Strategies for Managing Living Donors with Novel Microbes

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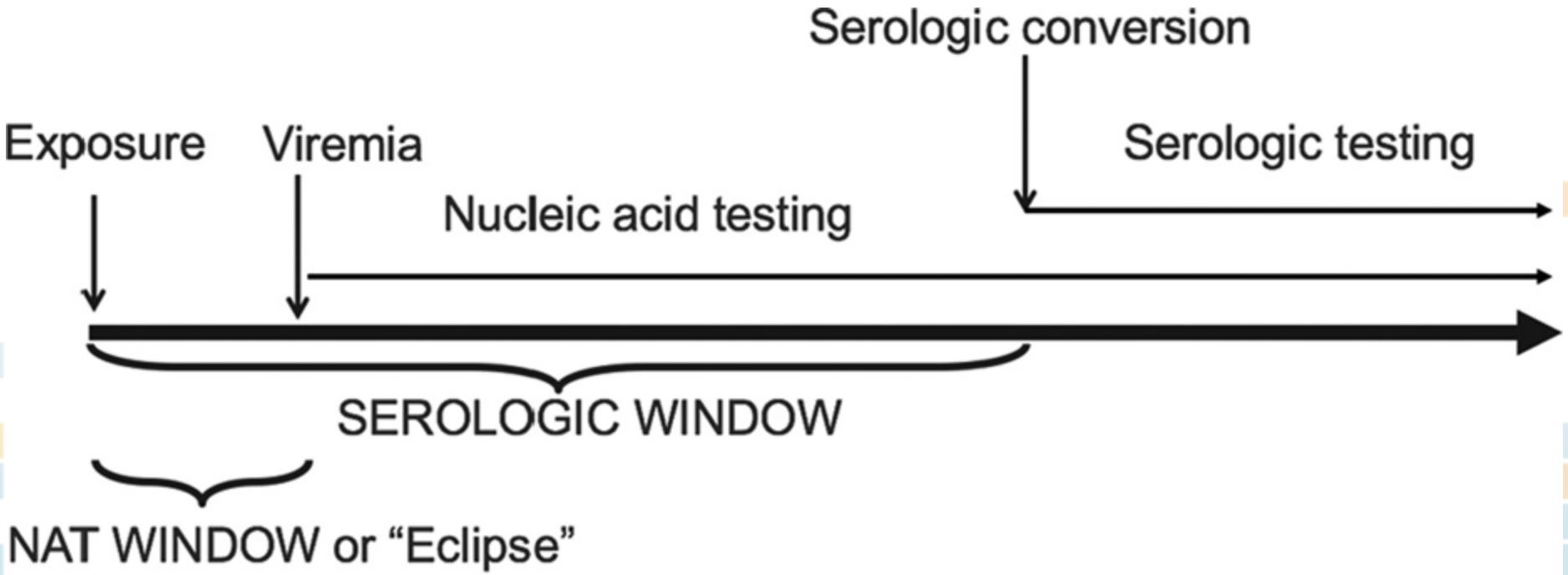
14th Annual Living Donation Conference
Presented by the American Foundation for Donation and Transplantation

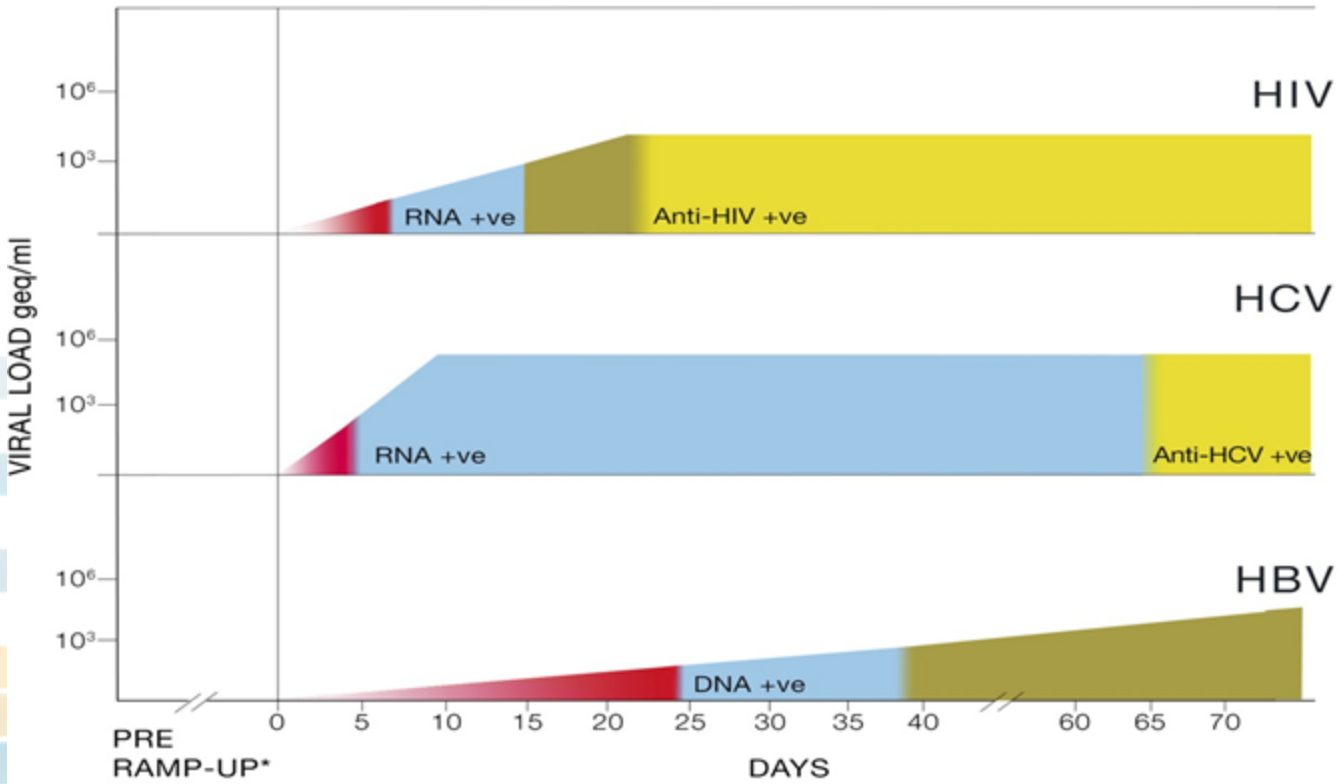
Transmissible disease screening	Infectious disease testing must be performed in a CLIA-certified laboratory or in a laboratory meeting equivalent requirements as determined by Centers for Medicare and Medicaid Services (CMS) using FDA-licensed, approved, or cleared tests. Testing must include *all* the following: 1. CMV (Cytomegalovirus) antibody 2. EBV (Epstein Barr Virus) antibody 3. HIV antibody (anti-HIV) testing or HIV antigen/antibody (Ag/Ab) combination test as close as possible, but within 28 days prior to organ recovery 4. HIV ribonucleic acid (RNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery 5. Hepatitis B surface antigen (HBsAg) testing as close as possible, but within 28 days prior to organ recovery 6. Hepatitis B core antibody (total anti-HBc) testing as close as possible, but within 28 days prior to organ recovery 7. HBV deoxyribonucleic acid (DNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery 8. Hepatitis C antibody (anti-HCV) testing as close as possible, but within 28 days prior to organ recovery 9. HCV ribonucleic acid (RNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery 10. Syphilis testing For tuberculosis (TB), living donor recovery hospitals must determine if the donor is at increased risk for this infection. If TB risk is suspected, testing must include screening for latent infection using *either*: • Intradermal PPD • Interferon Gamma Release Assay (IGRA)
Endemic transmissible diseases	Each living donor hospital must develop and follow a written protocol for identifying and testing donors at risk for transmissible seasonal or geographically defined endemic disease as part of its medical evaluation.

Unos 2023



Virus	Serology	NAT
HIV	22 days	5-10 days
HBV	38 - 50 days	20 – 26 days
HCV	38 - 94 days	6 - 9 days

Clin Transplant> Special Issue: Transplant Infectious Diseases Guidelines
September 2019



RNA/DNA undetectable in peripheral blood (eclipse phase)
RNA/DNA detectable by NAT
HIV-1 p24 antigen and HBsAg detectable by serological testing
Antibodies detectable by serological testing

*Phase of unknown duration between initial exposure and ramp-up phase, during which intermittent low-tier viraemia may occur.

Transplantation Direct5(1):e416, January 2019.

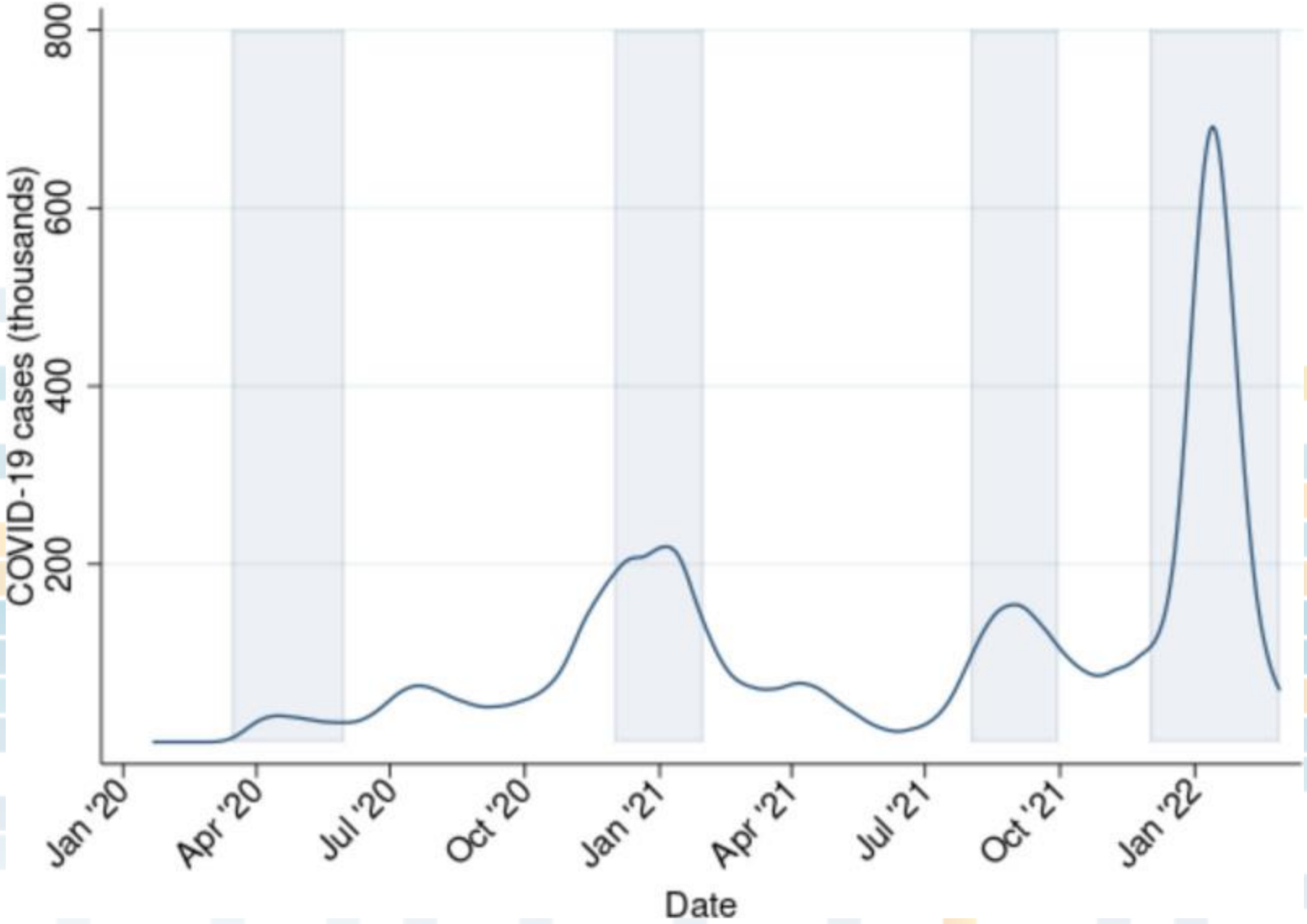
Table 2. Pathogens reported to be transmitted with solid organ transplantation

Bacteria	**Mycobacteria**
Staphylococcus aureus	*Mycobacterium tuberculosis*
Klebsiella species	Non-tuberculous mycobacteria
Bacteroides fragilis	
Pseudomonas aeruginosa	**Parasites/Protozoa**
Escherichia coli	*Toxoplasma gondii*
Salmonella species	*Strongyloides stercoralis*
Yersinia enterocolitica	*Plasmodium* species
Treponema pallidum	*Trypanosoma cruzi*
Brucella species	*Pneumocystis jirovecii*
Enterobacter species	

Table 2. Pathogens reported to be transmitted with solid organ transplantation

Acinetobacter species	**Viruses**
Legionella species	Cytomegalovirus
Nocardia species	Epstein-Barr virus
Listeria monocytogenes	Herpes simplex virus
	Varicella-zoster virus*
Fungi	Human herpesvirus-6
Aspergillus species	Human herpesvirus-7
Candida species	Human herpesvirus-8
Coccidioides immitis	Hepatitis B, D
Cryptococcus neoformans	Hepatitis C
Histoplasma capsulatum	Human immunodeficiency virus
Scedosporium apiospermum	Parvovirus B19
Prototheca species	Rabies
Zygomycetes	Lymphocytic choriomeningitis virus
	West Nile virus
	BK virus

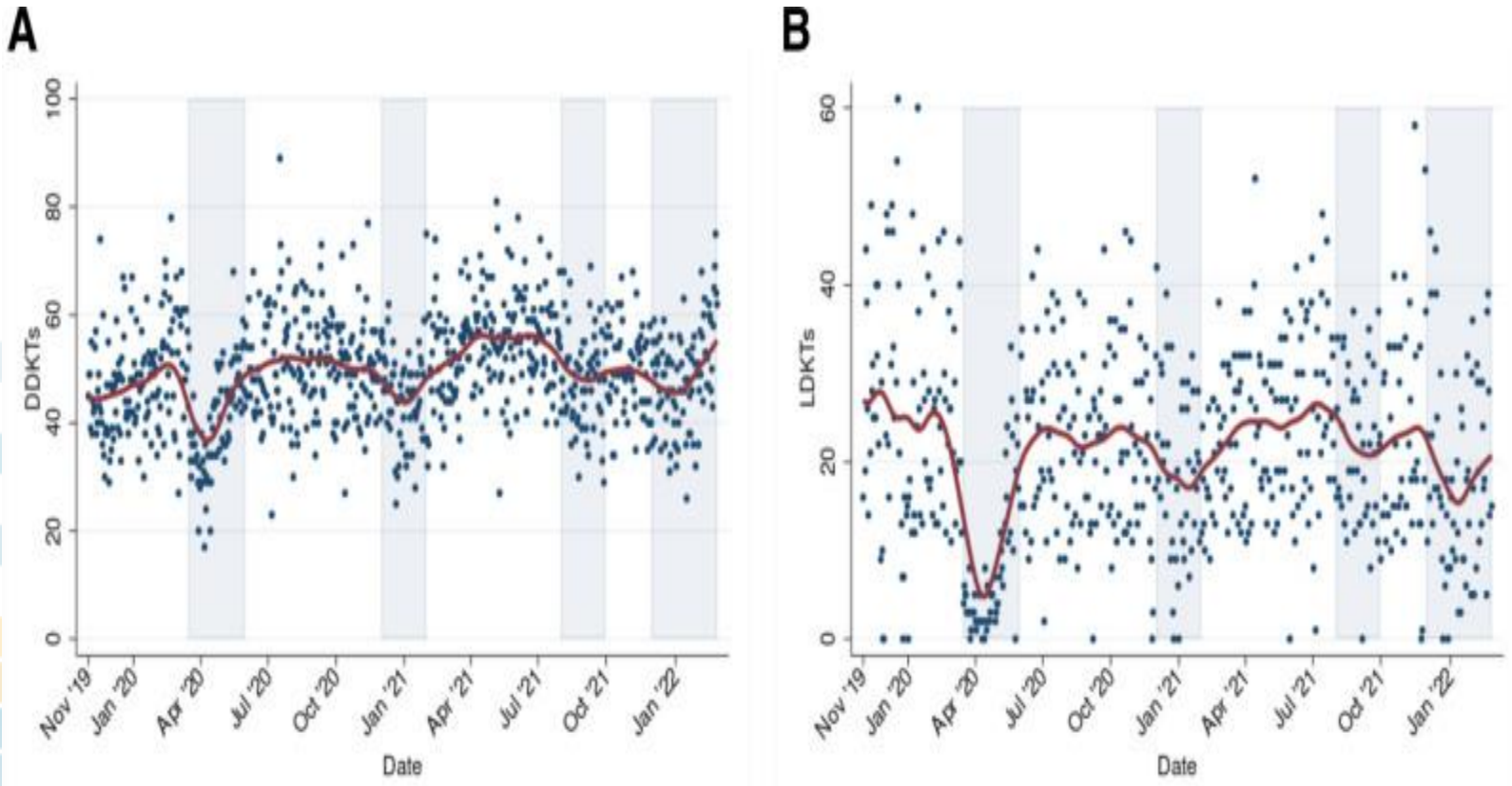
Malinis M, Boucher HW; AST Infectious Diseases Community of Practice. Screening of donor and candidate prior to solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep;33(9):e13548. doi: 10.1111/ctr.13548. Epub 2019 Apr 29.



COVID

Bisen SS, Zeiser LB, Boyarsky B, Werbel W, Snyder J, Garonzik-Wang J, Levan ML, Segev DL, Massie AB. Transplantation Amid a Pandemic: The Fall and Rise of Kidney Transplantation in the United States. Transplant Direct. 2022 Dec 12;9(1)

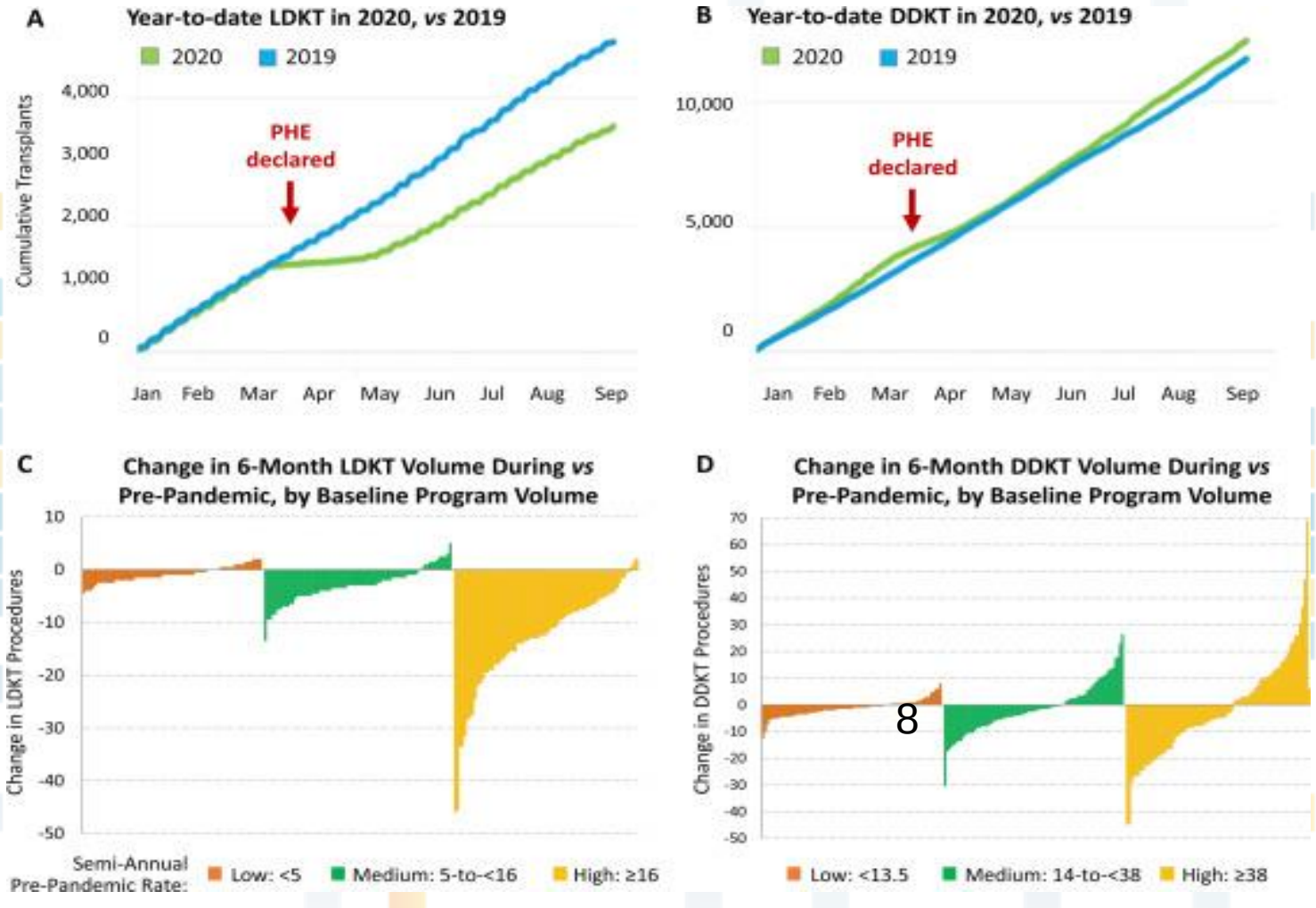
Reported COVID-19 cases in the United States, January 21, 2022, to March 8, 2022. Shaded areas depict the 4 COVID-19 waves. COVID-19, coronavirus disease 20



Kidney transplant occurrences. Counts of (A) DDKTs per day and (B) LDKTs per weekday, respectively, with running-mean smooth applied, November 2019 to February 2022. Shaded areas depict the 4 COVID-19 waves. COVID-19, coronavirus disease 2019; DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant.

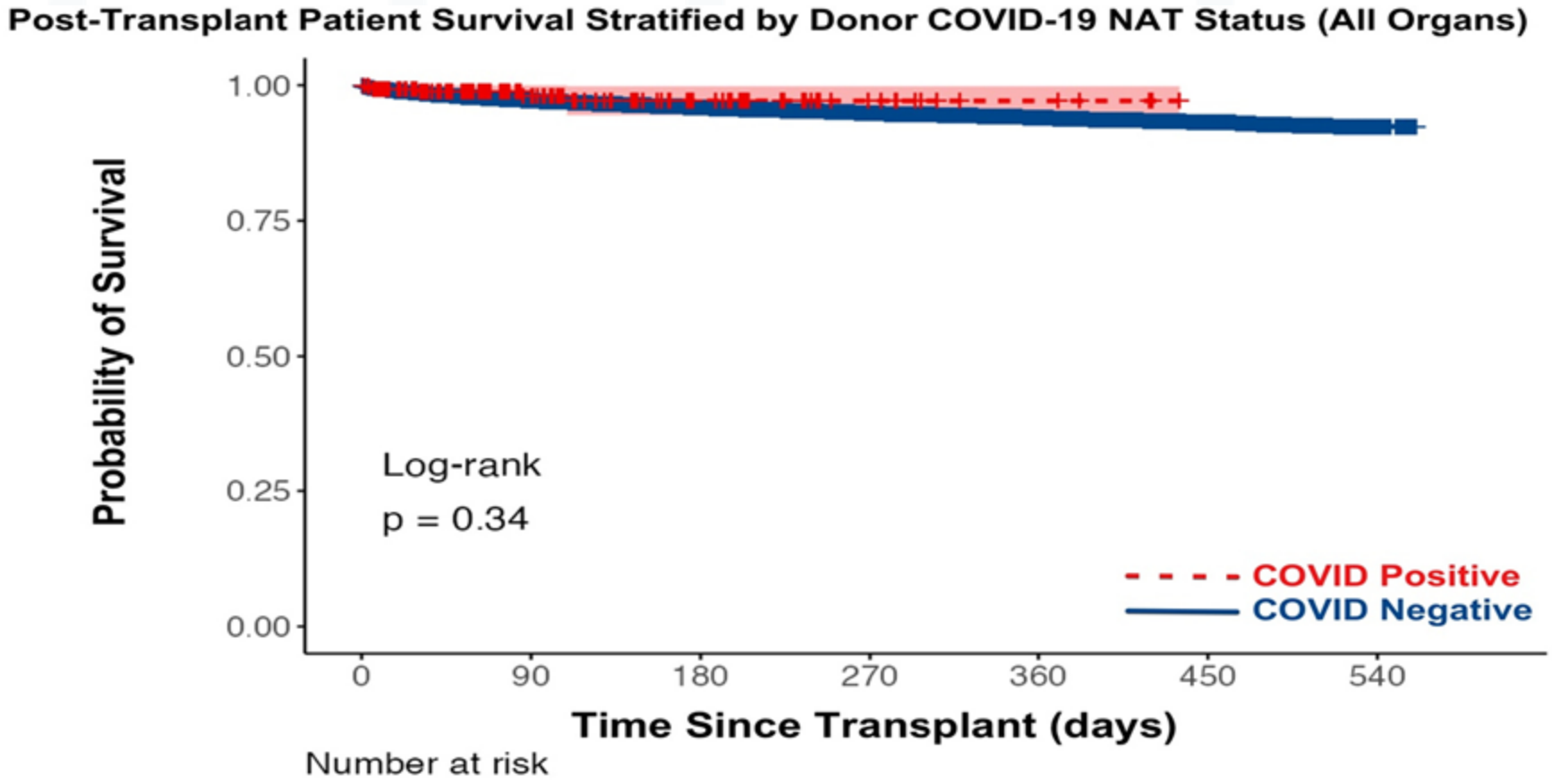
Bisen SS, Zeiser LB, Boyarsky B, Werbel W, Snyder J, Garonzik-Wang J, Levan ML, Segev DL, Massie AB. Transplantation Amid a Pandemic: The Fall and Rise of Kidney Transplantation in the United States. Transplant Direct. 2022 Dec 12;9(1)

Kidney Transplantation During the COVID-19 Pandemic



Lentine, AJKD, https://doi.org/10.1053/j.ajkd.2020.12.003

COVID positive Transplants: Pt survival

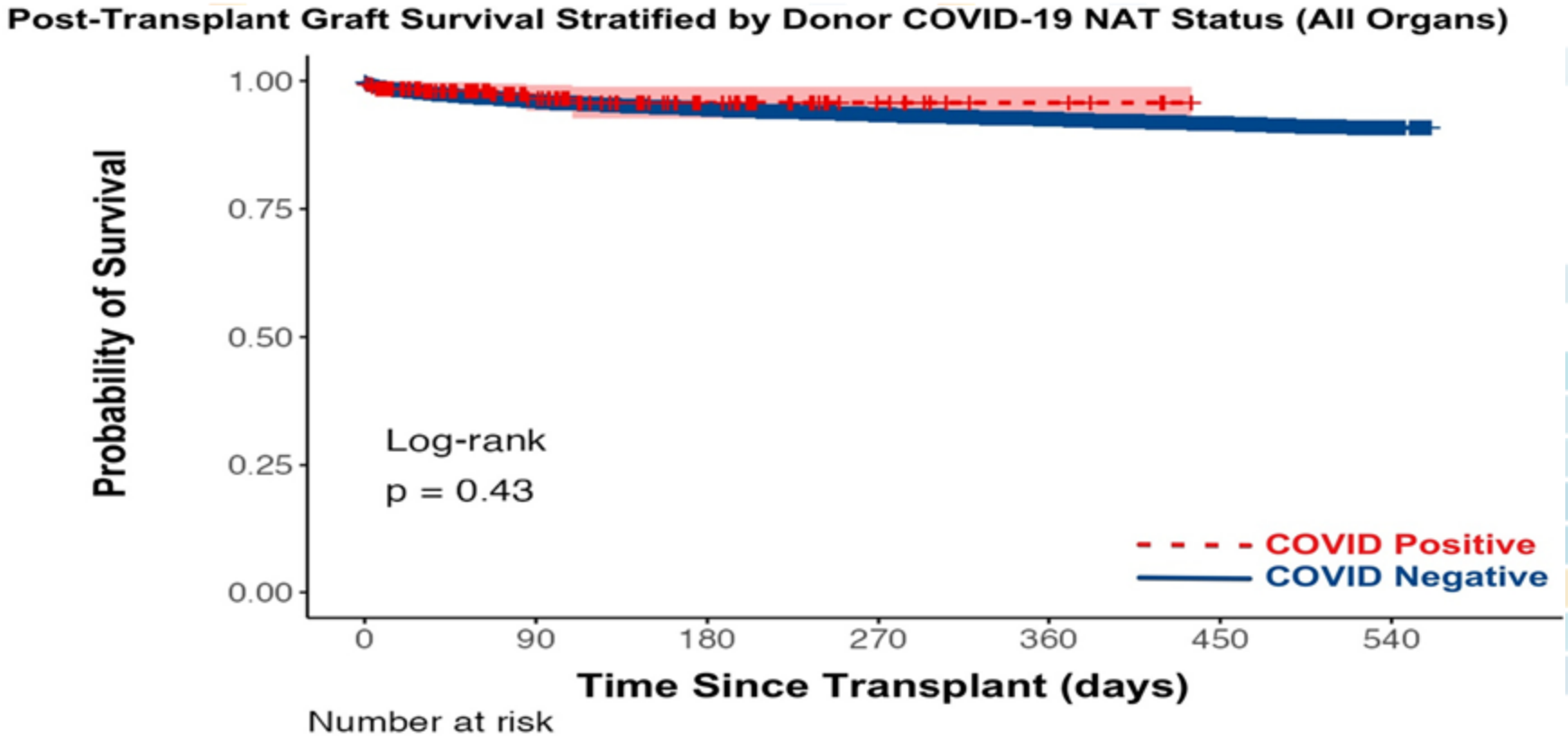


Number at risk

COVID Negative	44550	35565	26473	18463	11314	4477	78
COVID Positive	269	131	59	20	9	0	0

AJT, 13 July 2022
https://doi.org/10.1111/ajt.17145

COVID positive Transplants: Graft Survival



Number at risk

COVID Negative	44550	35116	26068	18159	11123	4402	77
COVID Positive	269	128	58	19	9	0	0

AJT, 13 July 2022
https://doi.org/10.1111/ajt.17145

A National Survey of Practice Patterns for Accepting Living Kidney Donors with Prior COVID-19

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

25-question survey

174 participants
12% transplant ID specialists
20% transplant surgeons
53% transplant nephrologists

115 US transplant centers
60% of US LKD programs
72% of 2019 LKD volume

LKD, Living kidney donor

LKD Evaluation during the Pandemic

(data collected Sept – Nov 2020)

Of the 115 transplant centers:

49% received LD candidate inquiries

44% currently evaluating donors

42/98 approved to proceed with donation

Willingness to accept COVID-19 recovered LDs

91% would wait for >1month from onset of infection to LD surgery

51% would wait for > 3 months from onset of infection to LD surgery

Most common reasons to exclude:

COVID-19 related AKI
COVID-19 related pneumonia

Most common concerns:

Kidney health post donation
Risk of transmission to recipient

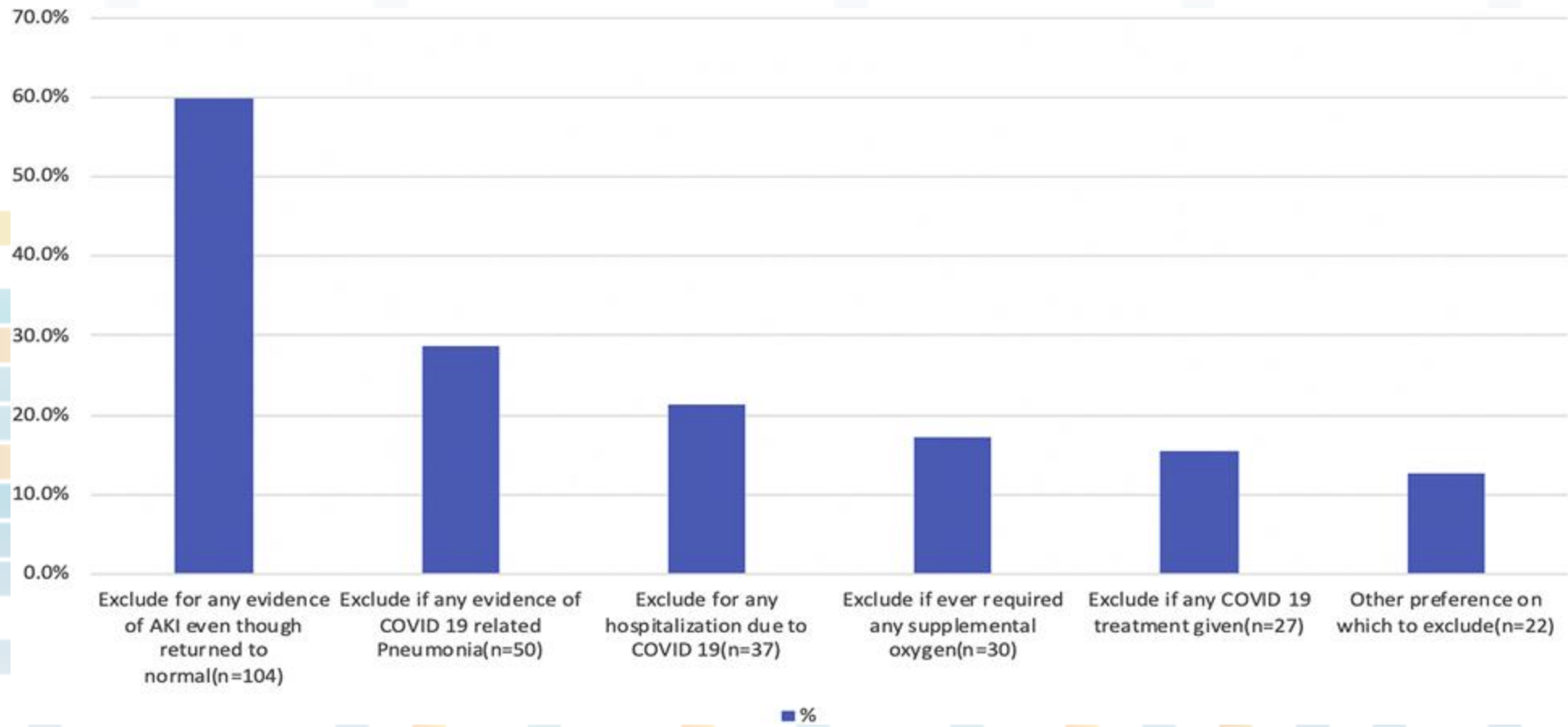
KI REPORTS
Kidney International Reports

Jan M et al, 2021

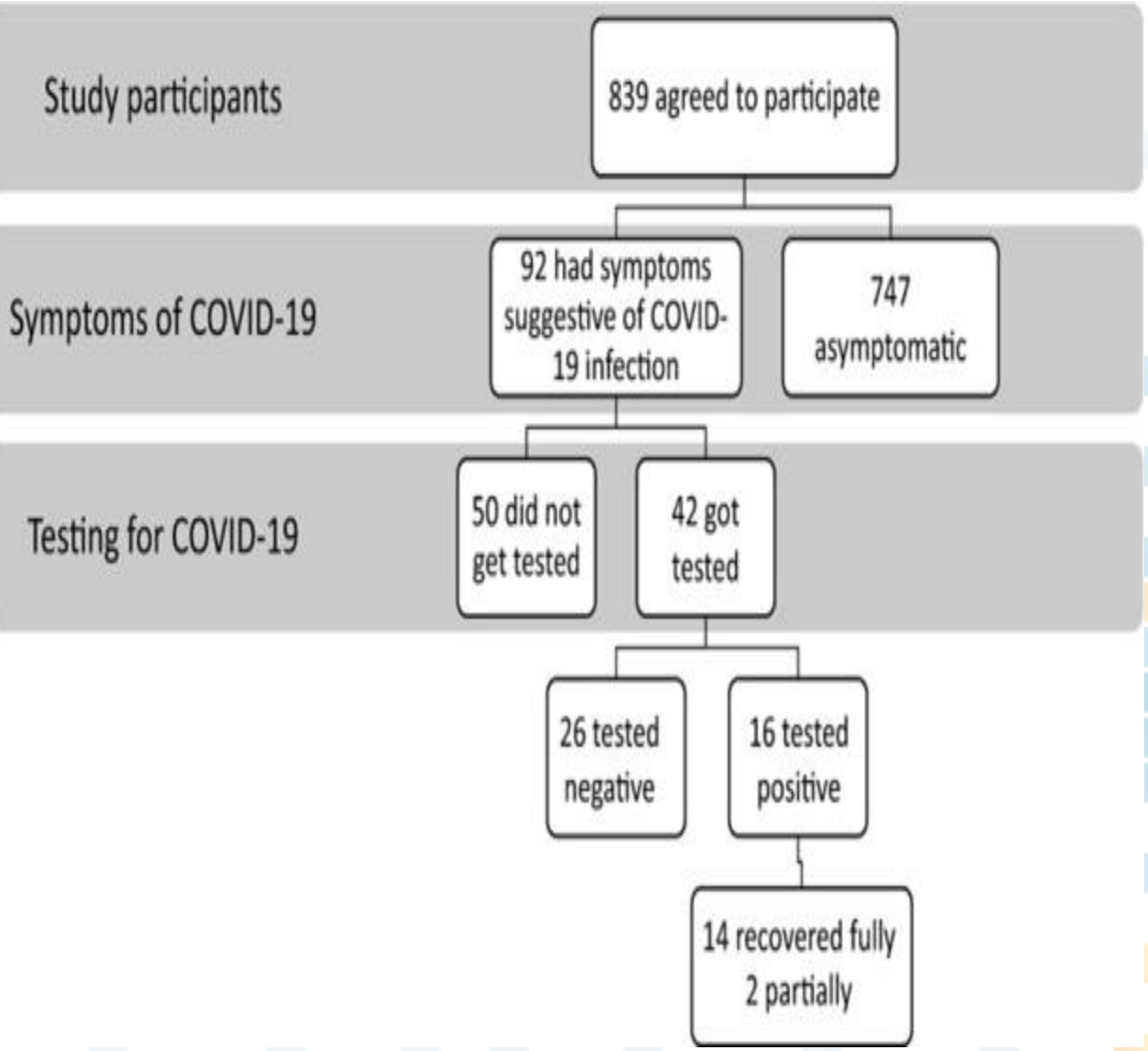
Visual abstract by:
Dominique Tomacruz, MD
@DTomacruzMD

Conclusion Practice patterns for acceptance of COVID-19 recovered LKD showed considerable variability. Ongoing research and consensus building are needed to guide optimal practices to ensure safety of accepting such donors. Long term close follow up of such donors is warranted.

Accepting Living Kidney Donors With Prior COVID-19



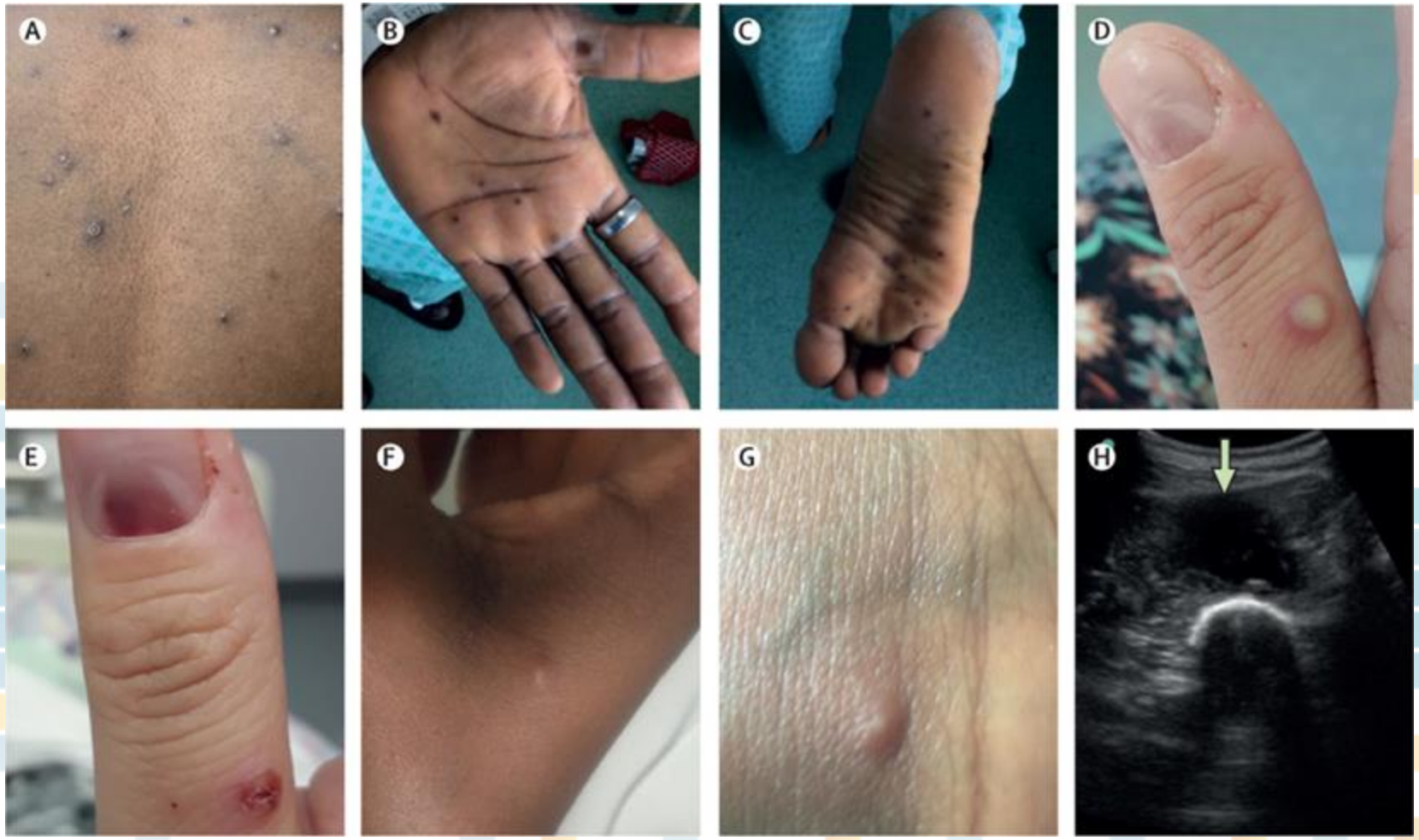
Jan MY, Jawed AT, Barros N, Adebiyi O, Diez A, Fridell JA, Goggins WC, Yaqub MS, Anderson MD, Mujtaba MA, Taber TE, Mishler DP, Kumar V, Lentine KL, Sharfuddin AA. A National Survey of Practice Patterns for Accepting Living Kidney Donors With Prior COVID-19. Kidney Int Rep. 2021 Aug;6(8):2066-2074.



How does COVID affect the donor?

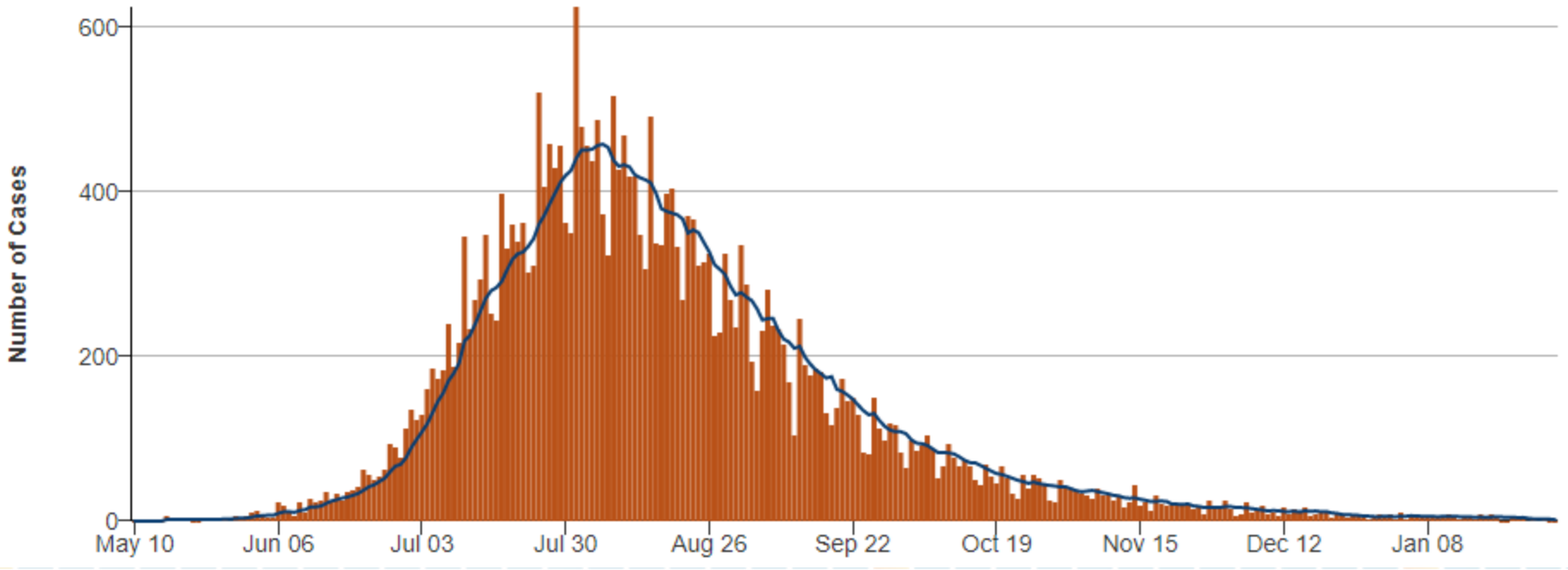
Among the donors with symptoms of a COVID-19 infection and those who tested positive, only one donor required hospitalization and all others were managed at home. None of the donors reported deterioration in their kidney function or required dialysis. Fourteen donors with confirmed infection have recovered completely, and two have reported partial recovery.

Doshi MD, Tsapepas D, Prashar R, Mohan S, Edusei E, Aull MJ, Sherman E, Dadhania DM. COVID-19 infection in former living kidney donors. Clin Transplant. 2021 Apr;35(4)



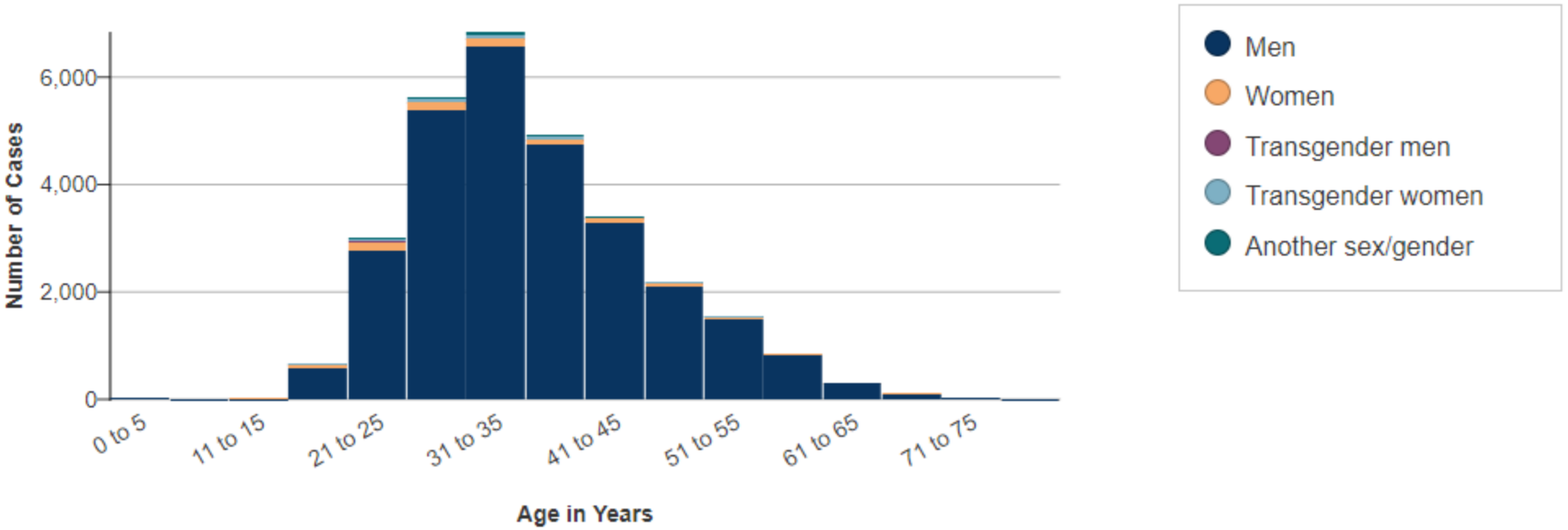
Lancet, VOLUME 22, ISSUE 8, P1153-1162, AUGUST 2022

Daily Mpox Cases and 7 Day Daily Average

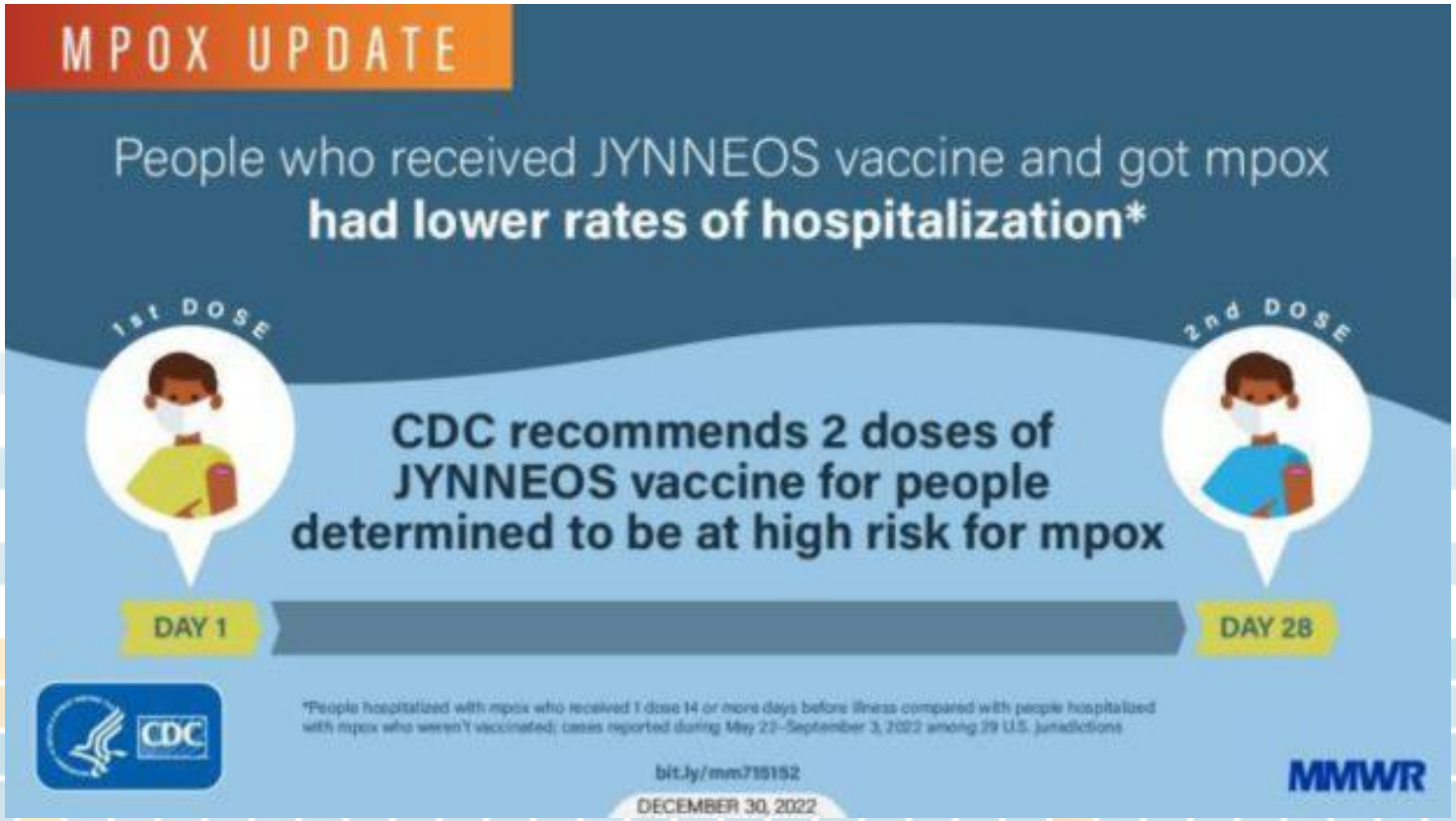


MPOX, CDC 2023: 30 K cases, 28 deaths

Mpox cases reported to CDC: Age and Gender



CDC, mostly men. JYNNEOS vaccine effective



REPORT FROM THE CDC: MMWR| VOLUME 23, ISSUE 2, P298-303, FEBRUARY 2023
2% hospitalized vs 8 %

Health care Exposure Monkey Pox

Among 313 Colorado HCP exposed to patients with monkeypox, recommended PPE use and receipt of postexposure prophylaxis vaccination was low. HCP were assessed for risk and actively monitored for 21 days when indicated; none acquired monkeypox.

Am J Transplant. 2022 Nov; 22(11): 2699–2703.
Published online 2022 Dec 30.

Latent TB in Donor

Of the 224 pairs with complete data, 24 transplant recipients with negative tuberculin skin test received organs from living donors with evidence of latent TB. Donors received INH but not recipients. None developed active TB, and kidney function one and three years later was preserved.

Our findings suggest that the risk of posttransplant TBI acquired from the donor kidney is rare, and that INH prophylaxis of LTBI-negative recipients in this setting provides no additional benefit.

Habhab WT, Alraddadi BM, Idris N, Alghamdi S, Zabani N, Fahmy A, Malik AA, Alwaassia M. Management and outcome of latent tuberculosis in living renal transplant donors. Saudi J Kidney Dis Transpl. 2019 Jan-Feb;30(1):151-152.

Latent TB in Donor (KDIGO)

Living donor candidates with latent TB infection should be offered chemoprophylaxis according to local or national guidelines.

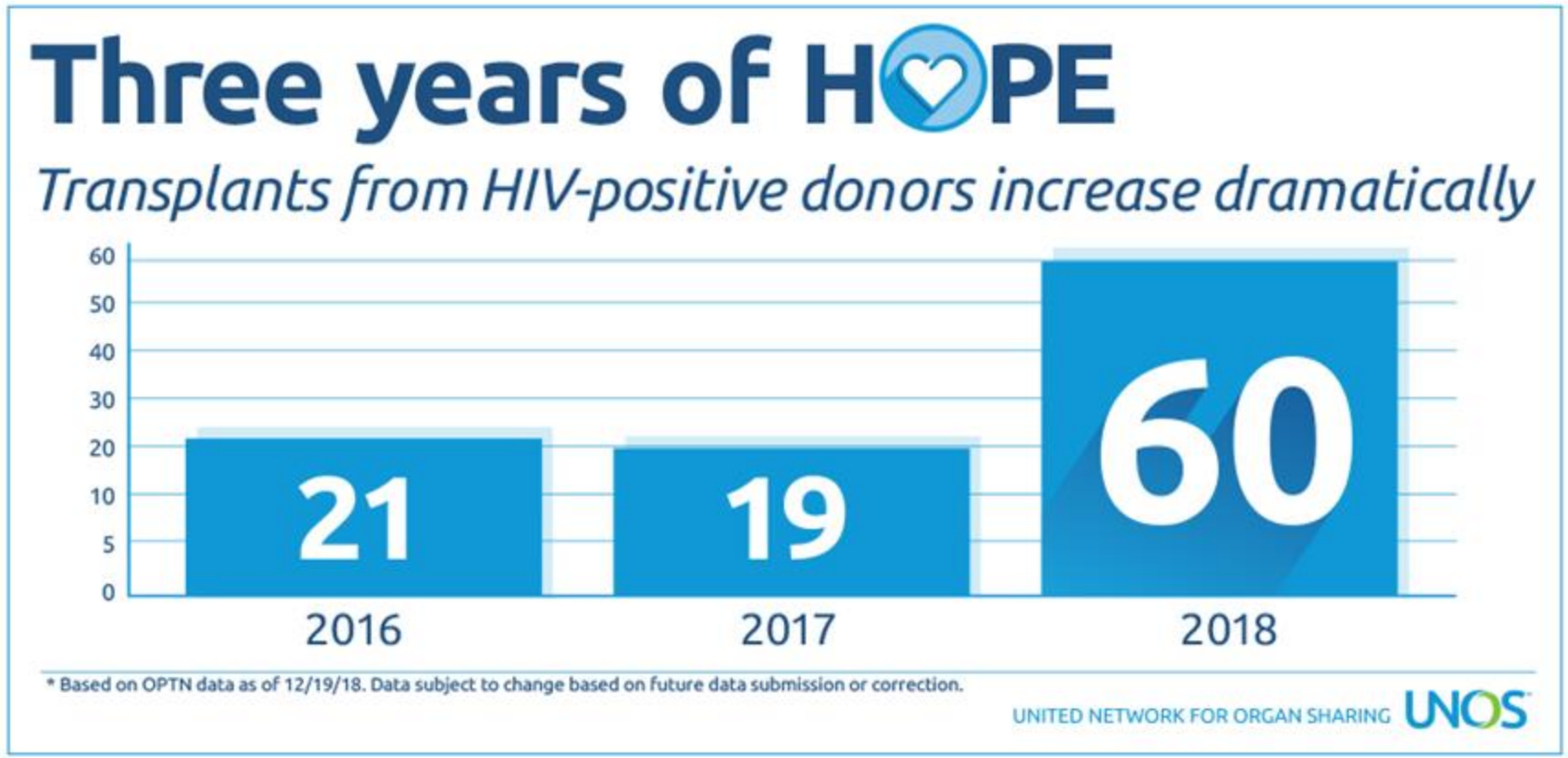
Donation may be considered from persons with latent TB infection with informed consent of the recipient and recipient monitoring after transplant.

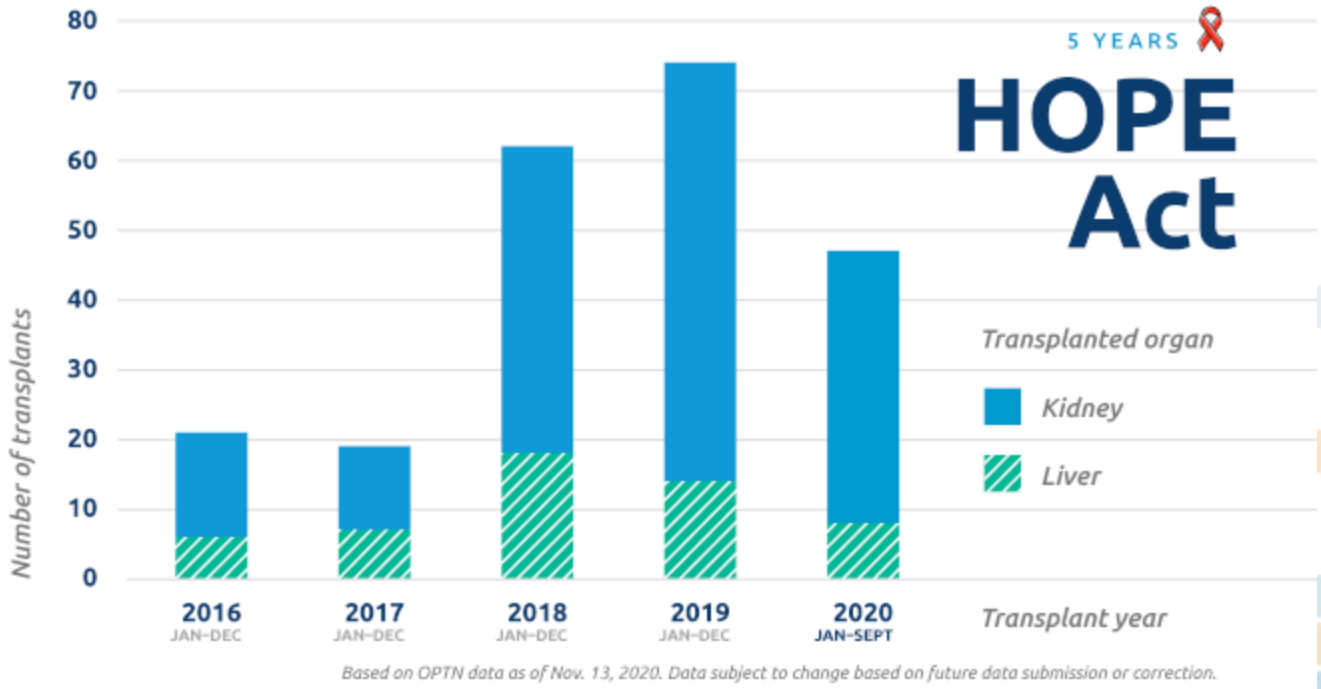
As there are no data on optimal duration of treatment before donation, individualization of the timing of donation in relation to start of donor chemoprophylaxis is recommended.

Chemoprophylaxis of recipients from donors with latent TB infection should also be considered, especially if the donor did not complete chemoprophylaxis before donation.

KDIGO, 2017

HIV in donor


Three years of HOPE
Transplants from HIV-positive donors increase dramatically
60
50
40
30
20
10
5
0
21
19
60
2016
2017
2018
* Based on OPTN data as of 12/19/18. Data subject to change based on future data submission or correction.
UNITED NETWORK FOR ORGAN SHARING
UNOS


5 YEARS
HOPE Act
Number of transplants
80
70
60
50
40
30
20
10
0
2016 JAN–DEC
2017 JAN–DEC
2018 JAN–DEC
2019 JAN–DEC
2020 JAN–SEPT
Transplant year
Transplanted organ
Kidney
Liver
Based on OPTN data as of Nov. 13, 2020. Data subject to change based on future data submission or correction.

General Overview of HOPE Implementation to Date

	March 2016–July 2021
HOPE approved transplant centers	35
OPOS that have evaluated HOPE donors	46
HOPE donors	144
Transplants within HOPE studies	*Kidney only*, 286
	True positive, 128
	False positive, 63
	Negative, 95
	Liver only, 73
	True positive, 39
	False positive, 13
	Negative, 21
	*Simultaneous Liver Kidney (SLK)**, 14
	True positive, 7
	False positive, 3
	Negative, 4

Klitenic SB, Levan ML, Van Pilsum Rasmussen SE, Durand CM. Science Over Stigma: Lessons and Future Direction of HIV-to-HIV Transplantation. Curr Transplant Rep. 2021;8(4):314-323.

Map Legend	
⊕	HOPE Approved Transplant Center(s)

Klitenic SB, Levan ML, Van Pilsum Rasmussen SE, Durand CM. Science Over Stigma: Lessons and Future Direction of HIV-to-HIV Transplantation. Curr Transplant Rep. 2021;8(4):314-323.

NIH Kidney Pilot Study

In the NIH kidney pilot study, 14 centers conducted **75 kidney transplants** encompass

ing **25 D+/R+** and 50 D-/R+ transplantation procedures. The median follow-up time was 1.7 years. No deaths. Graft survival was over 90 percent. There were no differences re serious adverse events, hospitalizations due to infections, opportunistic infections, HIV breakthrough, cancer incidence, or one-year renal function.

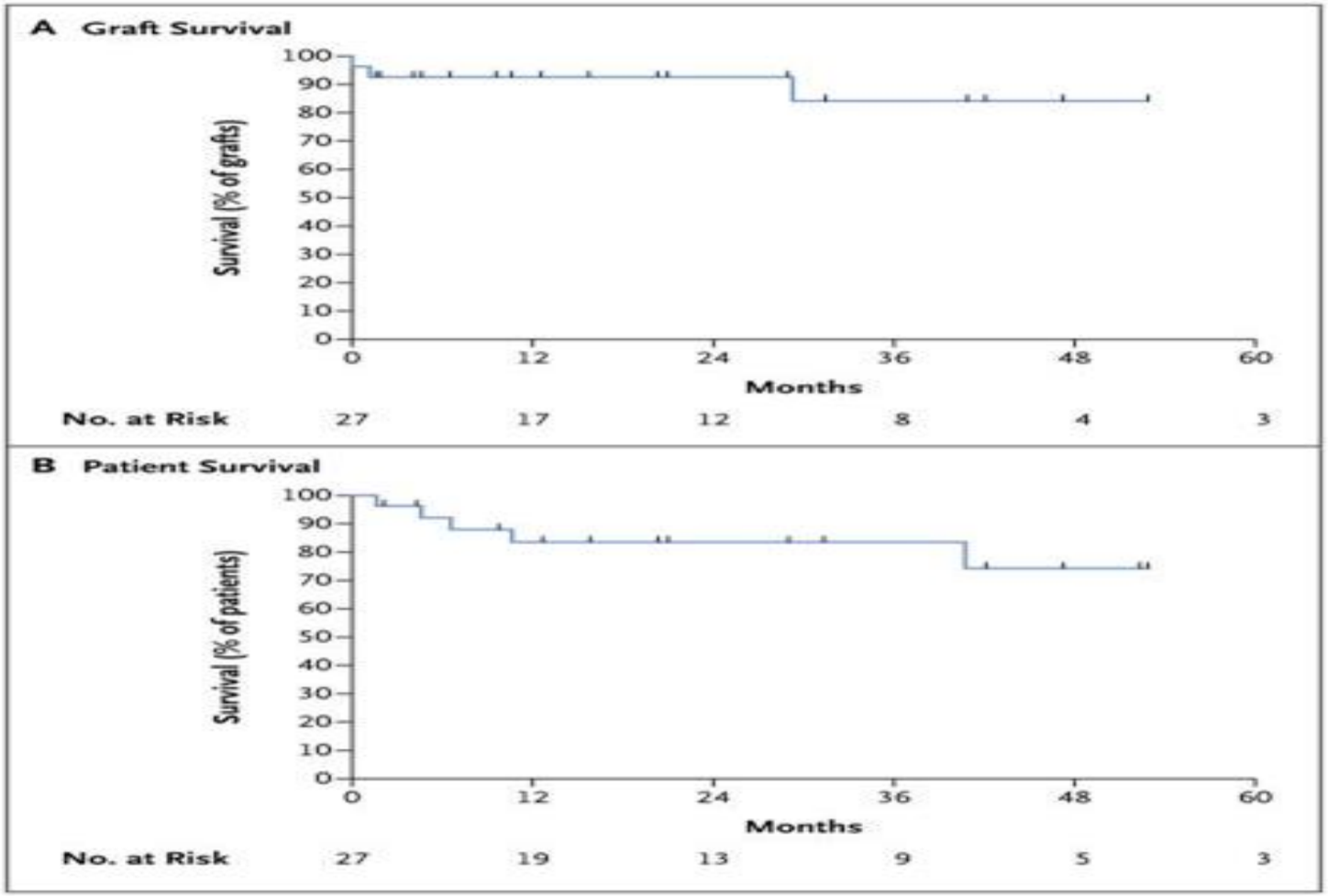
Allograft rejection was the most common complication among both donor groups.. **There was a higher rejection rate for HIV-positive donors (50 percent vs 29 percent for HIV-negative donors)** and Christine Durand emphasized that further study was needed; however, the study still clearly demonstrated a survival benefit.

Fifty-Sixth ACBTSA Meeting November 17, 2022 - Meeting Summary

https://www.hhs.gov/oidp/advisory-committee/blood-tissue-safety-availability/meeting-summary/2022-11-17/index.html

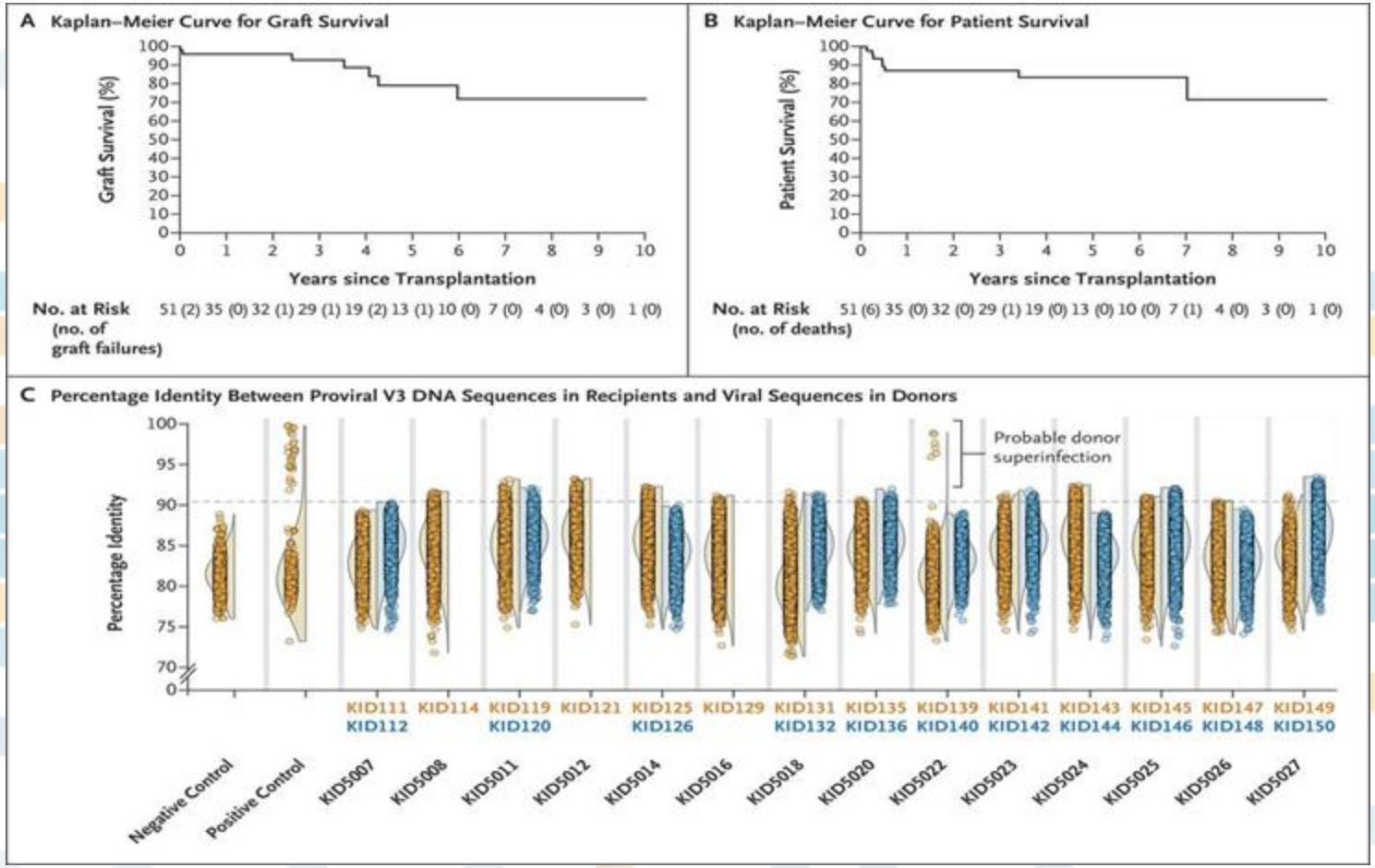
HIV to HIV

Landmark report



N Engl J Med 2015; 372:613–620. **S. Africa**, 27 pts, Thymo, AR 8% at 1 yr, undetectable VL

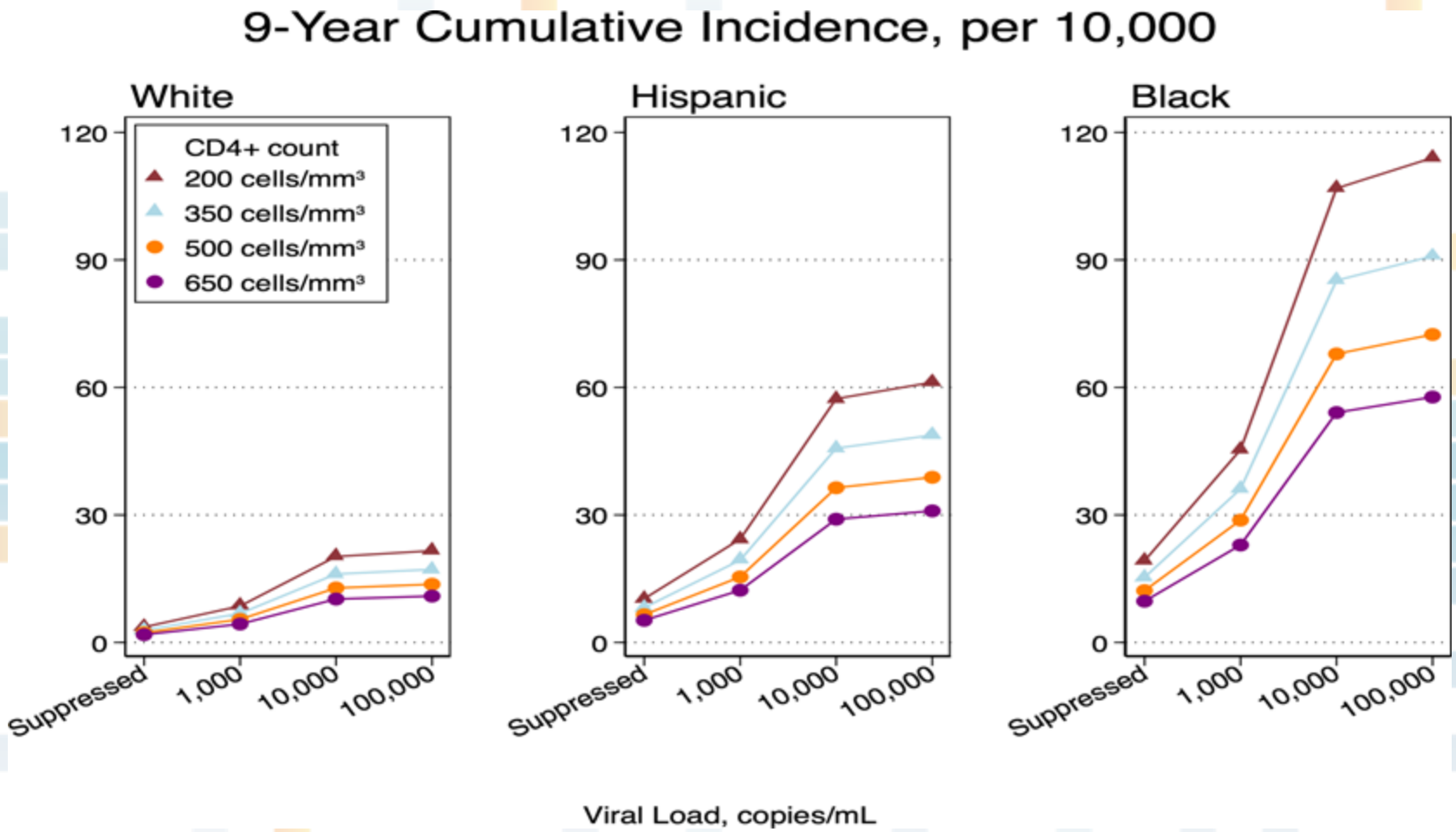
Clinical Outcomes and HIV Superinfection in HIV-Positive–to–HIV-Positive Renal Transplantation.



P Selhorst et al. N Engl J Med 2019;381:1387-1389. Now 51 pts, 5 yr F/U. Very little superinfection from donor

HIV live donors

Risk of End-Stage Renal Disease in **HIV-Positive Potential Live Kidney Donors**



Muzaale, et al, AJT, Volume: 17, Issue: 7, 1823-1832, 12 May 2017, donor risk not excessive in healthy HIV + (No DM, HTN, Hep C, on HAART). AA risk about 1.5%

Hep A and E

Hepatitis A (HAV) and E virus (HEV) infections are not a risk for transplantation except in cases of acute infection in the donor

EBV

EBV transmission to a seronegative recipient is the greatest risk factor for PTLD (RL3). Hence, EBV D+/R-, particularly in children, requires regular follow-up and consideration for specific monitoring strategies

Syphilis

not a contraindication to organ donation. Donors are screened for serological evidence of syphilis with a non-treponemal assay such as the rapid plasma reagin test, which should be confirmed later with a treponemal immunoassay (or the other way around). Syphilis is never a contraindication for using organs; penicillin should be administered to recipients of serologically reactive donors

Clinical Microbiology and Infection© 2014 European Society of Clinical Microbiology and Infectious Diseases, CMI, 20 (Suppl. 7), 10–18 16 Clinical Microbiology and Infection, Volume 20 Supplement 7, September 2014 CMI

Strongyloides

Can infected donors be considered for transplantation?

Given the availability of effective treatment options for *Strongyloides* infection, infected individuals can be considered for live donation. Ideally, infected donors should be treated with a minimum of two doses of ivermectin prior to donation (200 µg/kg orally daily on 2 consecutive days)

Chagas:

No live donor-derived *T. cruzi* infection has been reported in the United States but this has been described in Mexico and South America (screen donors from those areas).

Clinical manifestations include fever, malaise, anorexia, hepatosplenomegaly and acute myocarditis with a mean time to diagnosis of infection of 8 weeks. **DDKT transmission is 13-18%**, unknown for living donation. Posttransplant monitoring can be performed to identify subclinical infection and treatment can abort the development of clinical disease following infection(avoid hearts)

West Nile

Transmission has also occurred via blood and deceased organ donation with an incidence of neuroinvasive disease ranging between 50% and 75%. **No transmissions have been reported via live donor transplants** thus far. Few DDKT transmissions.

Live donors should be screened by WNV NAT within 7–14 days of donation. Initial testing: WNV IgM and IgG antibodies (best to do at high season, May to Nov)

A positive WNV NAT should lead to further evaluation of the live donor and donation should be deferred until repeat testing confirms resolution of viremia and infectivity.

Levi ME, Kumar D, Green M, Ison MG, Kaul D, Michaels MG, Morris MI, Schwartz BS, Echenique IA, Blumberg EA; AST ID Community of Practice. Considerations for screening live kidney donors for endemic infections: a viewpoint on the UNOS policy. Am J Transplant. 2014 May;14(5):1003-11

Other

Infectious agent	Donor and recipient screening	Tests	Recommendations
HTLV-1/2	Yes, systematic only in areas of endemicity with high seroprevalence and selective donor screening in non-endemic areas (RL1)	EIA-based serology. WB confirmatory test is not always readily available and requires additional time. NAT may be useful in identifying false-positive donors	If first test is positive, a second sample sh processed if time is available; if not done rejected; if second EIA is negative, organ but if both tests are positive, organs sho However, donation could be considered emergency, particularly in an older recip
WNV	Yes, only in donors from an area of endemicity with a declared epidemic outbreak (RL1)	Detection of viral antigens by NAT in CSF, tissue samples or blood; serology is not useful (antibodies usually appear after the period of viraemia)	Viraemic donors should be rejected
Rabies virus	Yes, if history of animal bite; consider also for donors with unexplained mental or neurological symptoms (RL1)	Antigen detection in tissues (IFAT); serology (neutralizing antibodies), NAT techniques	Donor with recent possible exposure to should not be accepted; donor with con virus infection should be rejected
Coccidioides immitis (coccidioidomycosis)	Yes, in donor and recipient who travelled to or live in endemic areas with a history of pulmonary disease or suggestive radiographical findings	Serology (ID, CF, EIA)	Not a contraindication; fluconazole shou lung transplant recipients until serology test is positive, prophylaxis should be co 6 months, and recipients should be mon
Histoplasma capsulatum (histoplasmosis)	Yes, in donor and recipient who travelled to or live in endemic areas with a history of pulmonary disease or suggestive radiographical findings	Serology (CF and ID) for latent infection. Detection of antigen (in urine, BAL or CSF) if acute disease suspected	Transplant not contraindicated; antifungal with itraconazole 3–6 months if donor t for lung transplantation, otherwise contr
Paracoccidioides brasiliensis	No (RL4). Considered in donors and recipients from endemic areas showing lung and skin lesions, particularly when they fail to identify acid-fast bacilli in samples		The use of trimethoprim-sulphamethoxaz prophylaxis for *Pneumocystis jiroveci* pneu effective against *P. brasiliensis*
Blastomyces dermatitidis (blastomycosis)	No (RL4). Considered in donors and recipients from endemic areas showing lung and skin lesions, particularly when they fail to identify acid-fast bacilli in samples	Serology and urine antigen assays may distinguish between acute or reactivated infection in donors and recipients from endemic areas	Azoles may reduce the incidence of trans infected donors are used
Plasmodium spp. (malaria)	Yes, in all donors and recipients who have resided in or travelled (3 preceding years) to areas of endemicity	NAT more sensitive to rule out parasitaemia. Thick and thin blood films, IC for diagnosis of malaria	Organs should be rejected if donor's dea to malaria (RL1). Otherwise, treat dono recipient (RL3)
Trypanosoma cruzi (Chagas' disease)	Yes, in all donors and recipients who have resided in endemic areas	Two different serology-based tests should be performed. Acute infection is diagnosed by Giemsa-stained thick and thin blood films, Strout's method or micromethod. NAT may be useful for both phases	Use of donors with acute infection is con use of heart or intestine from donor wi infection is contraindicated (RL1); close with NAT is recommended for other or promptly initiate therapy (RL2-3) [17]
Strongyloides spp. (strongyloidiasis)	Yes, in all donors and recipients who have resided in or travelled to zones of endemicity	Visualization of larvae in stool and serology	Treat the donor prior to transplantation recipient at anytime to prevent hyperinf syndrome
Taenia solium (cysticercosis)	Yes, in donors from an area of endemicity and clinical symptoms or suggestive brain imaging, especially for heart donation	Consider serology and imaging to rule out cysts from donor heart	Organs from a donor with neurocysticerc be used (RL4)
Echinococcus granulosus (cystic hydatidosis)	Yes, in all donors from an area of endemicity and suggestive images	Confirmation serology (IHA) or fine-needle aspiration if imaging suggests hydatid disease and serology is negative. Thoracic and abdominal CT scan to ascertain disease extension should be performed	Organ affected by hydatidosis should not transplantation except if cyst is very loc or calcified and may be radically excised *E. multiloculoris* donors should be dischar
Filariae (*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus* and *Loa loa*)	No (RL4). Only donors with a high index of suspicion of infection and the possibility of treatment prior to transplantation	Lysis-centrifugation or filtration and Giemsa staining of peripheral blood smears	
Clonorchis spp., *Opistorchis* spp., *Schistosoma* spp., *Paragonimus* spp., *Fasciola* spp.	Yes, in all donors and recipients from areas of endemicity, especially in the presence of peripheral blood eosinophilia	Stool (*Clonorchis* spp, *Opistorchis* spp and *S. mansoni*, *S. japonicum* and *S. intercalatum*), urine (*S. haematobium*) or sputum (*Paragonimus* spp) examination for ova. Serology for *Schistosoma* spp	Specific treatment; donation is not contra Strict follow-up is necessary
Babesia spp. (babesiosis)	No (RL4)		Transmission from organ donors describe
Entamoeba histolytica (amebiasis)	No (RL4)	Serology and faecal microscopy	Check donors and recipients from ender with history of diarrhoea
Trypanosoma brucei (sleeping sickness)			Due to the severe prognosis of the disea toxicity of the treatment, organs from a infected donor should be rejected

HTLV, human T lymphotrophic virus; EIA, enzyme immunoassay; WB, western blot; NAT, nucleic acid testing; WNV, West Nile virus; CSF, central system fluid; IFAT, indirect immunofluorescent antibody test; ID, immu complement fixation; BAL, bronchoalveolar lavage; IC, immunocromatography; IHA, indirect haemagglutination assay; CT, computed tomography.

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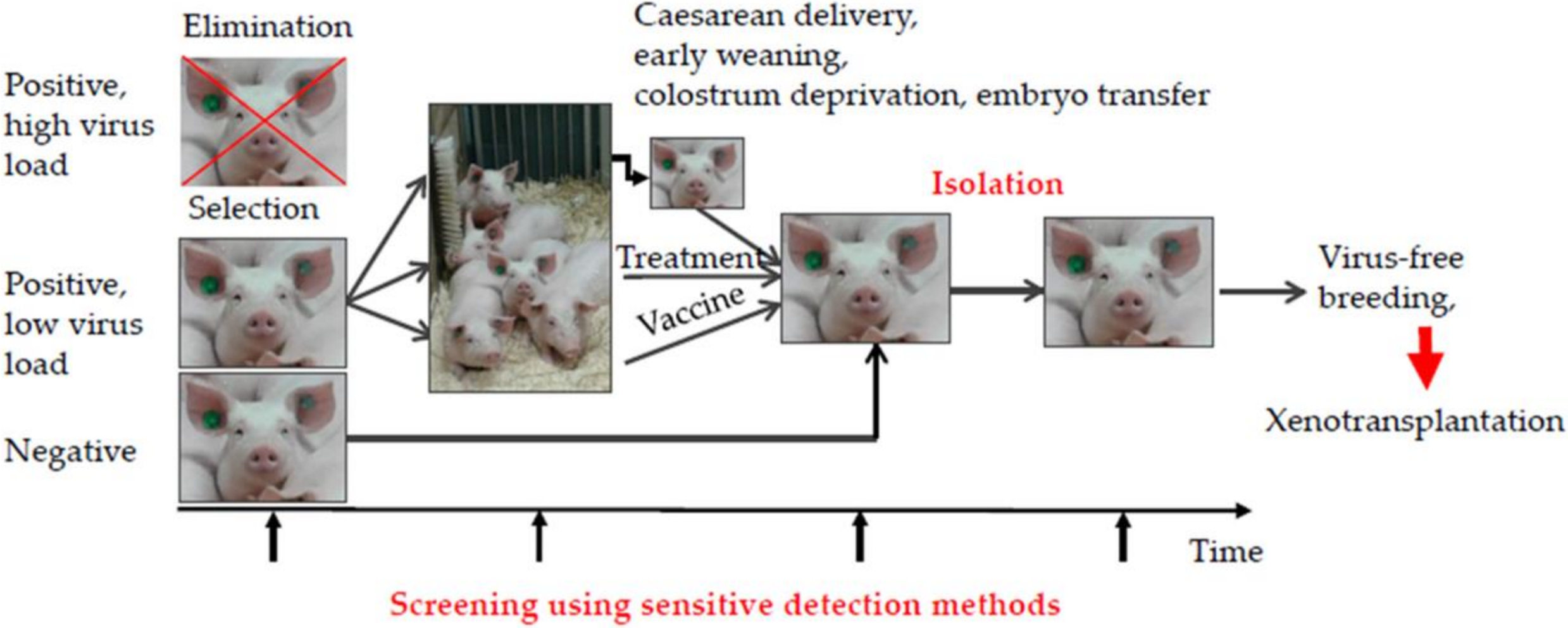
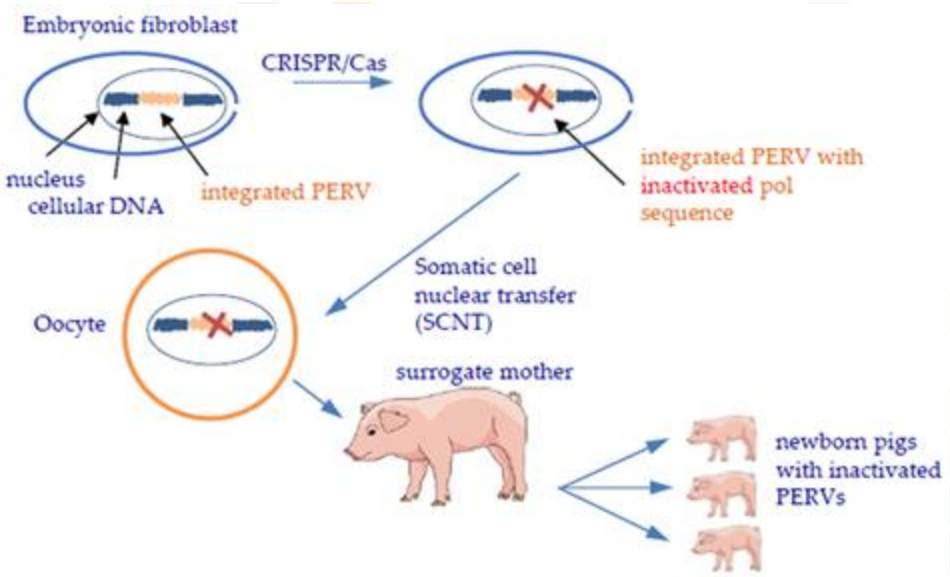


Denner, J. Virus Safety of Xenotransplantation. *Viruses* **2022**, *14*, 1926. https://doi.org/10.3390/v14091926

Table 8. Strategies to prevent PERV transmission.

• Vaccine, based on neutralizing antibodies against the transmembrane and surface envelope proteins of PERV [120,121,122,123]
• Antiretroviral drugs [83,124,125,126,127,128]
• Reduction of PERV expression by siRNA [129,130,131,132]
• Gene editing
• Zinc finger nuclease (ZFN) [133]
• Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated 9 (CRISPR/Cas9) [134,135] (Figure 3)



Denner, J. Virus Safety of Xenotransplantation. *Viruses* **2022**, *14*, 1926. https://doi.org/10.3390/v14091926. PERVS are in the genome and harder to eradicate

Conclusion

COVID

Monkey

TB

HIV

Syphilis

Endemics: Strong, Chaga, WNV

Session Survey

David Serur, MD | April 19th 1:15 PM-2:00 PM