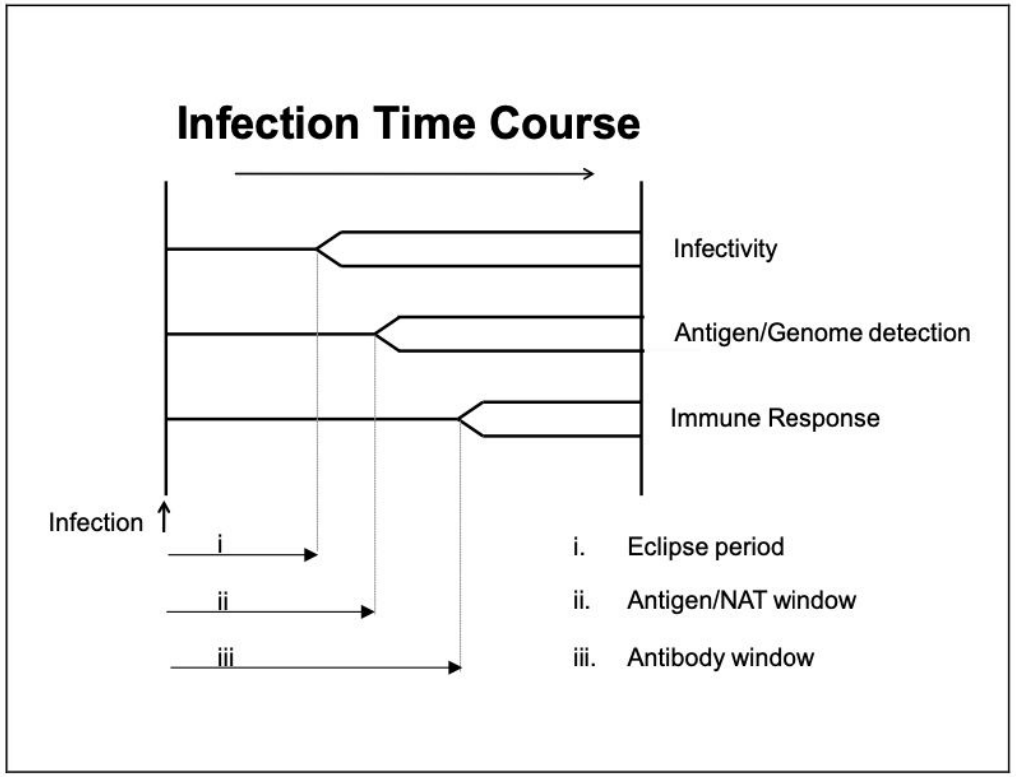
Table 1: Estimates of window period length for different testing methods*

Pathogen	Standard serology	Enhanced serology (fourth generation or combined antibody-antigen tests)	Nucleic acid testing
HIV	17–22 days (5–8)	~7–16 days (9,10)	5–6 days (5,6)
HCV	~70 days (5,8,11)	~40–50 days (12–14)	3–5 days (5,11)
HBV	35–44 days (15,16)	Not applicable	20–22 days (8,15)

Would you take the organ?

Interpreting donor test results

- Following exposure to, and infection by, a microbiological agent there is a period of time during which no microbe can be readily recovered from the host; this is classically called the eclipse period.
- Donations taken during this period are unlikely to be infectious but in practice this would not be safe and should be avoided.



** Not always correct

Case - What happened next?

Kidney implantation : uneventful

No damage to the kidney, 2 arteries one vein.

Long cold ischemic time - 23 hours

Delayed graft function

Named offer

Male 40 – (active on the TX list for 9 years).

Primary diagnosis IgA Nephropathy .

Previous renal transplant

No live donors.

HDX dependent, managing well no access issues.

Highly sensitised – tier score 9 – not suitable for imlifidase.

Day 3

Contact from NHSBT 3 days after implantation - extended provisional virology showing raised hepatitis C titres in donor.

Confirmation 24 hours later donor was now Hepatitis C positive at time of donation.

Screen the recipient

Hepatitis C transmission from donor to recipient

However

- We had identified that the donor was very high risk
- Hepatitis C was most likely infection to be transmitted but others could also be transmitted
- Hep C- readily treatable
- Hep B – lower risk, recipient vaccinated and good response
- HIV- with treatment , provides almost normal life expectancy (better than dialysis)
- Possibility of other unknown infections
- Discussed all of these with the donor prior to transplant. Discussed with virology, microbiology, Liver and Infectious diseases.

Consent – prior to transplant

- Full written and verbal consent for high risk donor
- Risk mediation considered
- Patients' family informed
- Screening pathway in place

- Everyone fully aware prior to transplant

- When transmission occurred - patient was very unbothered, much more excited to have a kidney

Outcome

- Recipient became Hepatitis C POSITIVE almost immediately after transplantation .
- Referred to liver specialist for treatment
- - Maviret given (Glecaprevir 100mgs/Pibrentasvir 40mgs) once GFR was suitable.
- HCV Converted from positive to negative within 8 weeks after treatment.
- Genotype 3

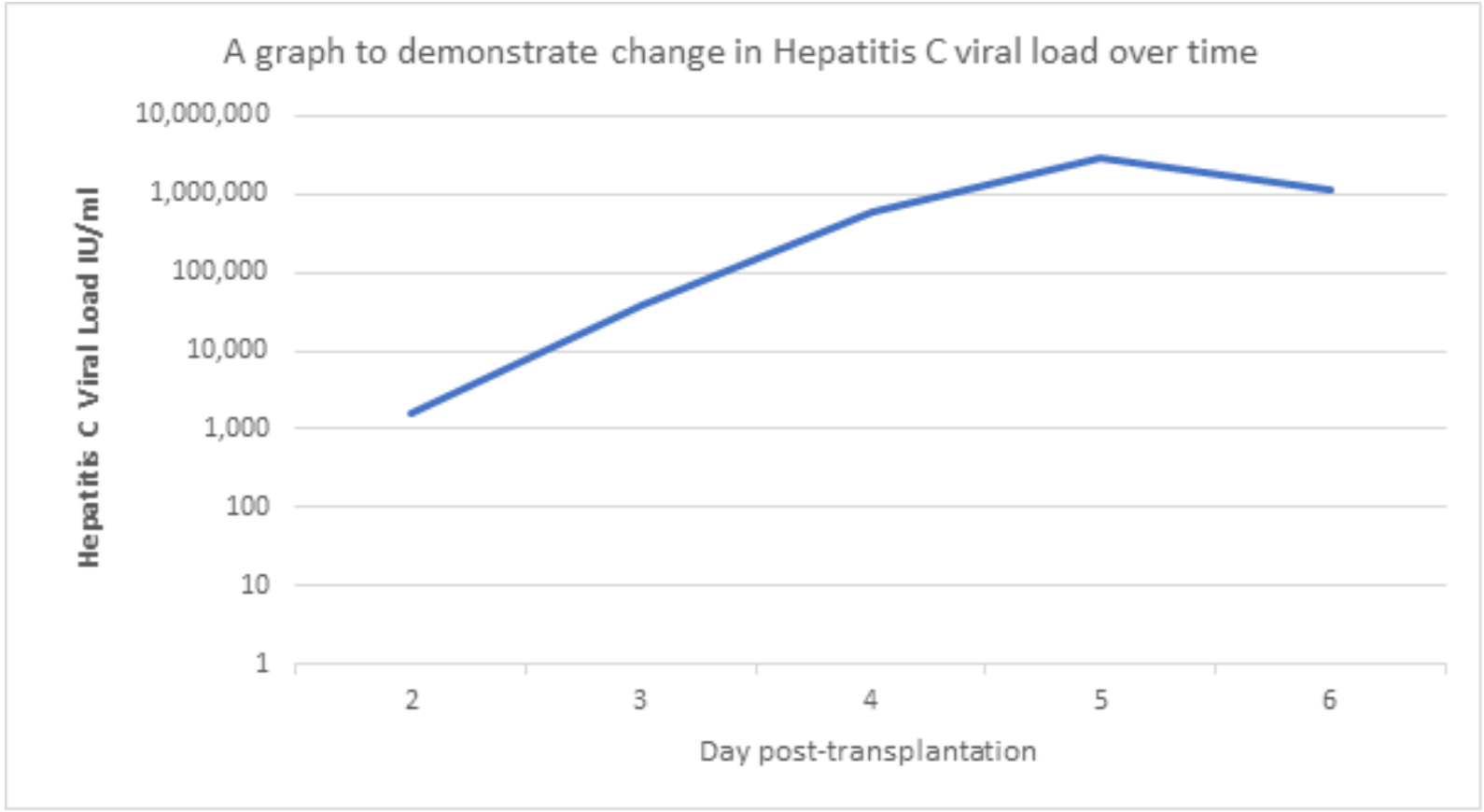
Outcome

- Inpatient on 38 for 13 days.
- Transplanted kidney started functioning from day 7.
- Small coffee ground vomit managed with PPI.
- USS- small focal collection – resolved with no intervention.
- Current eGFR > 79, Creatine 101
- On phased return to work
- Transplant kidney is now 6 months old

Viral transmission was much quicker than we expected

(pre transplant) - HCV RNA Not detected

d0, Transplant
d1 - 572 IU/ml
d2 - 1540 IU/ml
d3 - 38900 IU/ml
d4 - 467000 IU/ml (serum)
d4 - 581000 IU/ml (EDTA)
d5 - 2,910,000 IU/ml
d6 - 1,140,000 IU/ml



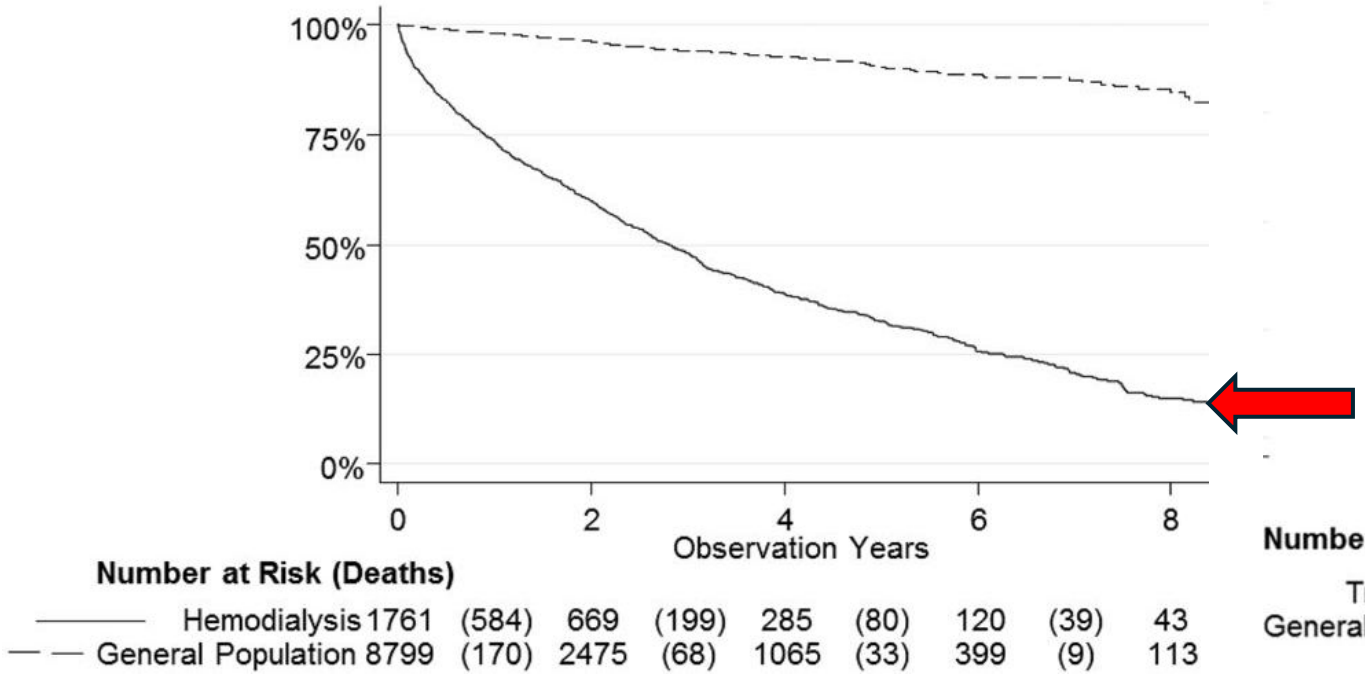
How does this impact transplantation?

Adult standard criteria DBD donor kidney offer decline rates

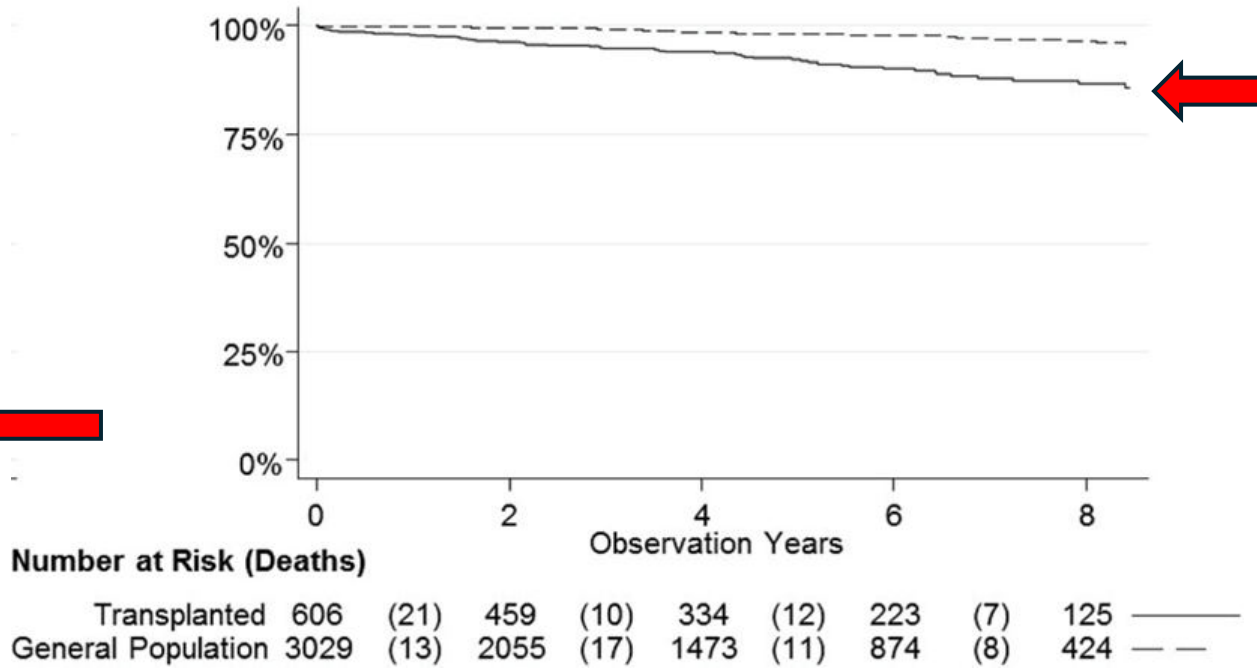
~50%

Survival

Dialysis



Transplant



We need more kidneys!

We need [redacted]

to use kidneys better and think outside of the box

CMV and EBV

- The majority of adult populations worldwide are latently infected with CMV and/or EBV,

- CMV: 20% to 100%
- EBV: 50% to 90%

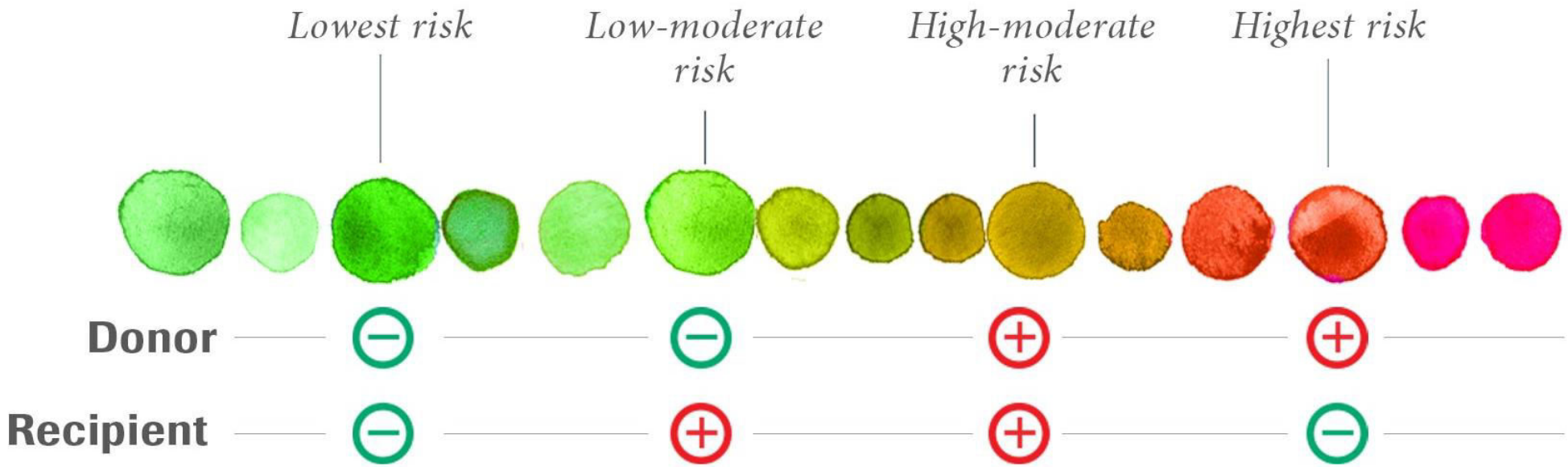
of populations older than 18 years, respectively

CMV and EBV

- CMV and EBV cause lifelong infection, and organs from seropositive donors may transmit infection, potentially causing severe disease in a seronegative recipient.

- Latent CMV and EBV may also reactivate in immunosuppressed seropositive patients post transplantation.

- No contraindications exist for organ donation in the case of donors with latent CMV infection, although recipient morbidity increases in the case of D+/R− combinations.


Lowest risk
Low-moderate risk
High-moderate risk
Highest risk
Donor
Recipient

Human T-cell Lymphotropic Virus (HTLV)

- The Human T-cell lymphocytic virus-1 (HTLV-1) is an oncogenic retrovirus that preferentially infects CD4+ T-cells.
- Transmission may occur as a result of breast feeding, IV drug use, sexual intercourse or blood transfusion.
- Although infection is usually asymptomatic in most individuals, approximately 2% to 5% of infected individuals will subsequently develop acute T-cell leukaemia/lymphoma (ATL) around 20 to 30 years after infection. (10 to 20 years if transplant related)
- Some studios show 40% risk of HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) in SOT (compares to <0.4% in non transplant) (+ve to +ve however is low risk)

Devastating Disease. Therefore generally don't take organs

Toxoplasma gondii

- Transmission of an infection with *T. gondii* occurs most commonly when a seronegative recipient receives an organ from a seropositive donor.
- Whereas the occurrence of toxoplasmosis following non-cardiac organ transplantation is low, the reported prevalence in serologically **mismatched (D+/R–) heart and heart-lung recipients** in the absence of antimicrobial prophylaxis can be as high as 75% due to the transmission of *T. gondii* cysts present within cardiac tissue.

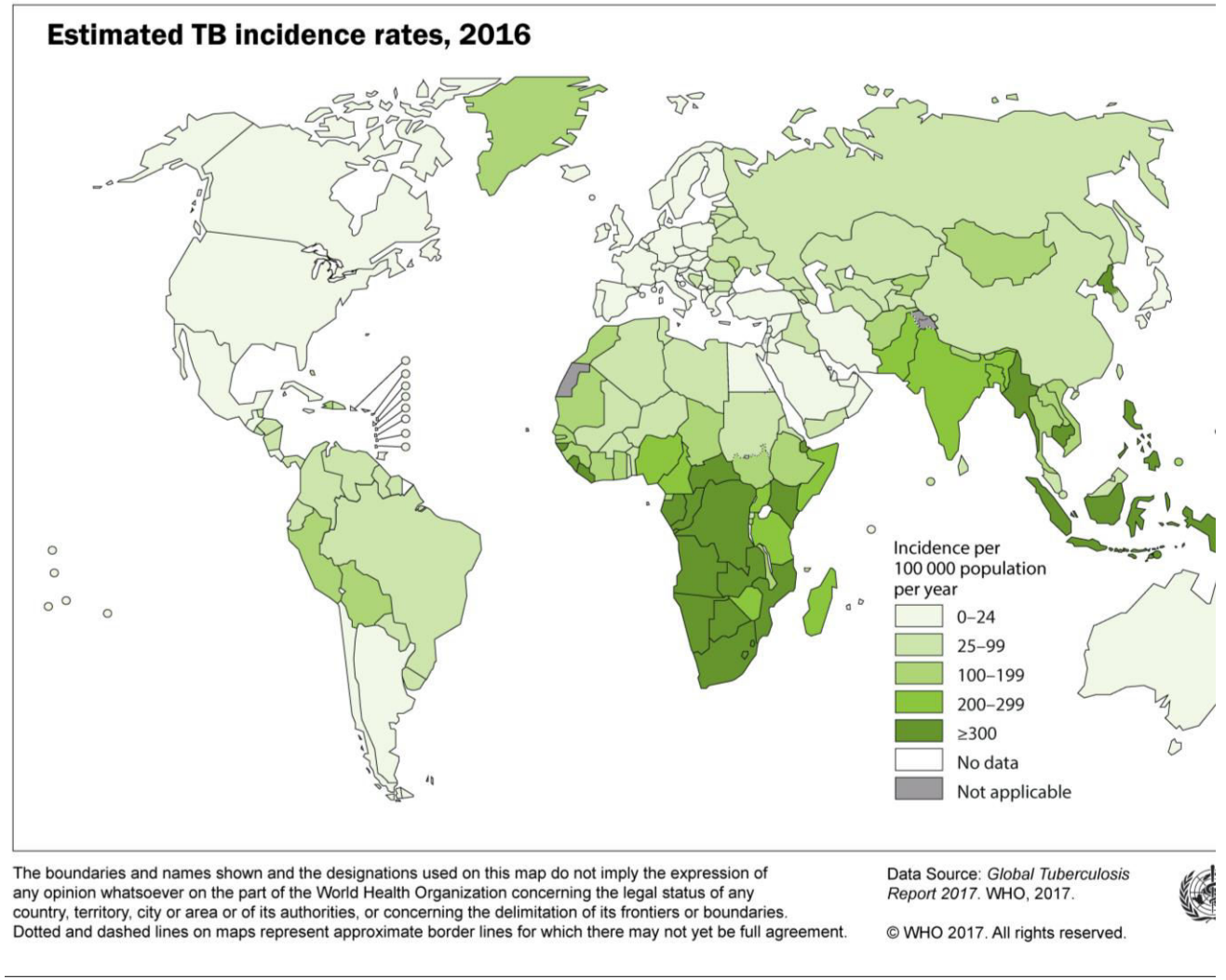
If positive

- Donation permitted
- Informs need for prophylaxis in heart recipients

TB - Tuberculosis

- Donation of organs and tissues is contraindicated from donors with active disease or within the first six months of anti-tuberculosis treatment.

- Previous disease or from a risk area - requires donor prophylaxis.



Hepatitis E Virus

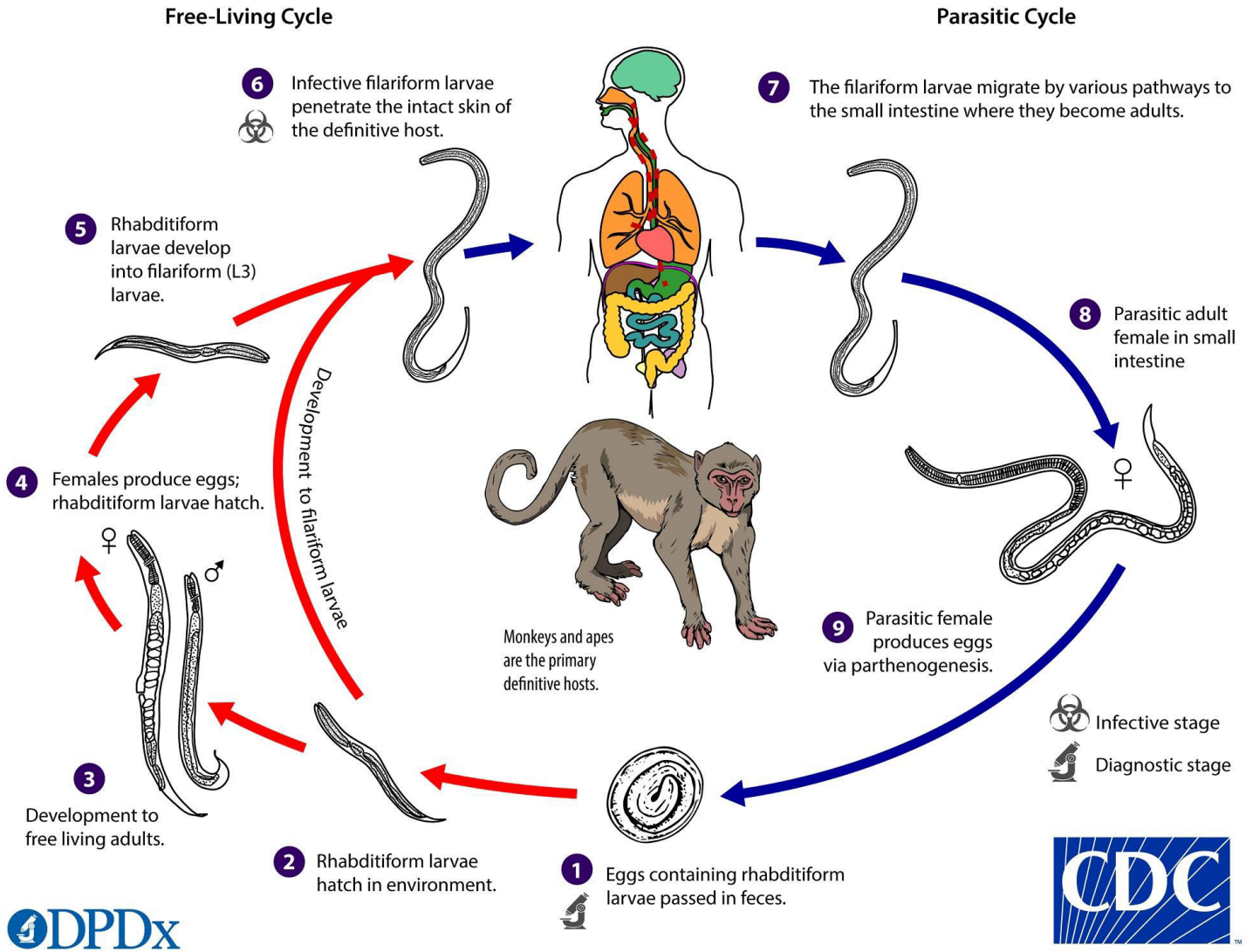
- Hepatitis E virus (HEV) is overall the world's most common cause of acute viral hepatitis.

- If positive
- Donation permitted. Informs post transplant management

Strongyloides stercoralis

- Asymptomatic carriage with strongyloides stercoralis has been reported most often in donors who were both born in and lived for some while in endemic areas which include most of the Tropics and Sub-tropics.
- An Eosinophilia may or may not be present. Transmission to immuno-compromised recipients is often associated with significant morbidity and a high mortality rate.
- Pre-donation identification from stool sampling and serology, most practicable for a live donor allows for effective recipient prophylaxis.

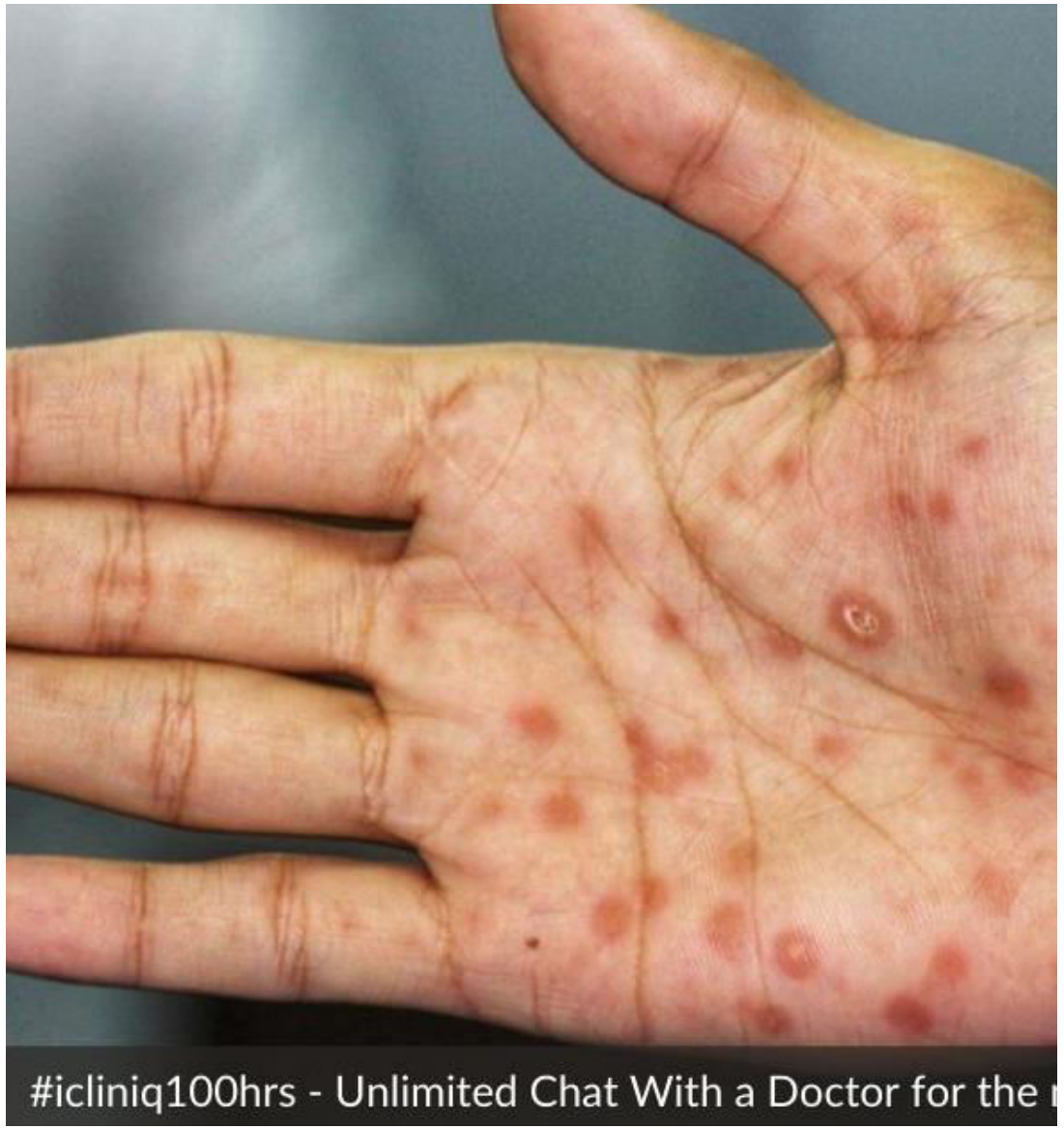
Strongyloides fuelleborni



Treponema pallidum (Syphilis)

- Syphilis is never a contraindication for using organs

- Penicillin should be administered to recipients of serologically reactive donors.



Drug resistant bacteria e.g. methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant Enterococcus (VRE), carbapenemase-producing Enterobacteriaceae (CPE)

Drug resistant bacteria can be transmitted from donor to recipient. Transmitted infections are difficult to treat and are associated with poorer outcome in the recipient.

- The presence of drug resistant bacteria in the donor is a relative contraindication to solid organ transplantation.
- Specialist microbiological advice must be sought.
- Careful consideration of benefits from transplant is required.

Yearly Epidemic Influenza

- UK guidelines state that **lungs and bowel** should not be used from donors with confirmed influenza infection.
- Other organs may be offered, and the final decision lies with the transplanting surgeon.

Meningoencephalitis of unknown cause

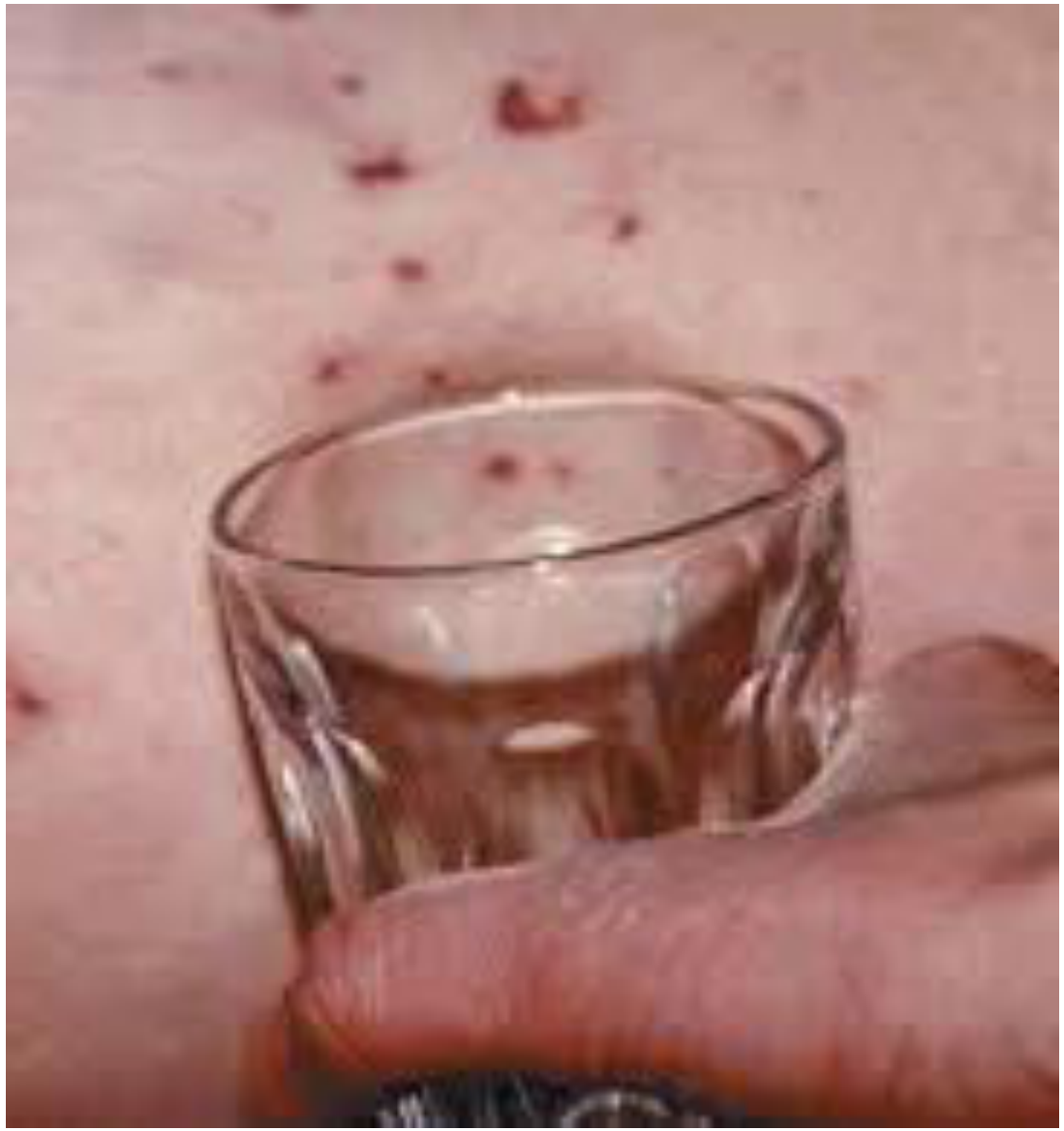
- Donors with undiagnosed meningoencephalitis are an uncommon but potentially lethal source of donor-derived infection.

- Transmission of rabies, LCMV, WNV, *Mycobacterium tuberculosis*, *Cryptococcus*, *Coccidiodes immitis*, *Aspergillums,* and *Balamuthia* have occurred when donors with meningitis or encephalitis of unknown cause have been used as organ donors.

- For this reason, any meningitis or encephalitis without a proven cause should be an absolute contraindication to transplantation, according to the international guidelines

Bacterial meningitis

If bacterial meningitis has been confirmed, and there is no visible damage or local infection in the organ or tissues required at retrieval, the donation of the organs, tissues and cells are acceptable provided appropriate treatment has been administered to the donor.



Transmissible Spongiform Encephalopathies (TSEs) (Prion)

TSEs (otherwise known as prion diseases) are a group of fatal transmissible neurodegenerative disorders that in humans occur in sporadic, genetic and acquired forms.

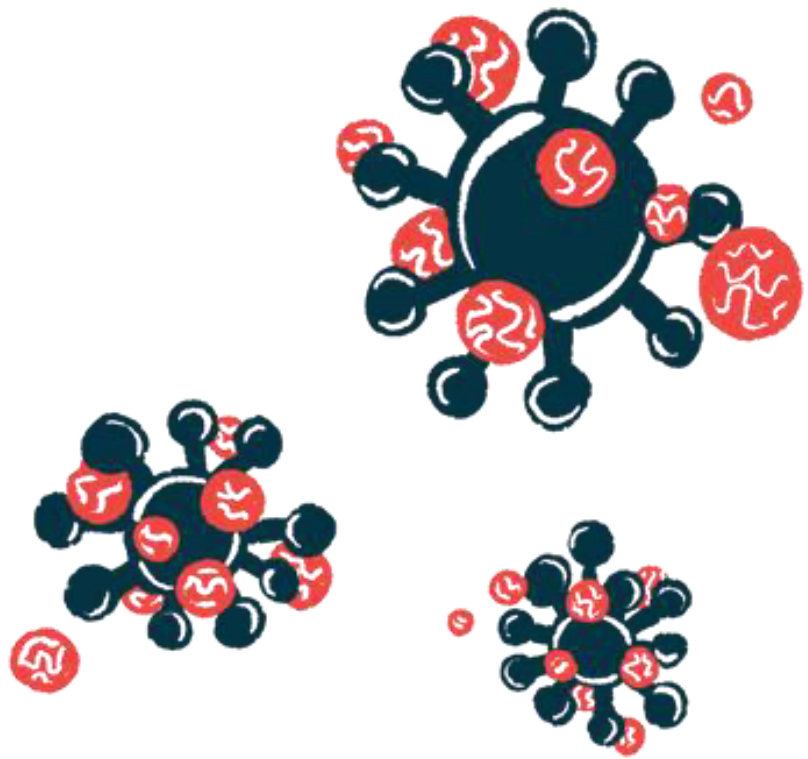
The commonest human TSE, Creutzfeldt-Jakob disease, occurs in all three forms:

1. Genetic (gCJD),
2. Sporadic (sCJD)
3. Acquired (Variant CJD,vCJD, and iatrogenic CJD,iCJD).

Exclusions from organ and/or tissue donation based on possible TSE exposure

	Solid Organ Donors
Definite, probable or possible case of human TSE, including CJD and vCJD	Absolute contra-indication
Individual with a neurological disease of unknown aetiology	Absolute contra-indication
Individual whose blood relatives have had familial CJD [1]	Absolute contra-indication
Individual "presumed infected" with vCJD[2]	Absolute contra-indication
Individual "at increased risk of CJD/vCJD" (for public health purposes)[3]	**Individual assessment required [4]**
History of definite [5] or probable [6] blood transfusion since 1980	**Individual assessment required [4]**
History of receipt of *dura mater* graft	**Individual assessment required [4]**
History of definite receipt of tissue since 1980	**Individual assessment required [4]**
History of receipt of pituitary derived growth hormone and/or gonadotrophin	**Individual assessment required [4]**
History of receipt of organ	**Individual assessment required [4]**

BK Nephropathy

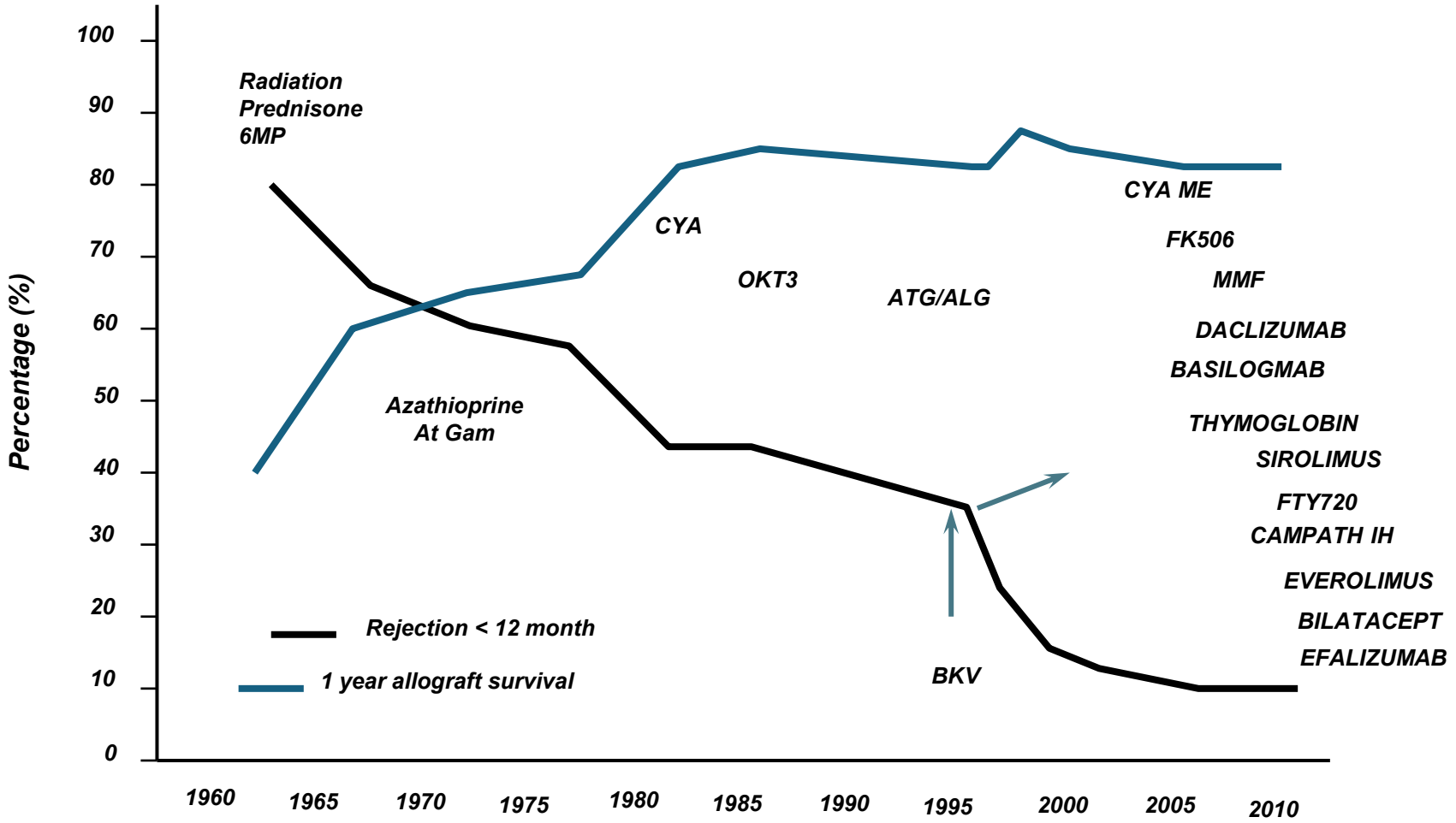


BK virus-associated nephropathy (BKpyVaN) is an important cause of graft loss in kidney transplant recipients

Directly or indirectly

BK Polyomavirus (BKpyV) causes pre-mature allograft failure in 10-20% of kidney transplant without monitoring

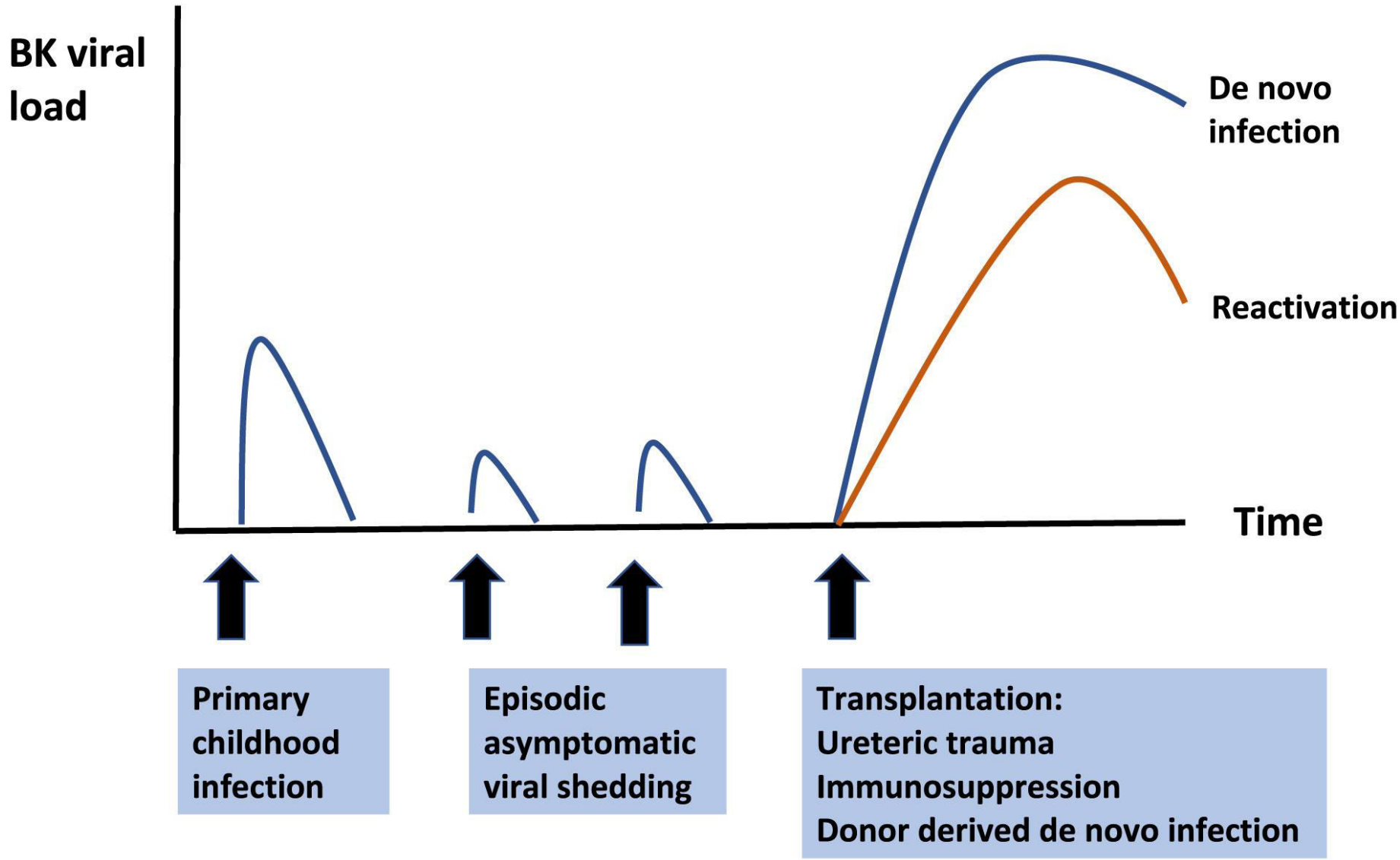
Immunosuppression is the main risk factor for BKV reactivation



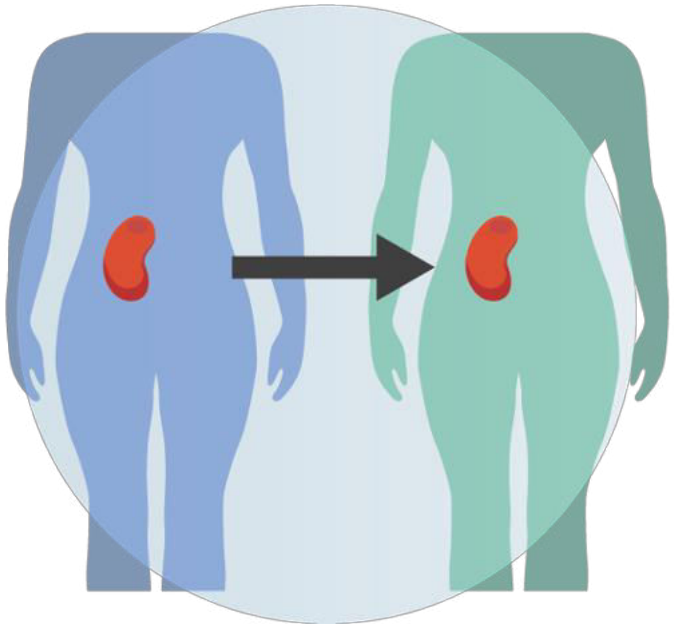
The successful advent of increasingly efficacious immunosuppression has been accompanied by high rates of BK viremia (BKV) in up to 30% of kidney transplant recipients

Epidemiology

- Prevalence:
  - primary infection in childhood without specific symptoms
  - 80% individuals having antibodies against BK virus
- Mode of spread :
  - respiratory droplets, The most common mode of transmission is through respiratory secretions, resulting in a mild self-limited respiratory infection
  - organ transplantation.
  - Other speculated modes are urine, semen, blood transfusion
  - Viral spread to other organs is believed to be via bloodstream and in immunocompetent individuals, it remains clinically silent in renal tubular epithelium.
- Kidney transplant :
  - BK viruria can be seen in 60% of kidney transplant recipients
  - BK viremia is seen in up to 13% kidney transplant recipients
  - BK nephropathy in 10%


BK viral load
De novo infection
Reactivation
Time
Primary childhood infection
Episodic asymptomatic viral shedding
Transplantation:
Ureteric trauma
Immunosuppression
Donor derived de novo infection

Risk Factors



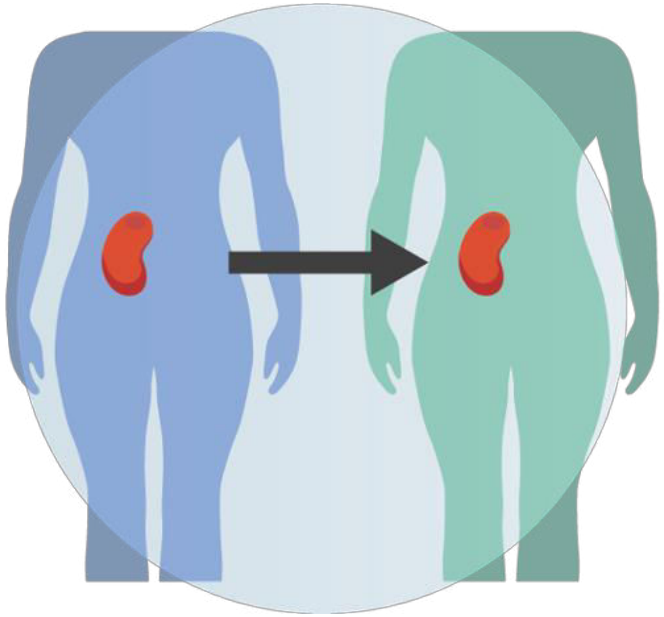
Donor factors:

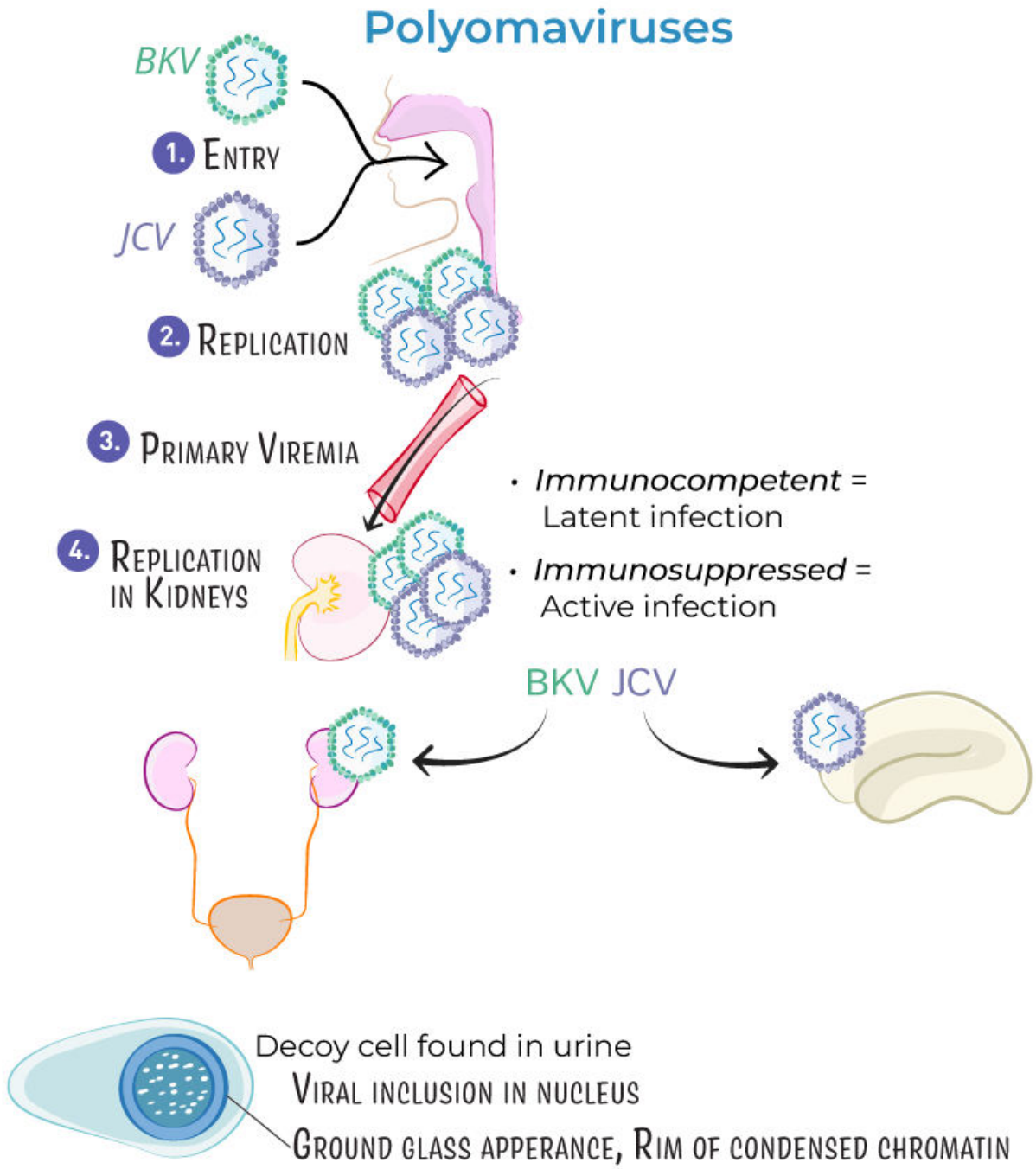
- donor urinary BKPyV shedding,
- very high donor antibody levels against BKPyV major capsid protein Vp1,
- certain donor BKPyV genotypes,
- BKPyV genotypes different from the recipient (mismatching).

Risk Factors

Transplantation factors:

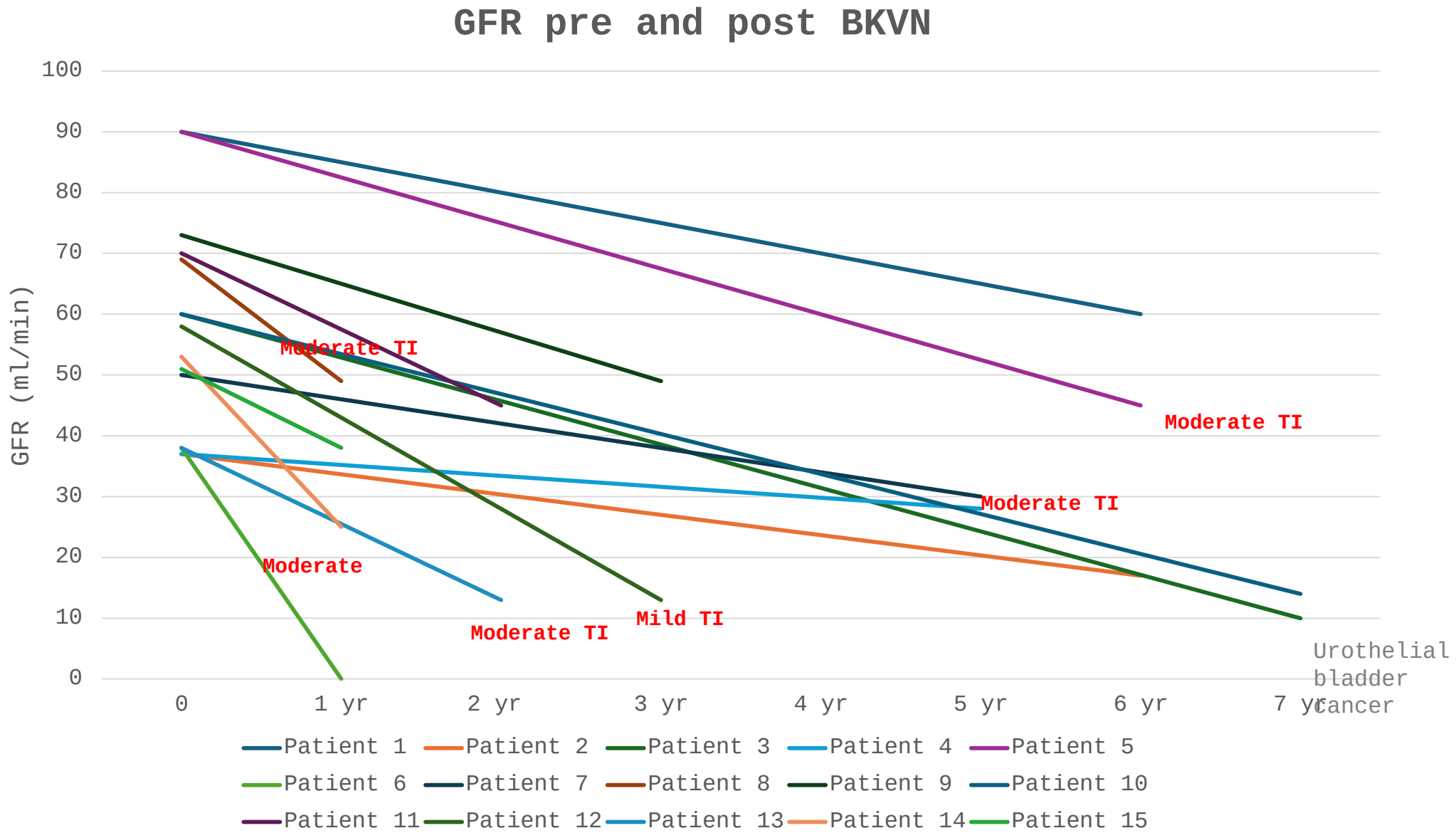
- use of tacrolimus compared with cyclosporine
- T cell–depleting agents
- acute rejection episodes
- higher corticosteroid exposure
- AB0-incompatible transplants
- ureteric stents.



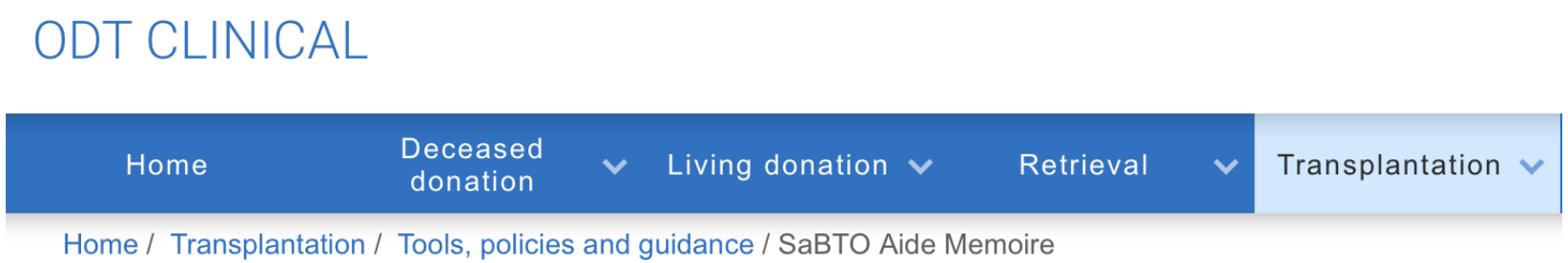


BK is most commonly associated with renal involvement, such as ureteral stenosis, hemorrhagic cystitis and nephropathy. Less commonly, it is associated with pneumonitis, retinitis, liver disease and meningoencephalitis

Progressive multifocal leukoencephalopathy


GFR pre and post BKVN
GFR (ml/min)
100
90
80
70
60
50
40
30
20
10
0
0
1 yr
2 yr
3 yr
4 yr
5 yr
6 yr
7 yr
Moderate TI
Moderate TI
Moderate TI
Moderate
Moderate TI
Mild TI
Urothelial bladder cancer
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15

Aide Memoire



https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/sabto-aide-memoire/

Thank you