22 | HUMAN PARVOVIRUS (PARV4)

This fact sheet is being archived and will not be routinely updated absent relevant new data suggesting risks from transfusion.

22.1 | Disease agent

- Human parvovirus 4 (PARV4) with comments about human bocaparvoviruses

22.2 | Disease agent characteristics

- Family: *Parvoviridae*; Subfamily: *Parvovirinae*; Genus: *Tetraparvovirus*; Species: human parvovirus 4.
- Virion morphology and size: Nonenveloped, icosahedral nucleocapsid symmetry, spherical particles, 20–25 nm in diameter.
- Nucleic acid: Linear, single-stranded DNA, ~5.6 kb in length, mostly negative-strand DNA or both DNA strands encapsulated in virus particles. The genome comprises two main open reading frames (ORFs), but unlike B19V, the two ORFs do not overlap.
- Physicochemical properties: Not well described in the literature but it is expected that due to similarity to B19V and other parvoviruses it might have similar properties. Thus, it should be resistant to wet or dry heat during the manufacturing of clotting factors from plasma pools and to solvent/detergent treatment. It is presumably inactivated by formalin, β-propiolactone and gamma irradiation. B19V genotypes 1 and 3 were inactivated below the limit of detection at 56°C for 30 min, pH 4 at 37°C and at pH 4.5 at 23°C.

22.3 | Disease name

- No established clinical manifestations.
- Reports of PARV4 detection in CSF of two patients with encephalitis of unknown etiology, and in cases of fetal hydrops and severe acute respiratory illness.

22.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical for blood components; disease associations and transfusion transmission have not been proven, but if so, immunocompromised patients expected to be at greatest risk.
- Public perception and/or regulatory concern regarding blood safety: Very low in the United States; concern exists about the possible pathogenicity of PARV4 in manufactured plasma pool derivatives.
- Public concern regarding disease agent: Absent.

22.5 | Background

- PARV4 was discovered in 2005 from an injection drug user (IDU) with general symptoms of primary viremia. Evidence of infection also was found in individuals with a history of IDU or HIV or HCV infection. PARV4 occurs mainly in lymphoid tissues, bone marrow and blood of IDUs. Specific antibodies and nucleic acids have been found in injection drug users, patients with HCV, commercial plasma and blood and plasma donors and persons with hemophilia.
  - 3 genotypes of PARV4:
- Genotype 1 most prevalent: DNA detected in plasma pools world-wide ranging from 4% to 5% in currently manufactured plasma pools in Europe to 26% in China. Prevalent in younger European and US populations
- Genotype 2 was first identified in plasma pools.
- Genotype 3 is restricted to healthy individuals in sub-Saharan Africa. It is found in children suggesting a different route of transmission such as respiratory or fecal-oral routes or even through unrecognized blood contact.
- Global and endemic PARV4 infection strongly associated with HIV and HCV in developed countries
- Blood component transmission suspected but not proven
- High seroreactivity in injection drug user populations in developed countries indicates a likely source of transmission may be associated with unsafe injection practices.
- Other newly described human parvoviruses include the bocaviruses (HBoV) 1-4. They are closely related to bovine and canine parvoviruses. HBoV genotypes have been found worldwide, indicating their global circulation. HBoV DNA was detected by quantitative, real-time PCR in 5.5% of serum samples obtained from healthy blood donors in Italy.
  - HBoV1 was originally identified from nasopharyngeal aspirates of children with respiratory tract infections; specific DNA and antibodies have been detected in association with acute respiratory illness. DNA also found in serum, feces, urine, saliva and CSF of children in Spain. Seroprevalence among adults exceeds 90%; DNA reported in 4%–32% of

tonsils and adenoids of young children (versus none for HBoV2-4 or PARV4 DNA). The presence of mRNA as an indication of DNA replication has been demonstrated in the nasopharynx.
  - HBoV2-4 have been detected in stool samples from young children with acute gastroenteritis (nausea and watery, bloody diarrhea).

22.6 | Common human exposure routes

- Injection drug use
- Possibly *in utero* (transplacental) as reflected by detection in cases of fetal hydrops
- Other routes possible for PARV4 genotype 3 in sub-Saharan Africa

22.7 | Likelihood of secondary transmission

- Likely, as virus appears to be readily transmissible within the drug user population in developed countries and in general population in African countries

22.8 | At-risk populations

- Possibly immunocompromised plasma product recipients
- Possibly pregnant women

22.9 | Vector and reservoir involved

- Unknown

22.10 | Blood phase

- Cellular tropism unknown. Viral DNA is found in plasma, bone marrow, lymphoid tissue, liver and other organs and tissues.
- High-titer DNA during primary infection (up to 10^{10} copies/mL), but usually $<10^5$ copies/mL especially in pre-school children.
- Reported detection of low-level PARV4 DNA in plasma from approximately 2% of 200 US blood donors from Los Angeles; this may reflect low-level chronic viremia or nucleic acid circulating in the blood similar to B19V. The extent of cross-neutralization by seroreactive plasma in plasma pools, as is assumed for B19V, is unknown.

22.11 | Survival/persistence in blood products

- PARV4 DNA has been detected in blood components, in source and frozen plasma, and in virally inactivated clotting factors

22.12 | Transmission by blood transfusion

- Transmission from blood components has not been formally assessed.
- Transmission from plasma products strongly suspected from studies of seroconversion in hemophiliacs.
- Solvent-detergent and heat-treated plasma lots can be infectious.

22.13 | Cases/frequency in population

- PARV4 DNA detected in approximately 2% of 200 blood donors from Los Angeles, CA.
- Seroprevalence in injection drug use populations is approximately 6%.

22.14 | Incubation period

- Unknown

22.15 | Likelihood of clinical disease

- No confirmed disease associations; most infections asymptomatic. Causal relationships for reported associations have not been established.
  - PARV4 detected in CSF and plasma of two encephalitis patients in India. PARV4 DNA detected in three cases of fetal hydrops.
  - PARV4 was detected in a significantly higher number of patients in India with severe acute respiratory illness (18.2% with PARV4 alone and 8.2% co-detected with other pathogenic viruses) in comparison with controls (0.7%). PARV4 genotype 2 was the only strain circulating.
  - PARV4 seroconversion observed among patients with hemophilia, concurrent with rash and unexplained hepatitis

22.16 | Primary disease symptoms

- Association with disease is unknown; the interrelationship of human PARV4 with severe acute respiratory illness merits further study.

22.17 | Severity of clinical disease

- Association with disease is unknown.

22.18 | Mortality

- Unknown

22.19 | Chronic carriage

- Viral particles are detected in multiple tissues and possibly sequestered there for life as is the case for B19V. The high rate of detection (2% in healthy blood donors) may be explained by low-level viremia or nucleic acid circulating in the blood over extended periods, as has been reported for B19V.

22.20 | Treatment available/efficacious

- None reported

22.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because of the absence of confirmed transfusion transmission and associated clinical disease
- No sensitive or specific question is feasible.

22.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening or diagnostic test exists.
- Nested PCR and real-time PCR assays have been used.
- IgG and IgM antibody tests have been developed by academic laboratories using virus-like particles for antibody capture.

22.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.

22.24 | Impact on blood availability

- If low-level NAT-positive donors are excluded, the results of one reported study indicate that approximately 2% of donors in the United States would be deferred from donation.

22.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable.
- Laboratory test(s) available: NAT screening could decrease transmission rate by removal of viremic units. Clinical disease from transfusion transmission is not described but theoretical; therefore, benefits of screening may be small. However, outcomes could theoretically be severe in particular populations of transfusion recipients such as immunosuppressed patients. It has been speculated that these recipients might benefit from PARV4-safe components.

22.26 | Leukoreduction efficacy

- Unknown but highly unlikely

22.27 | Pathogen reduction efficacy for plasma derivatives

- PARV4 is not totally inactivated by heat and solvent-detergent treatment.

22.28 | Other prevention measures

- None

SUGGESTED READING

1. Benjamin LA, Lewthwaite P, Vasanthapuram R, Zhao G, Sharp C, Simmonds P, et al. Human parvovirus 4 as potential cause of encephalitis in children. India. Emerg Infect Dis. 2011; 17:1484–7.
2. Bonvicini F, Manaresi E, Gentilomi GA, Di Furio F, Zerbini M, Musiani M, et al. Evidence of human bocavirus viremia in healthy blood donors. Diagn Microbiol Infect Dis. 2011;71:460–2.

3. Brown KE. The expanding range of parvoviruses which infect humans. Rev Med Virol. 2010;4:231–44.
4. Chen MY, Yang SJ, Hung CC. Placental transmission of human parvovirus 4 in newborns with hydrops, Taiwan. Emerg Infect Dis. 2011;17:1954–6.
5. Delwart E. Human parvovirus 4 in the blood supply and transmission by pooled plasma-derived clotting factors: does it matter? Transfusion. 2012;52:1398–403.
6. Drexler R, Reber U, Muth D, Herzog P, Annan A, Ebach F, et al. Human parvovirus 4 in nasal and fecal specimens from children, Ghana. Emerg Infect Dis. 2012;18:1650–3.
7. Fryer JF, Delwart E, Bernardin F, Tuke PW, Lukashov VV, Baylis SA. Analysis of two human parvovirus PARV4 genotypes identified in human plasma for fractionation. J Gen Virol. 2007;88:2162–7.
8. Fryer JF, Delwart E, Hecht FM, Bernardin F, Jones MS, Shah N, et al. Frequent detection of the parvoviruses, PARV4 and PARV5, in plasma from blood donors and symptomatic individuals. Transfusion. 2007;47:1054–61.
9. Fryer JF, Hubbard AR, Baylis SA. Human parvovirus PARV4 in clotting factor VIII concentrates. Vox Sang. 2007;93: 341–7.
10. Fryer JF, Kapoor A, Minor PD, Delwart E, Baylis SA. Novel parvovirus and related variant in human plasma. Emerg Infect Dis. 2006;12:151–4.
11. Jones MS, Kapoor A, Lukashov VV, Simmonds P, Hecht F, Delwart E. New DNA viruses identified in patients with acute viral infection syndrome. J Virol. 2005;79:8230–6.
12. Lahtinen A, Kivelä P, Hedman L, Kumar A, Kantele A, Lappalainen M, et al. Serodiagnosis of primary infections with human parvovirus 4, Finland. Emerg Infect Dis. 2011; 17:79–82.
13. Lurcharchaiwong W, Chieochansin T, Payungporn S, Theamboonlers A, Poovorawan Y. Parvovirus 4 (PARV4) in serum of intravenous drug users and blood donors. Infection. 2008;36:488–91.
14. Ma YY, Guo Y, Zhao X, Wang Z, Lv MM, Yan QP, et al. Human parvovirus PARV4 in plasma pools of Chinese origin. Vox Sang. 2012;103:183–5.
15. Manning A, Willey SJ, Bell JE, Simmonds P. Comparison of tissue distribution, persistence, and molecular epidemiology of parvovirus B19 and novel human parvoviruses PARV4 and human bocavirus. J Infect Dis. 2007;195:1345–52.
16. May J, Drexler JF, Reber U, Sarpong N, Adjei O, Panning M, et al. Letter: human parvovirus 4 viremia in young children, Ghana. Emerg Infect Dis. 2012;18:1690–2.
17. Norja P, Hedman L, Kantola K, Kemppainen K, Suvilehto J, Pitkäranta A, et al. Occurrence of human bocaviruses and parvovirus 4 in solid tissues. J Med Virol. 2012;84:1267–73.
18. Norja P, Hokynar K, Aaltonen LM, Chen R, Ranki A, Partio EK, et al. Bioportfolio: lifelong persistence of variant and prototypic erythrovirus DNA genomes in human tissue. Proc Natl Acad Sci USA. 2006;103:7450–3.
19. Norja P, Lassila R, Makris M. Parvovirus transmission by blood products—a cause for concern. British J Haemat. 2012;159: 385–93.
20. Panning M, Kobbe R, Vollbach S, Drexler JF, Adjei S, Adjei O, et al. Novel human parvovirus 4 genotype 3 in infants. Ghana. Emerg Infect Dis. 2010;16:1143–6.
21. Prakash S, Shukla S, Ramakrishna V, Mishra H, Bhagat AK, Jain A. Human parvovirus 4: a harmless bystander or a pathogen of severe acute respiratory illness. Int J Infect Dis. 2020;90: 21–5.
22. Schneider B, Fryer JF, Oldenburg J, Brackmann HH, Baylis SA, Eis-Hübinger AM. Frequency of contamination of coagulation factor concentrates with novel human parvovirus PARV4. Haemophilia. 2008;14:978–86.
23. Servant-Delmas A, Laperche S, Mercier M, Elghouzzi MH, Lionnet F, Stankovic K, et al. Human parvovirus 4 in recipients of cellular products and in blood donors: epidemiologic similarity with B19 parvovirus. Transfusion. 2009;49: 1771–3.
24. Sharp CP, Lail A, Donfield S, Gomperts ED, Simmonds P. Virologic and clinical features of primary infection with human parvovirus 4 in subjects with hemophilia: frequent transmission by virally inactivated clotting factor concentrates. Transfusion. 2012;52:1482–9.
25. Sharp CP, Lail A, Donfield S, Simmons R, Leen C, Klenerman P, et al. High frequencies of exposure to the novel human parvovirus PARV4 in hemo-philiacs and injection drug users, as detected by a serologitcal assay for PARV4 antibodies. J Infect Dis. 2009;200:1119–25.
26. Sharp CP, Vermeulen M, Nebie Y, Djoko CF, Lebreton M, Tamoufe U, et al. Epidemiology of human parvovirus 4 infection in Sub-Saharan Africa. Emerg Infect Dis. 2010;16: 1605–7.
27. Simmonds P, Manning A, Kenneil R, Carnie FW, Bell JE. Parenteral transmission of the novel human parvovirus PARV4. Emerg Infect Dis. 2007;13:1386–8.
28. Szelei J, Liu K, Li Y, Fernandes S, Tijssen P. Parvovirus 4-like virus in blood products. Emerg Infect Dis. 2010;16:561–4.
29. Tuke PW, Parry RP, Appleton H. Parvovirus PARV4 visualization and detection. J Gen Virol. 2010;91:541–4.