Human Pegivirus: A common, bloodborne, persistent RNA virus contributing to the microvirome



Iowa City VA



University of Iowa

Jack T. Stapleton, MD

Professor, Departments of Internal Medicine, Microbiology & Immunology

Director, Helen C. Levitt Center for Viral Pathogenesis

The University of Iowa and Iowa City Veterans Administration, Iowa City, IA USA

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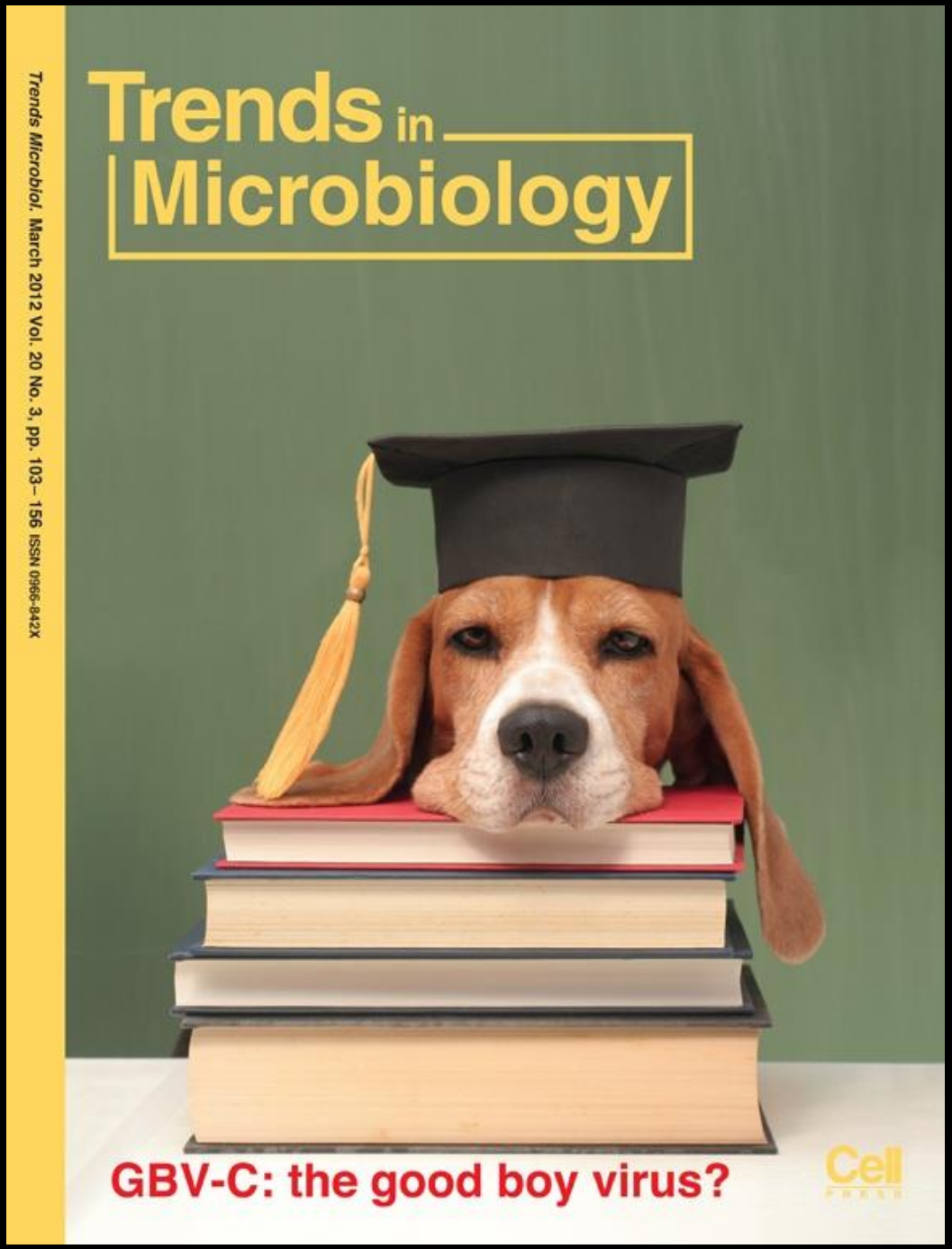




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Bhattarai & Stapleton, 2012

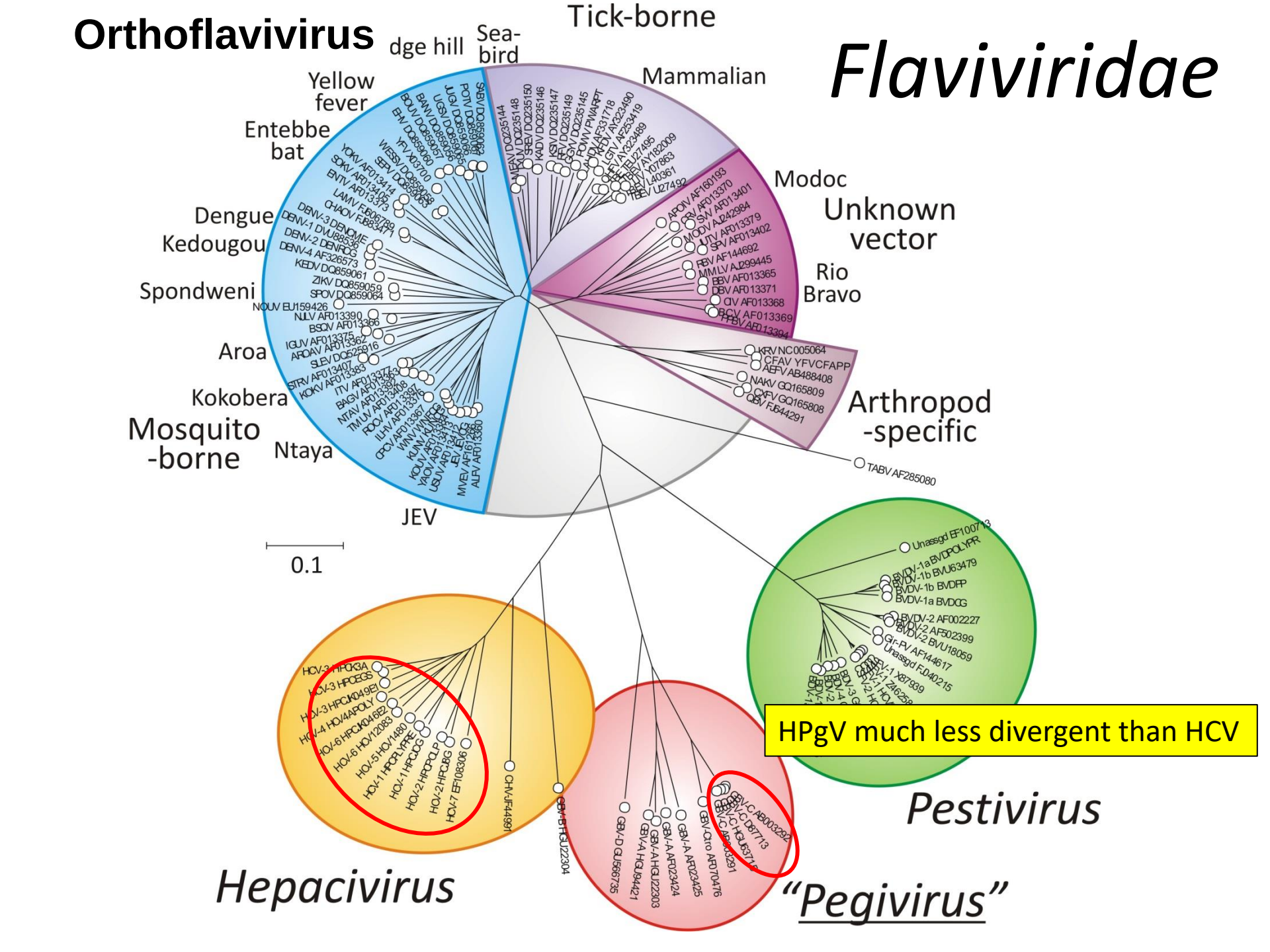
Human Pegivirus

Originally called
Hepatitis G virus (HGV)
or GB virus C (GBV-C)

Discovered in 1995
by two groups

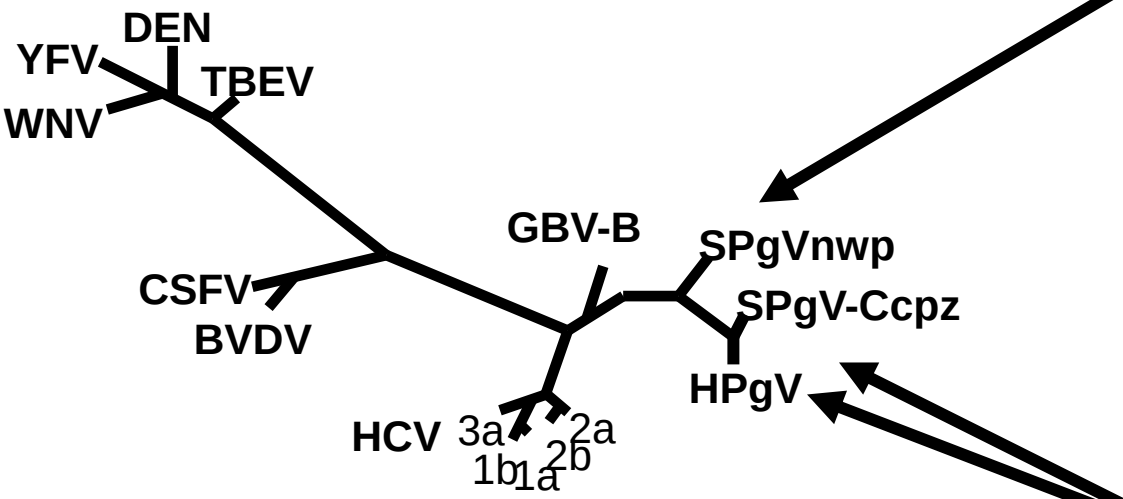
The Good Boy virus?

Stapleton, et al., JGV 2011


Orthoflavivirus
Flaviviridae
Tick-borne
Mammalian
Modoc
Unknown vector
Rio Bravo
Arthropod-specific
Mosquito-borne
Yellow fever
Entebbe bat
Dengue
Kedougou
Spondweni
Aroa
Kokobera
Ntaya
JEV
dge hill
Sea-bird
TABV AF285080
0.1
HCV-3 HPCJK3A
HCV-3 HPCEGS
HCV-3 HPCJK049E1
HCV-4 HCV4APOLY
HCV-6 HPCJK046E2
HCV-6 HCV12083
HCV-5 HCV1480
HCV-1 HPCPOLYPRE
HCV-1 HPCJCG
HCV-2 HPCPOLP
HCV-2 HPCJ8G
HCV-7 EF108306
CHV JF449991
GBV-B HQ317222
GBV-D GU566735
GBV-A HQ994421
GBV-A HQ922303
GBV-A AF023424
GBV-A AF023425
GBV-Cstro AF070476
GBV-C AB003292
GBV-C D87713
GBV-C HGU63714
GBV-C AB003291
Unassgd EF100713
BVDV-1a BVDPOLYPR
BVDV-1b BVU63479
BVDV-1b BVDRP
BVDV-1a BVDCG
BVDV-2 AF002227
BVDV-2 AF502399
BVDV-2 BVU18059
Gir-PV AF144617
Unassgd FJ040215
BVDV-1 X87939
BVDV-1 Z46259
HPgV much less divergent than HCV
Hepacivirus
Pestivirus
"Pegivirus"

HPgV: An Ancient Virus?

1. Relationship to GBV-A and GBV-B





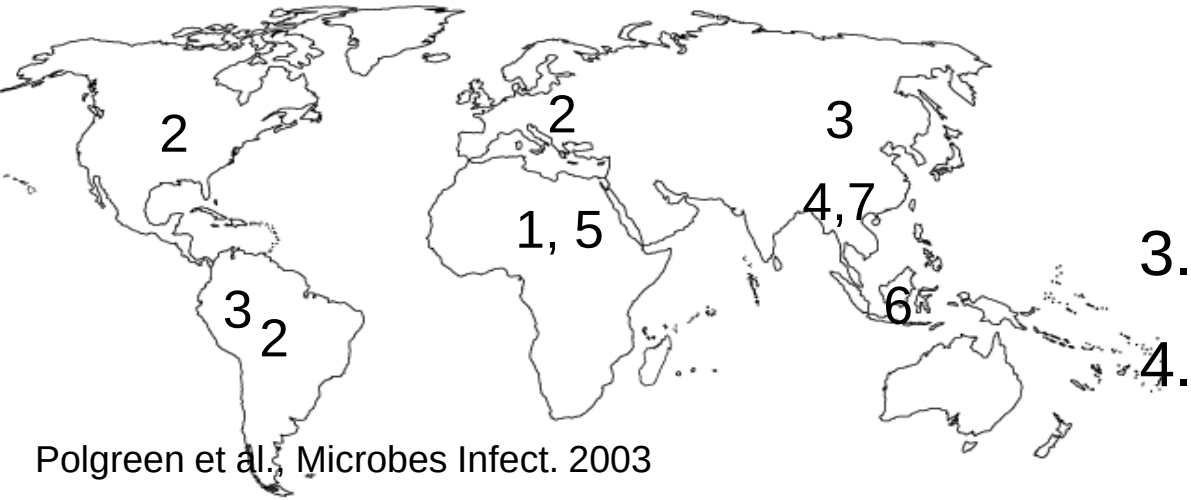


New World Primates

Old World Primates



2. Human Migration - Genotypes



Polgreen et al., Microbes Infect. 2003

3. Phylogeny and race

Smith et al. JGV, 1999

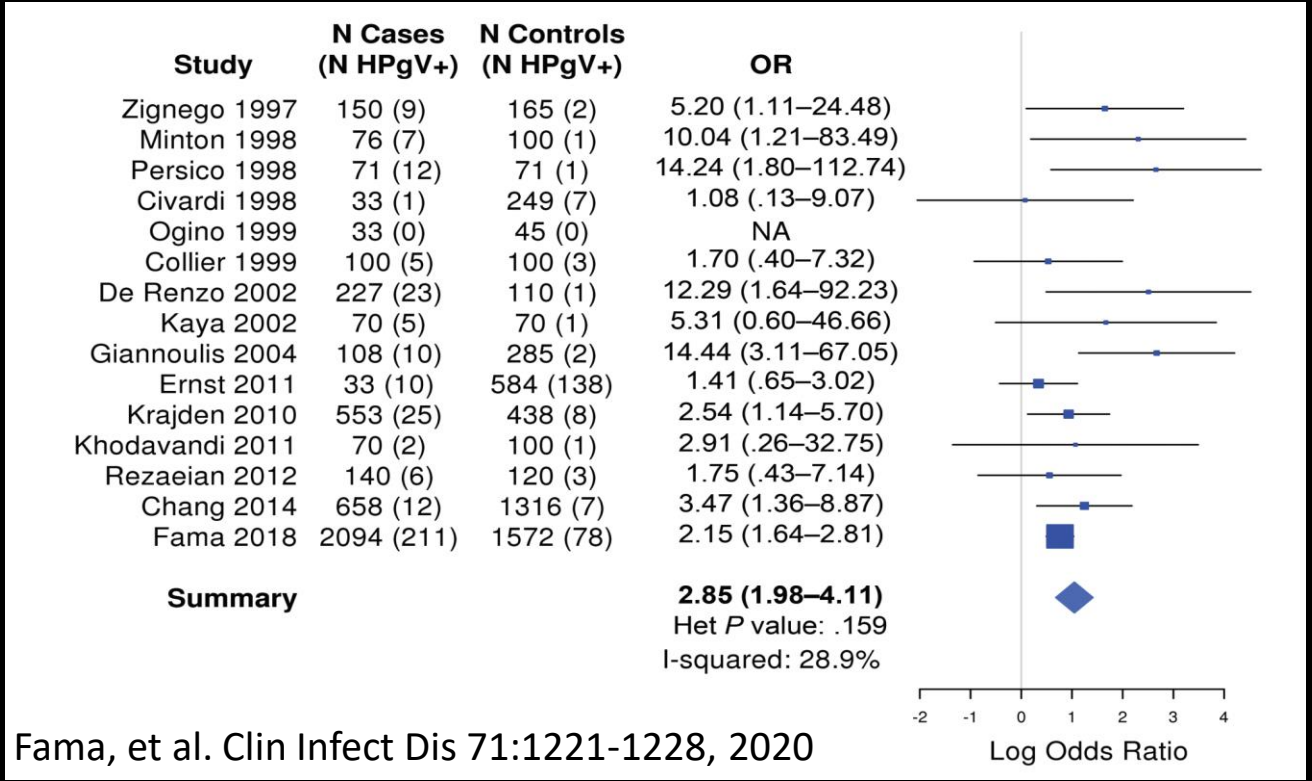
4. Indigenous populations

Alvardo-Mora et al., Virol J, 2011.

Horemheb-Rubio et al., PLoS One 2017.

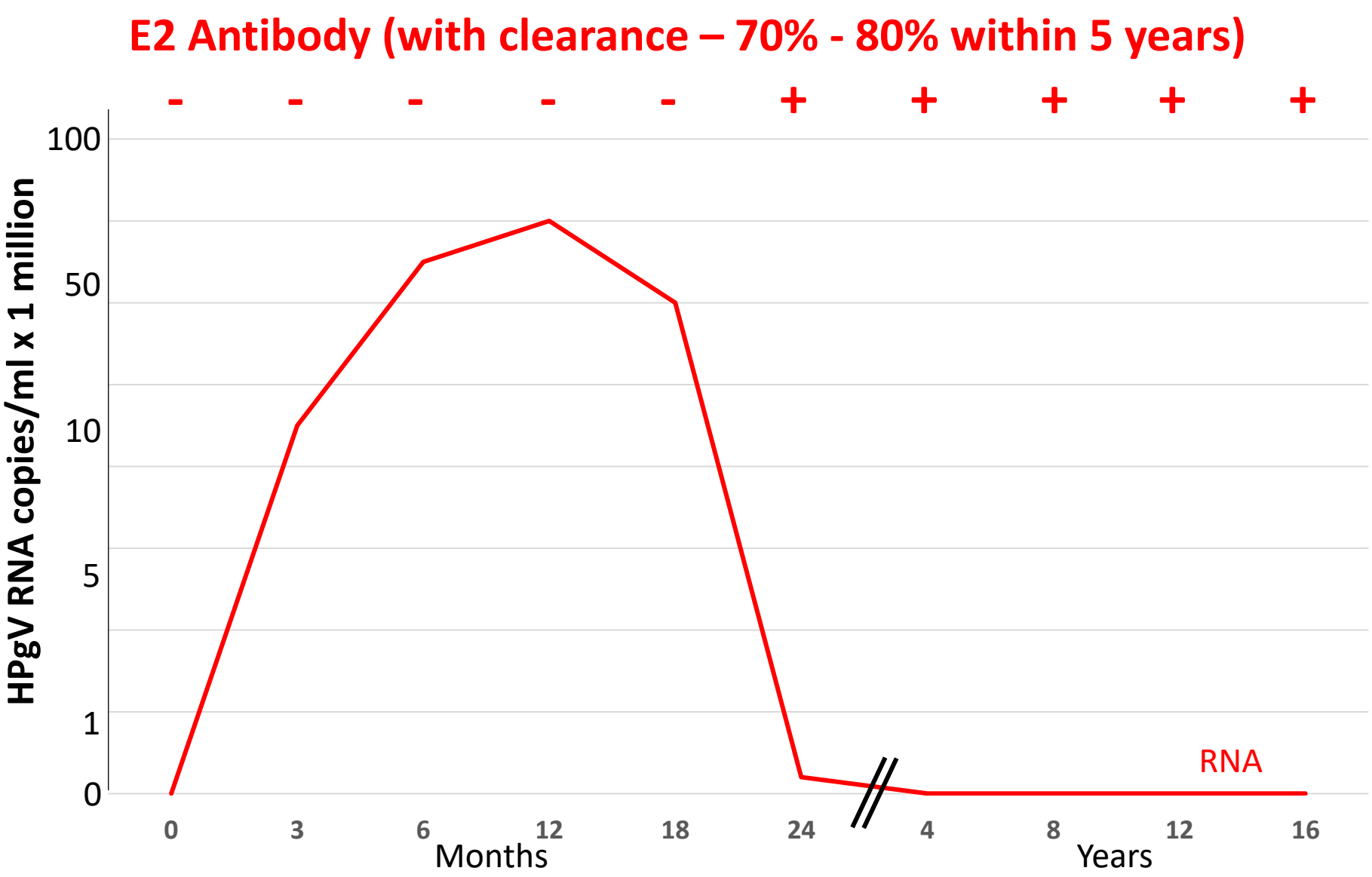
HPgV Disease Association

- No causal relationship to acute or chronic hepatitis, autoimmunity, other illness
- Associated with increased lymphoma risk
- ? Sporadic encephalitis – limited data

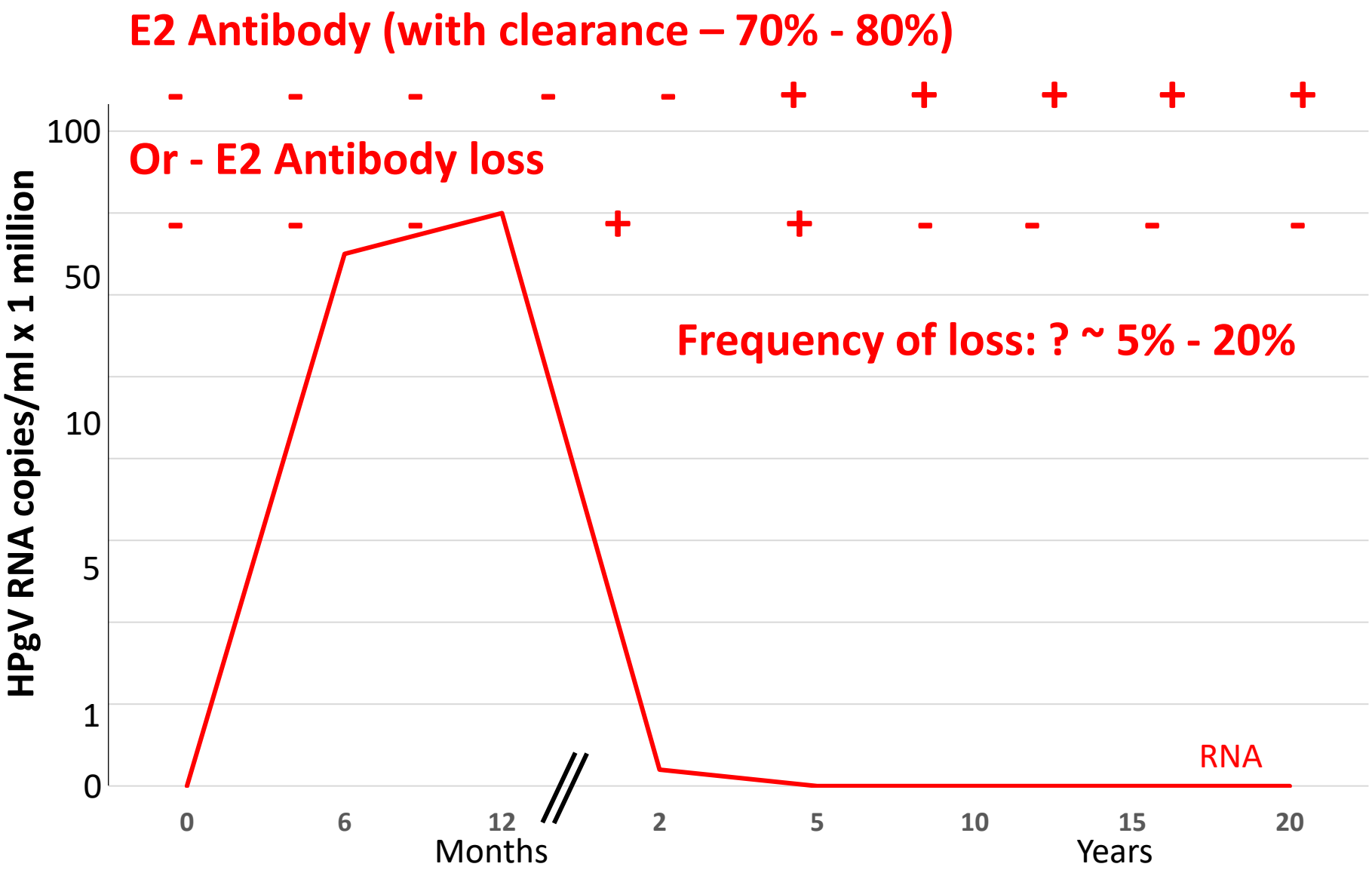


Fama, et al. Clin Infect Dis 71:1221-1228, 2020

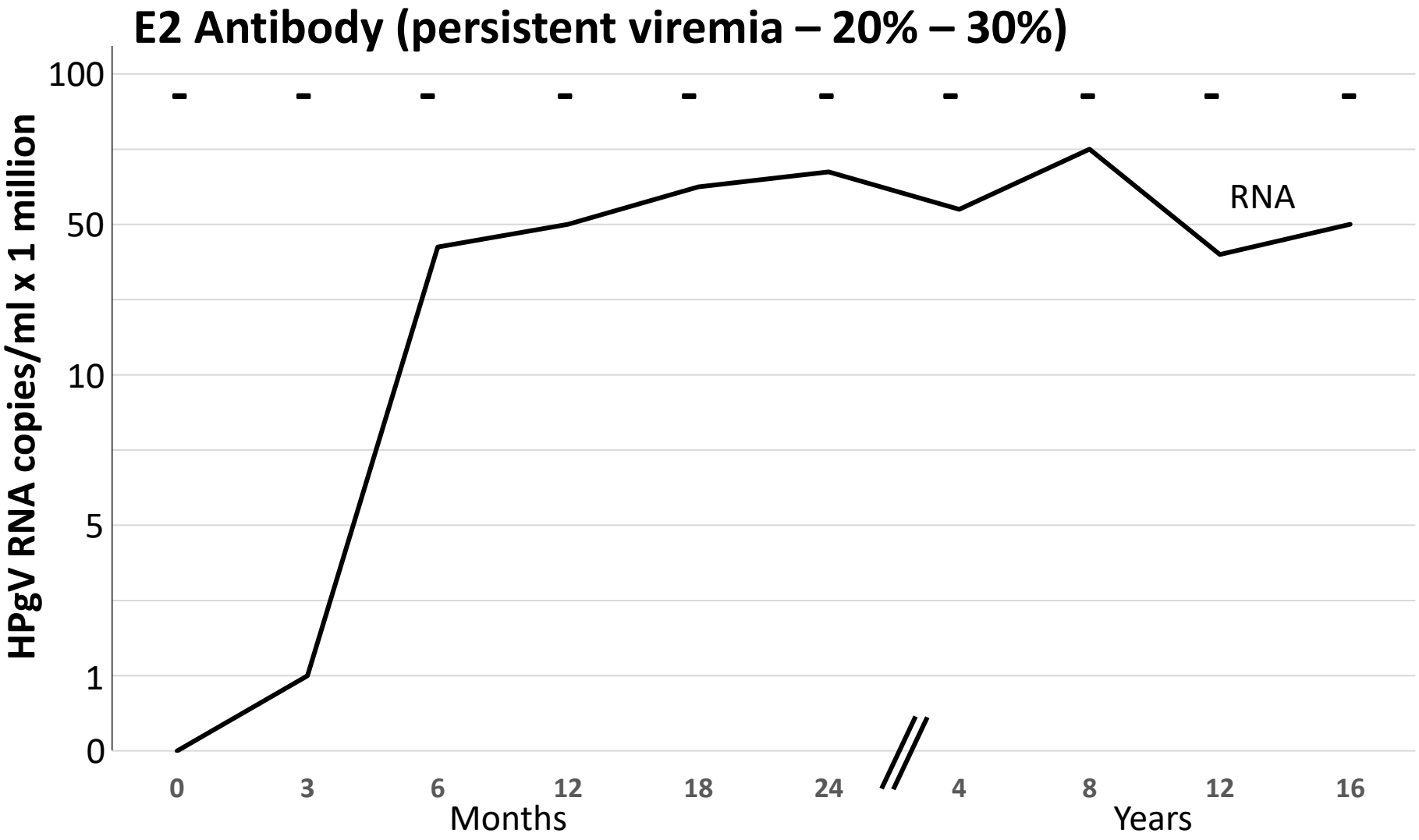
HPgV Natural History



HPgV Natural History



HPgV Natural History



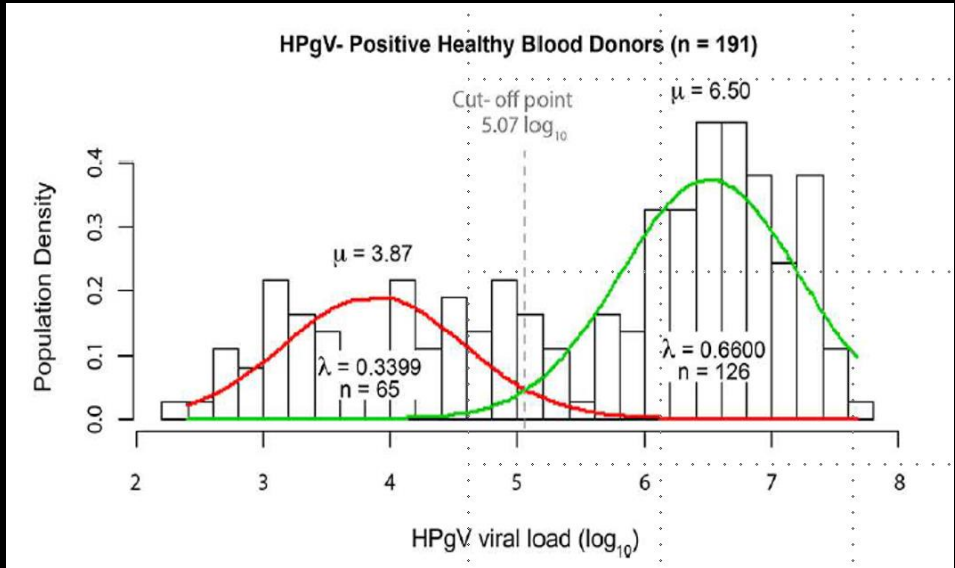
HPgV Post-transfusion

- **Viremia detected early post-transfusion**
- **Clearance usually ≥ 6 months**
- **15% - 30% do not clear within 2 years**
- **Viremia documented for 16 years (> 32 yrs HIV+)**
- **Geographic and risk differences in viremia**

Cohort	RNA Pos (%)	E2Ab Pos (%)
U.S. donors	3%	13.2%
Brazilian donors	5%-14%	??
HCV/IDU	15%-20%	20%-60%
HIV Pos	15%-40%	20%-46%

Clinical Informartion

- Sexual, parenteral, vertical transmission
- E2 Ab develops with RNA clearance (70%-85%)



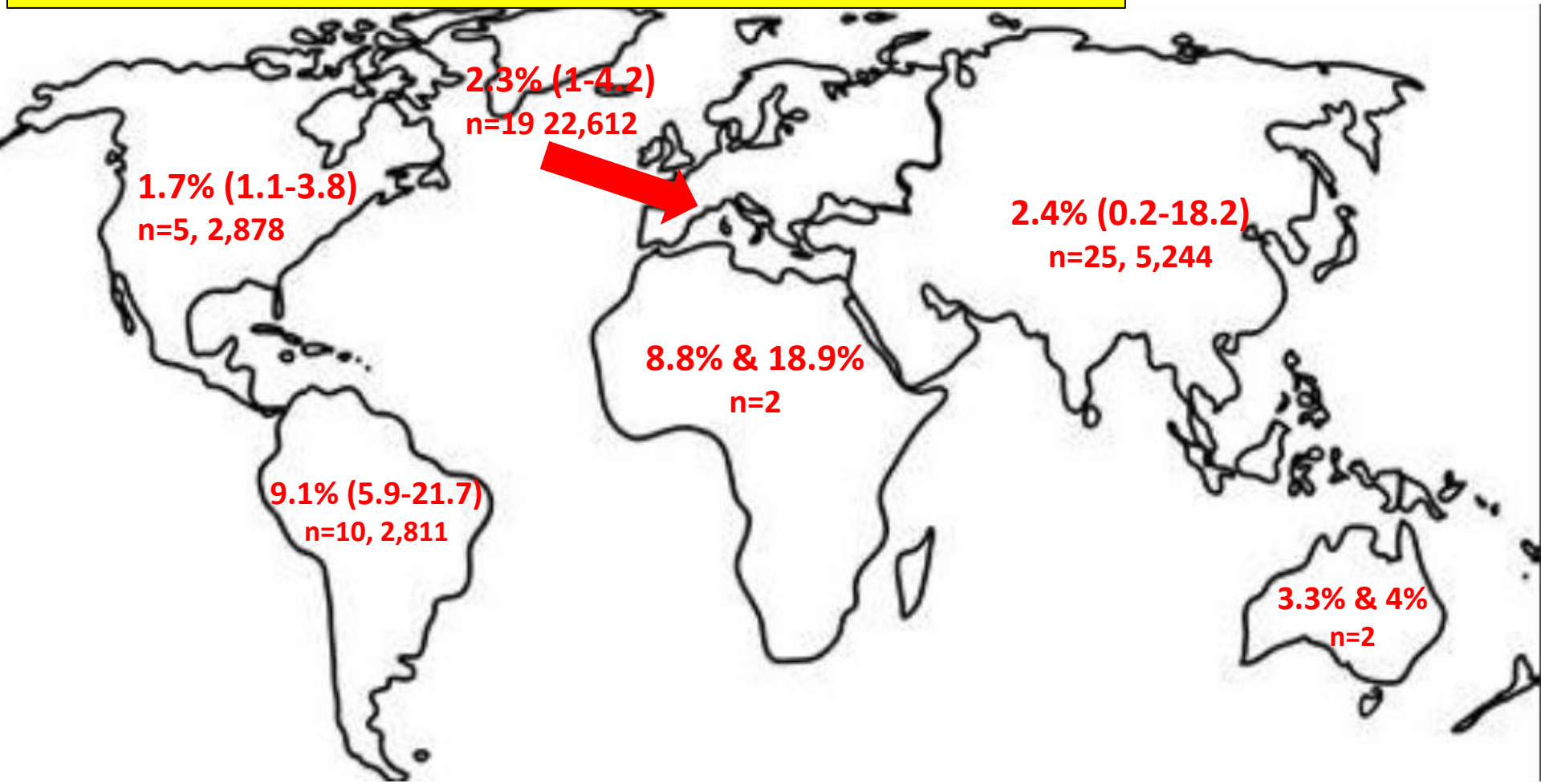
Horemheb-Rubio, G et al., PLoS One, 12:e0184494, 2017.

- High RNA titers
- Biphasic pattern
- May lose Ab over time
- No standard Ab test
- BEWARE Ab tests
- Common infection

Reviewed Stapleton, Front Immunol, 13:887760, 2022

Prevalence of HPgV Viremia in blood donors

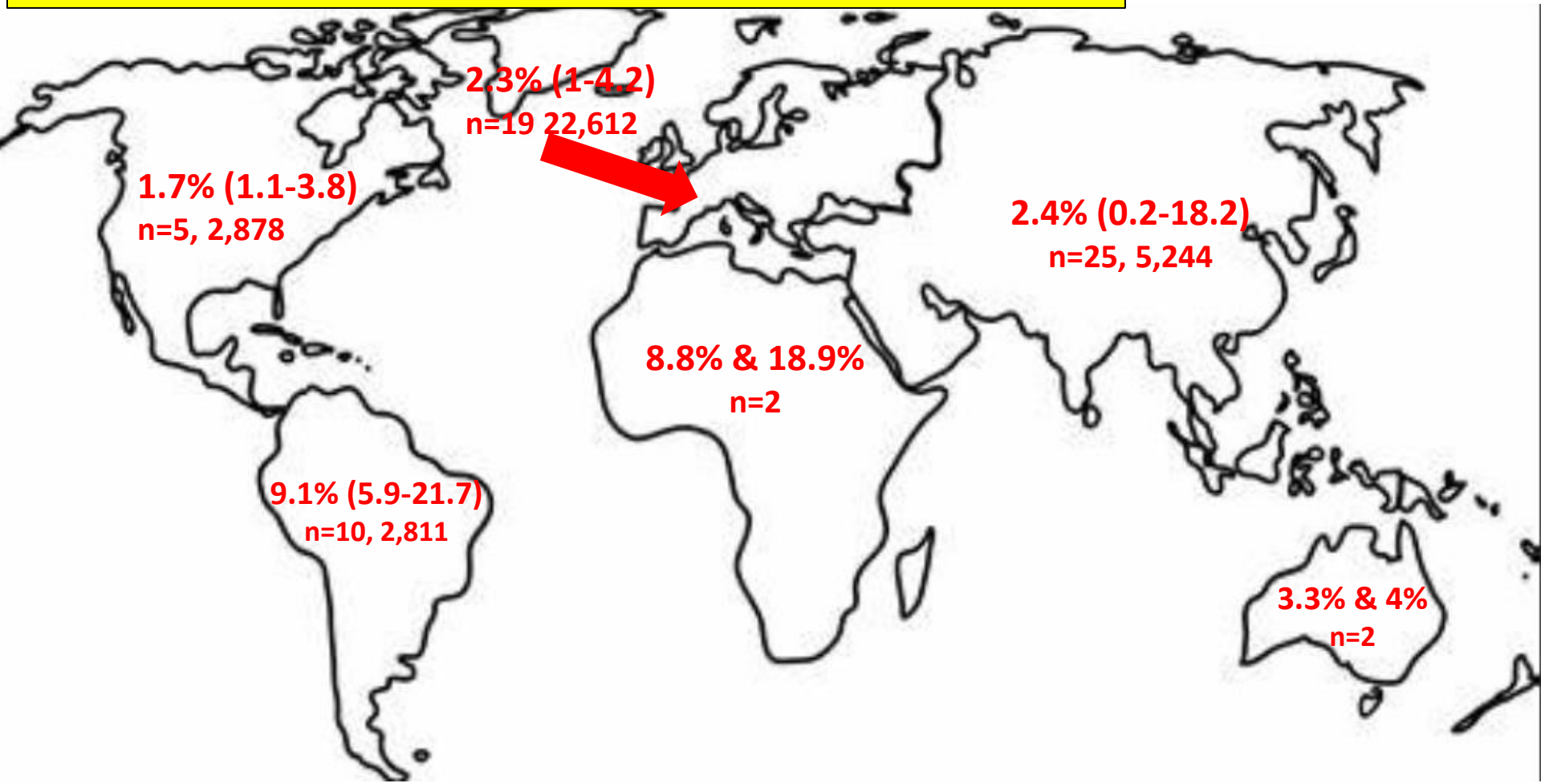
Viremia: 3.1% overall, range 0.5% to 24.5%.
Differences in geography, socioeconomics, testing methods



Yang N, et al. Vox Sanguinis 114:107, 2020
Mohr & Stapleton. J Viral Hep, 16:757, 2009

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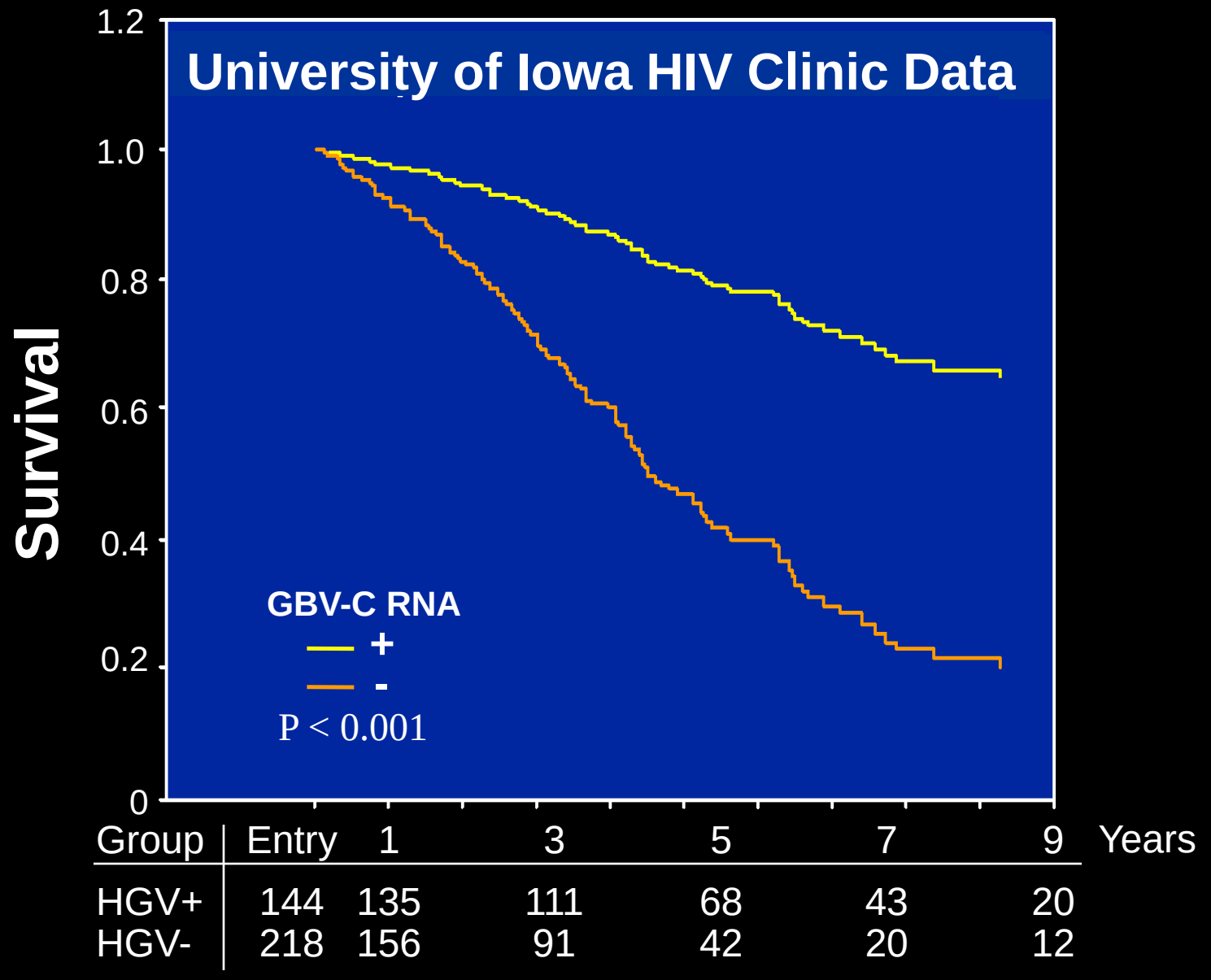


E2 Antibody prevalence (18 studies)
8,925 individuals 9% range 3.2 – 25.7

Yang N, et al. Vox Sanguinis 114:107, 2020
Mohr & Stapleton. J Viral Hep, 16:757, 2009

HPgV / GBV-C: Why study it?

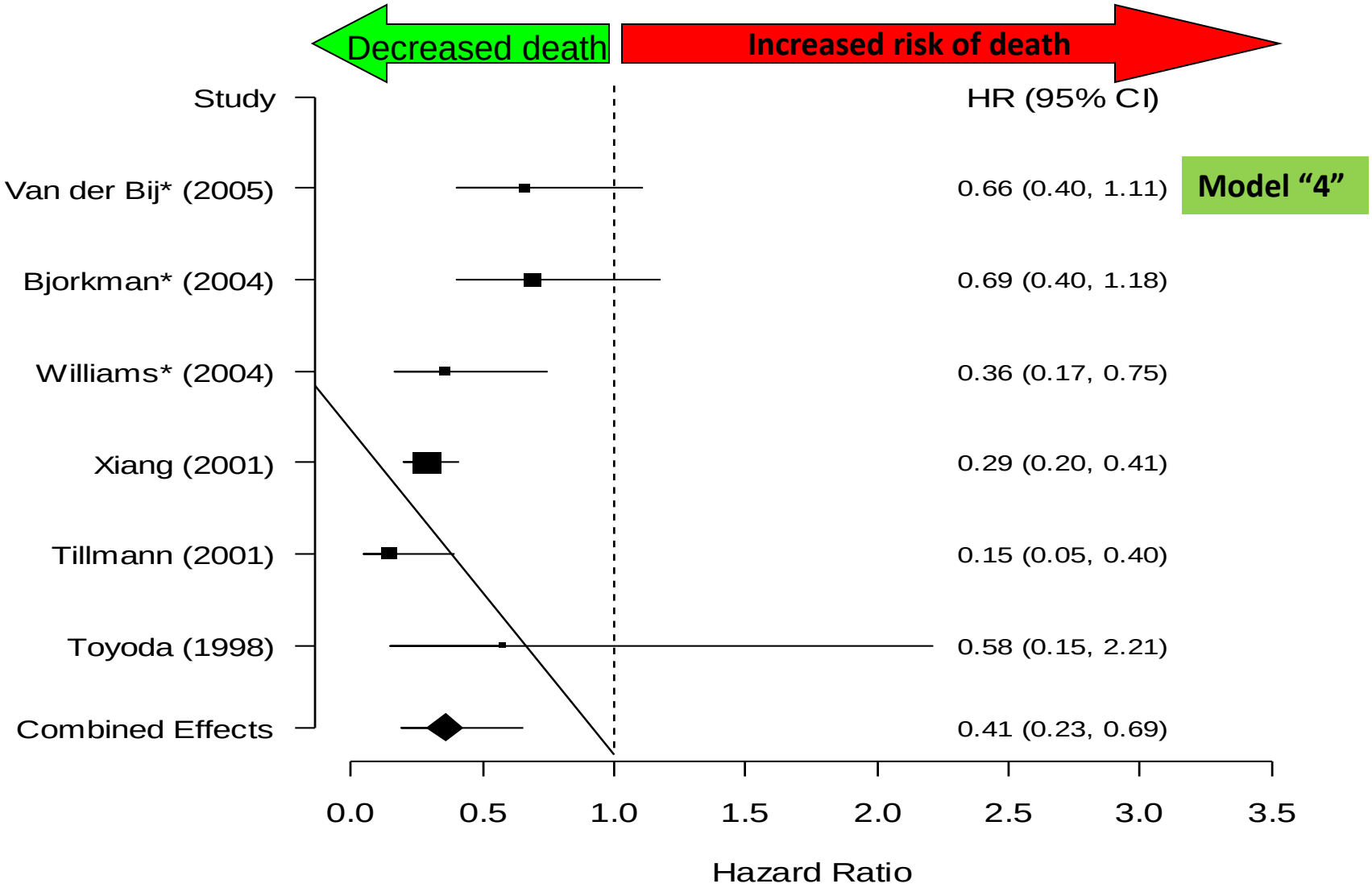
- Related to HCV. Pathogenesis insights
- Interesting features (no core protein)
- Model of viral persistence
- Gene therapy vector
- Something unexpected?



Controlled for: age, sex, race, HIV Treatment, PCP prophylaxis, CD4 count, HCV Ab, HIV transmission category.

Xiang et al., NEJM, 2001.

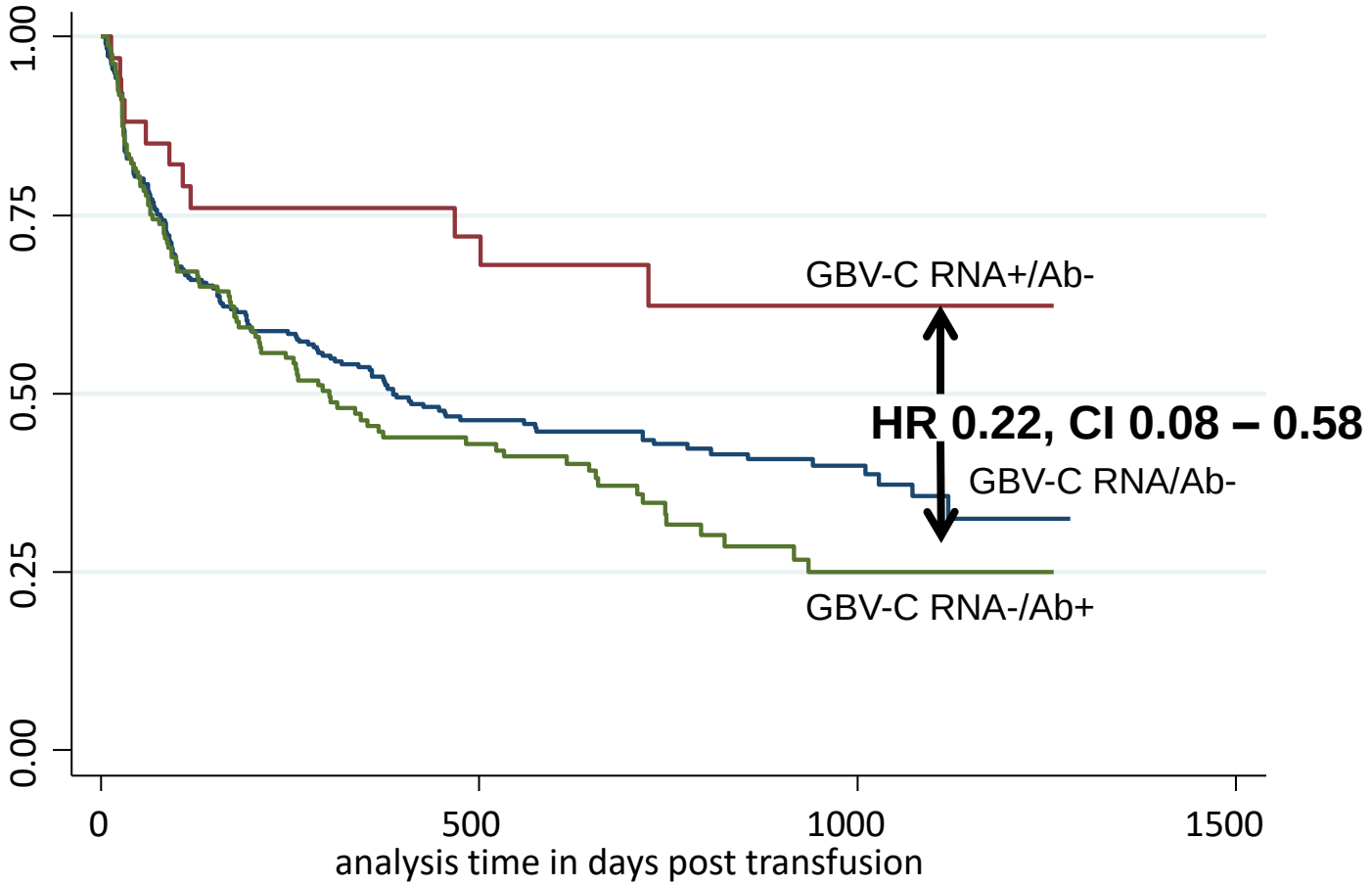
Meta-Analysis



Wang, Chaloner, Williams, Tillmann, Stapleton, HIV Med 7:173-80, 2006

Fulfilling Koch's Postulates?

Incident HPgV (GBV-C) infection and HIV Survival (VATS)

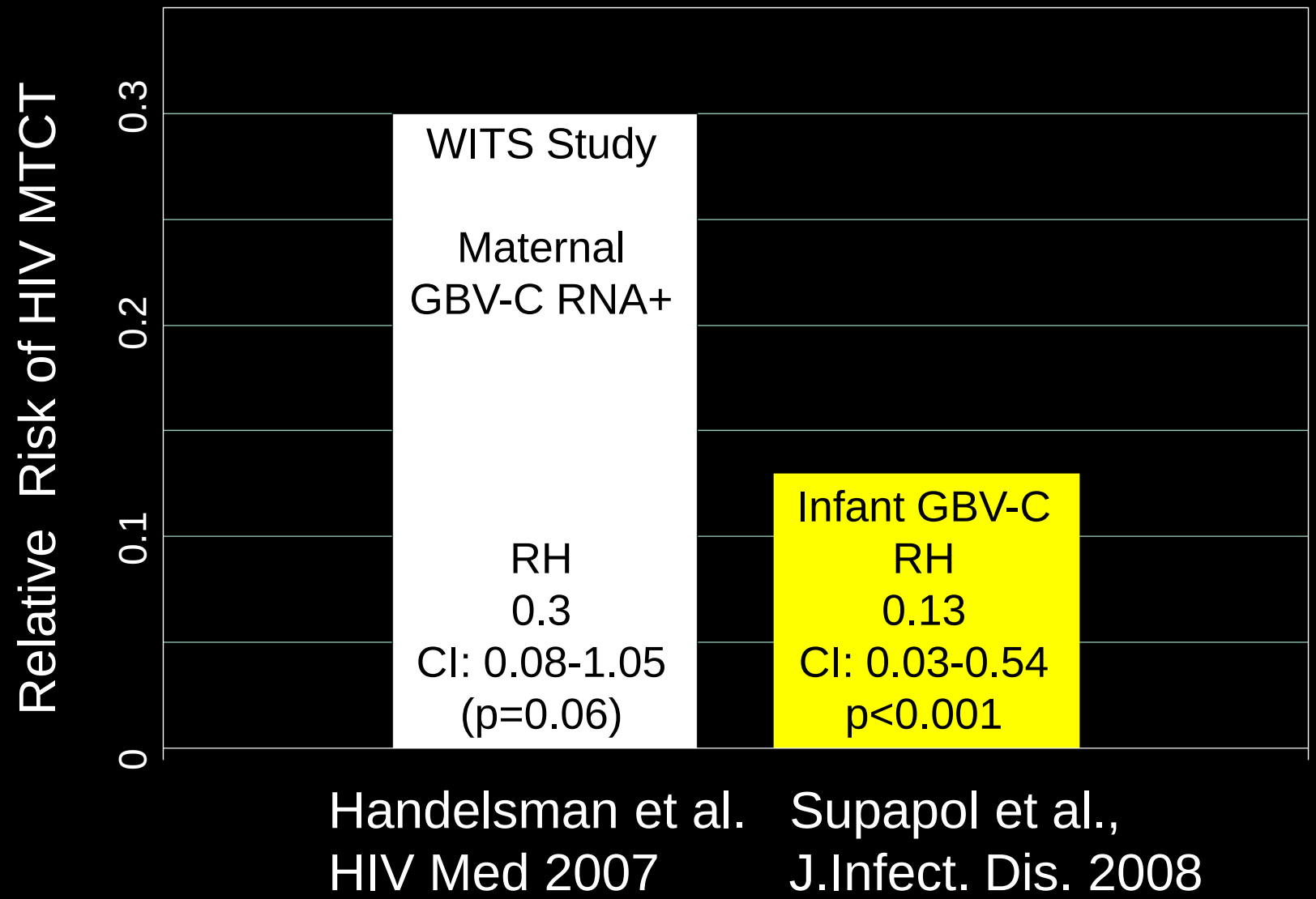


Number at risk

RNA/Ab -	294	178	154	125	99	84	71	56	42	19	6	0	0
RNA+/Ab-	34	25	23	21	18	15	12	10	5	1	1	0	0
RNA-/Ab+	161	98	75	56	49	43	27	18	14	10	2	0	0

Vahidnia et al., CID 2012

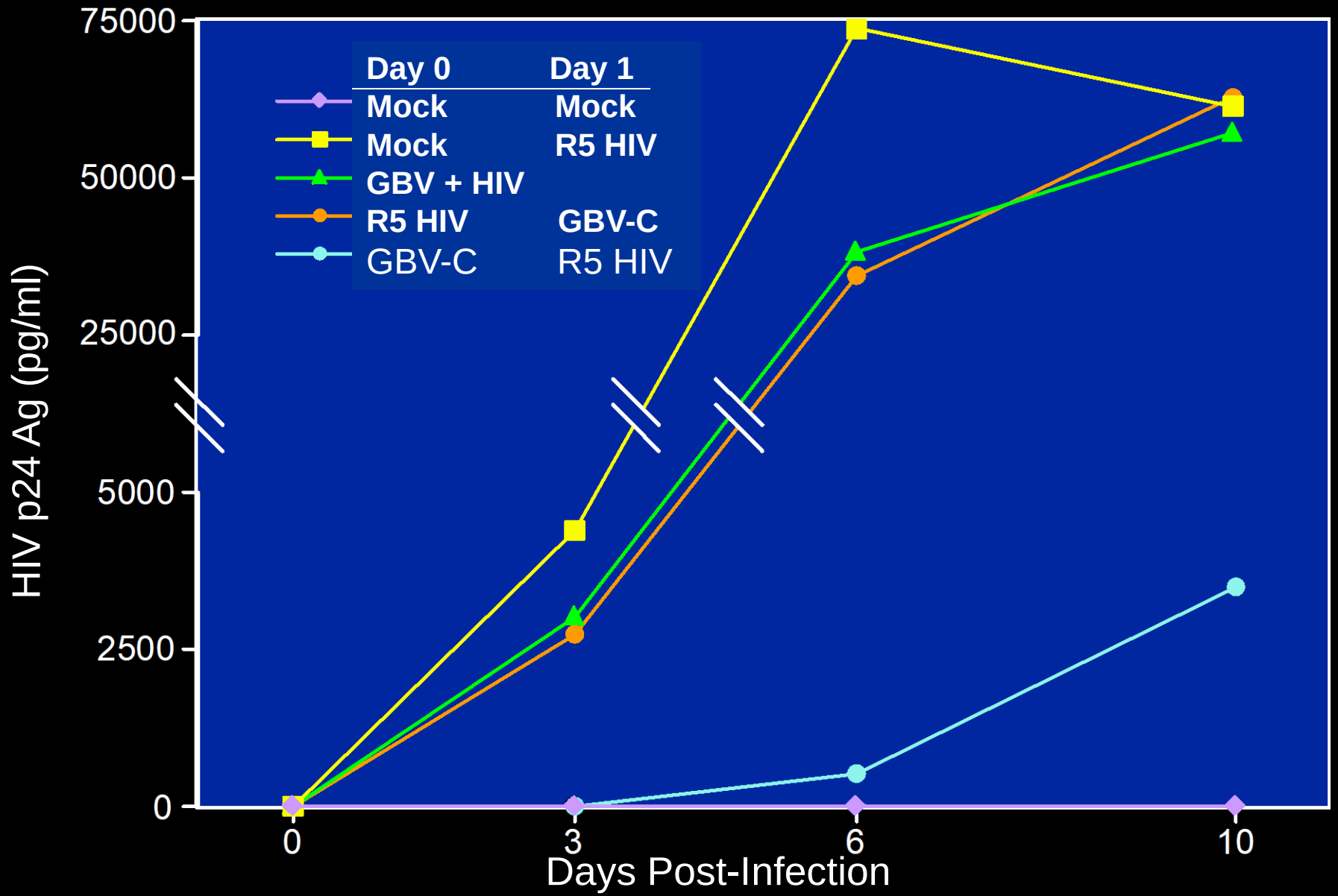
GBV-C and HIV MTCT



Thus:
HPgV prolongs survival in PLWH

How?

HPgV – HIV Coinfection



Xiang et al. NEJM 345:707, 2001

Mechanisms of HIV Inhibition

HPgV ↓ T cell Activation

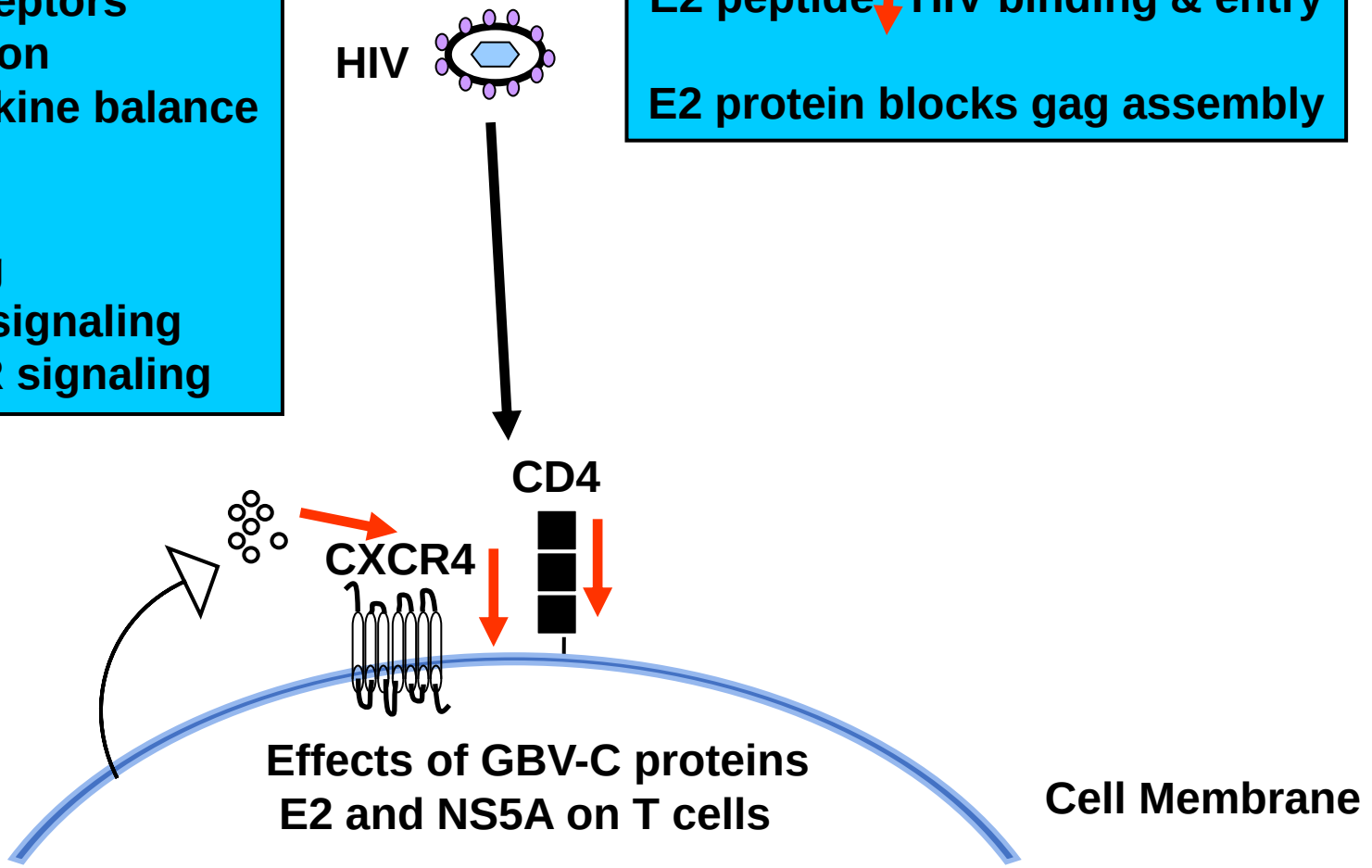
NS5A reduces:
- HIV entry receptors
- T cell activation
- Th1/Th2 cytokine balance

E2 reduces:
- TCR signaling
- IL-2 receptor signaling
- NK cell IL-12R signaling

Direct antiviral effects

E2 peptide ↓ HIV binding & entry

E2 protein blocks gag assembly



Stapleton. Front Micro, 2022. Bhattarai *et al.* Trends Microbiol. 20

Tranfusion Points

Common virus in blood donors

No acute or chronic illness

Increased risk of lymphoma

Inactivated by pathogen reduction

No FDA licensed tests (RNA/Ab)

Survival benefit in HIV, Ebola, SCT?

Mohr & Stapleton, Trends Microbiol 2013, Lauck et al., J Virol, 2013, Stapleton Front Micro 2022

Potential Future Uses?

- Gene therapy vector?
  - Need better cell culture system
- E2 peptide – immune modulator
  - Modulate transgene responses in gene Rx
- Direct inoculation (biotherapy)
  - Suggested (CID, 2012)
  - Mathmatical model supports use (AJ Epi)

HPgV-2

Prevalence (0.1 – 0.2%) in population

Associated with HCV
- 1-5% in HCV, up to 10% HIV+HCV

Not associated with hepatitis

Lymphotropic?

Natural history unclear

Transfusion Questions?

1. **Should we screen donors for HPgV-1 RNA?**
   Pros – reduce lymphoma risk
   Cons – reduce donors by average of 3% globally
   even more in developing countries

   Caveat: May change if encephalitis proves true

2. **Should we screen donors for E2 Ab?**

   No reason to – these are mostly RNA negative
   Also, would exclude 9% to 28% of donors

3. **Should we screen for HPgV-2 RNA?**
   Need more information

Conclusions



Estimated 750 million people infected

Perhaps 2 billion active or prior infection

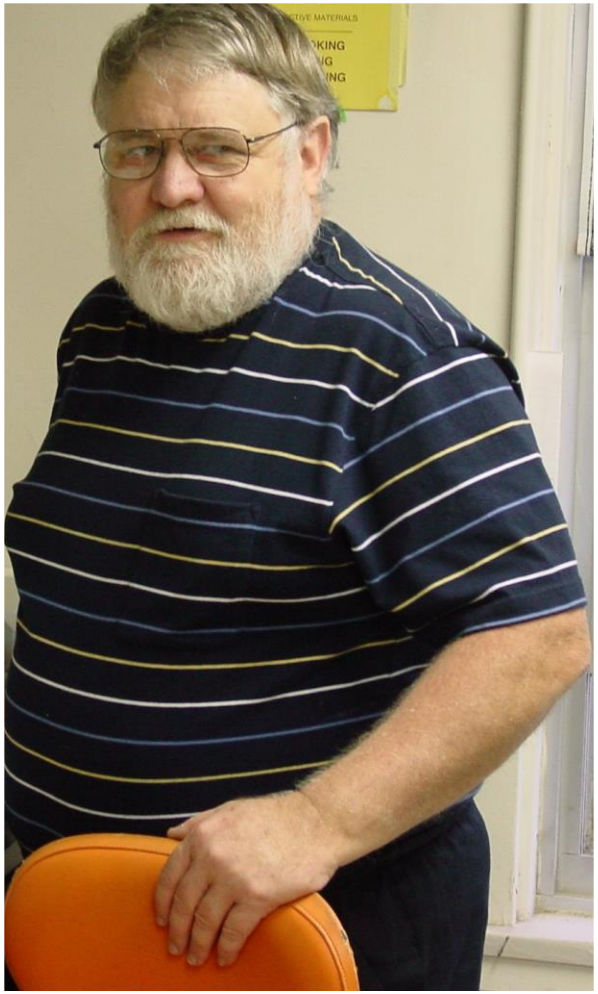
Persistent (prolonged) infection in ~ 20%

Humoral immune response delayed/absent

Not associated with any acute illness

Associated with increased risk of lymphoma







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Stapleton Lab

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UI HIV-AIDS Clinic Staff
HCV positive donors
Liver Clinic Staff

Current Address:
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** University of Wisconsin
*** University of Nebraska
† Medical College of Wisconsin

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