# Comparison: Haemovigilance versus Pharmacovigilance in Germany

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# Definitions

- **Pharmacovigilance, WHO 2002: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.**

- **DG Sanco, 2002: 'Haemovigilance' shall mean a set of organised surveillance procedures relating to serious adverse or unexpected events or reactions in donors or recipients, and the epidemiological follow-up of donors**

# Definitions in Pharmacovigilance

- Adverse reaction: A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

  ADR means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

- Serious adverse reaction means an ADR which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect .

- Adverse event: Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

# Definitions in Haemovigilance

- ‘serious adverse event’ shall mean any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity

- ‘serious adverse reaction’ shall mean an unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity;

# Definitions in Haemovigilance

- ‘imputability’ means the likelihood that a serious adverse reaction in a recipient can be attributed to the blood or blood component transfused or that a serious adverse reaction in a donor can be attributed to the donation process

- ‘traceability’ means the ability to trace each individual unit of blood or blood component derived thereof from the donor to its final destination, whether this is a recipient, a manufacturer of medicinal products or disposal, and vice versa

# European Legislation regulating Haemovigilance

- 2002/98/EC
- 2005/61 EC
- 98/79/EC In-Vitro-Diagnostics – standards for screening tests
- 93/42/EEC Medical Devices – standards for blood bags systems

# National Haemovigilance Regulation: Germany

- German Medicinal Product Act
  - Article 63 c (following 2005/61 EC) + PSUR, + § 22 (2001/83)
- German Transfusion Act
  - Collection, testing, use of blood components
- Look back procedure “Arbeitskreis Blut”(Votum 34)
- Guidelines (“Richtlinie”) of the German Medical Association

# European Legislation regulating Pharmacovigilance

- Regulation 726/2004 EC
- Directive 2001/83 EC
- Volume 9a Guidelines on Pharmacovigilance (234 pages)

# National Pharmacovigilance Regulation: Germany

- German Medicinal Product Act (following 2001/83/EC)
  - Article 63 b
  - Article 22 Pharmacovigilance and Risk Management System
- Guidelines on reporting of ADRs (following Vol 9a) including eletronic reporting (E2B format)

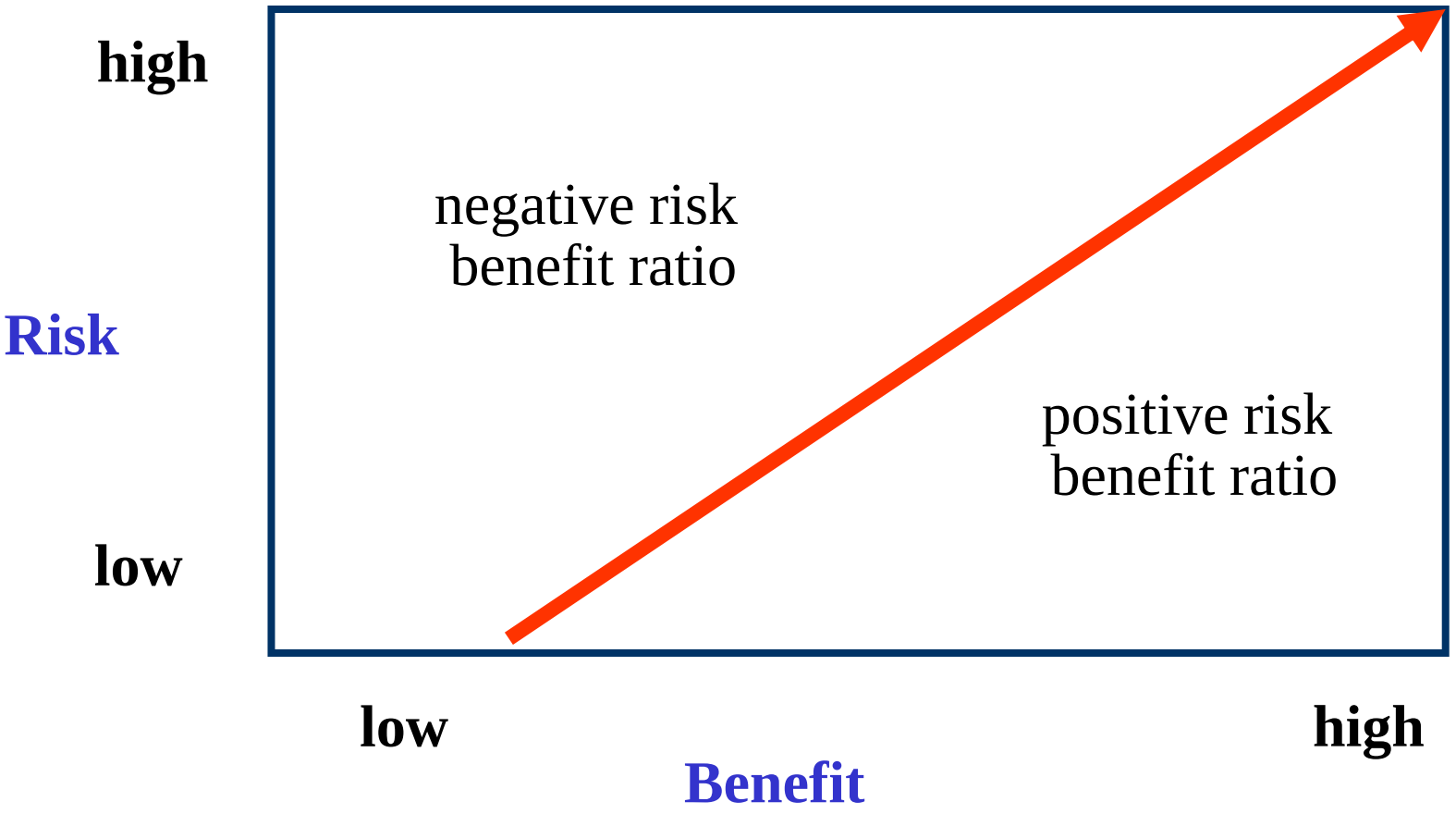
# Pharmacovigilance and Haemovigilance

- Pharmacovigilance is highly regulated and harmonised in the EU
- Harmonisation of Haemovigilance in the EU is less advanced than in PhV
- Haemovigilance in Germany
  - is highly regulated
  - has a close link to Materiovigilance
  - traceability is a key aspect

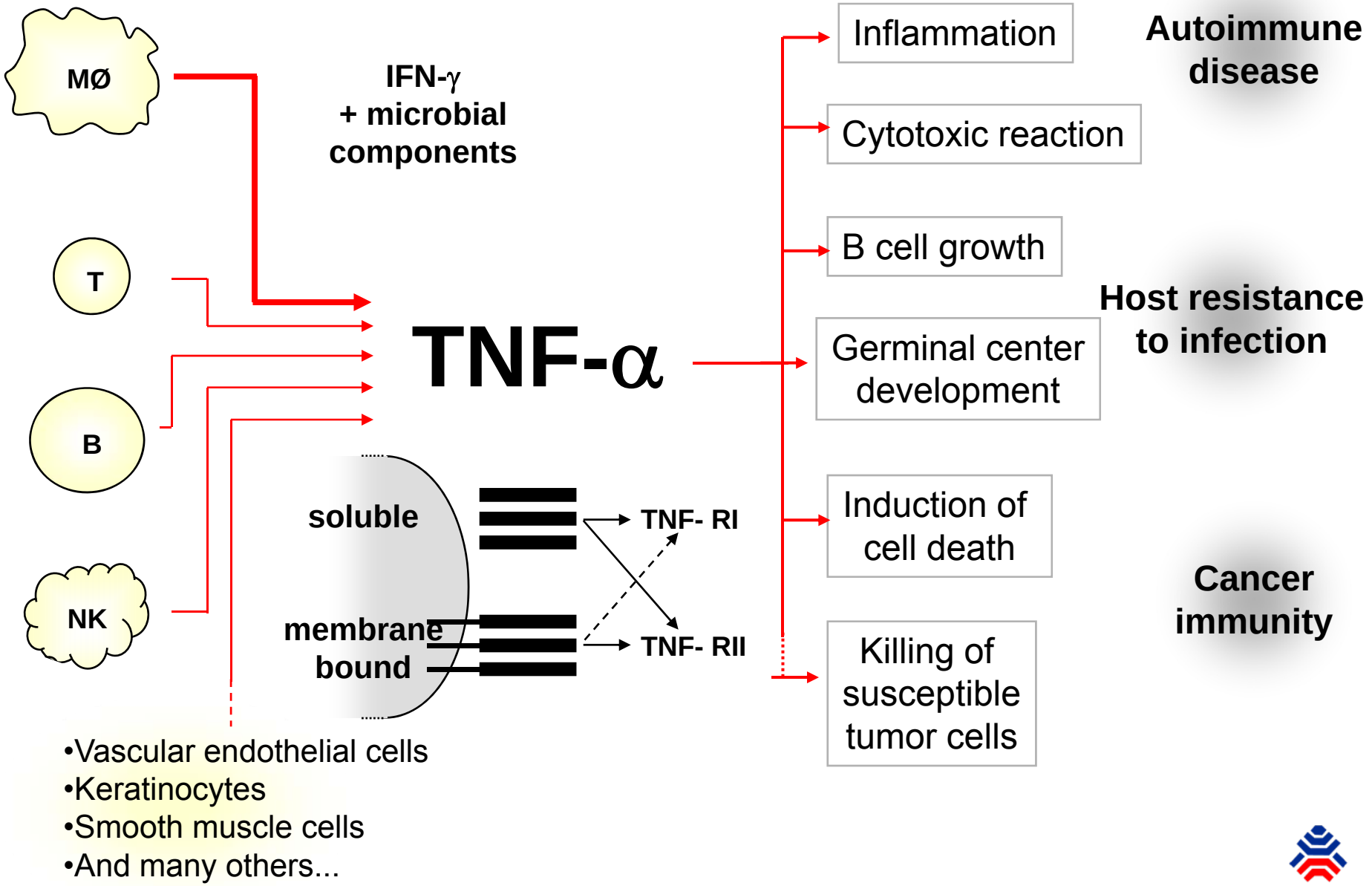
- Terminology is different between PhV and HaemoV

→ **Major difference: perception of risk**

# Risk and Benefit: Pharmacovigilance



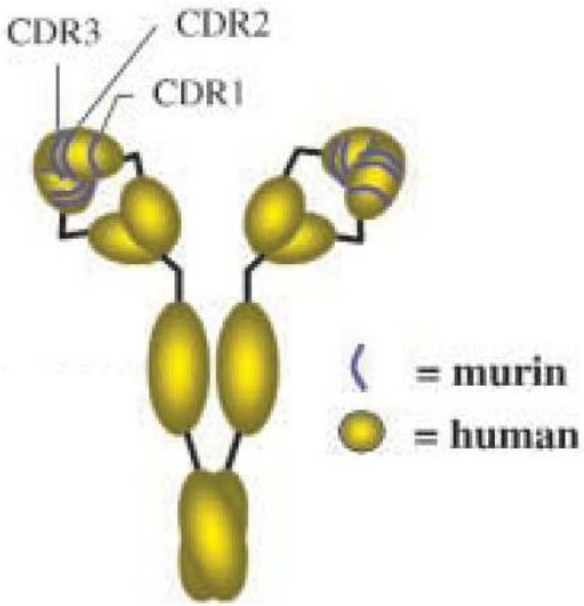
# Pleiotropic TNF-α effects



# Section 4.8 of the SPC of Remicade (TNF-α inhibitor)

- Common ≥ 1/100 to < 1/10: Viral infections, serum-sickness, infusion-related reactions, fatique, fever, elevated hepatic transaminases, nausea, dyspepsia
- Uncommon ≥ 1/1000 to < 1/100: Anaphylactic reactions, tuberculosis, exacerbation of demyelinating disease, lupus-like reactions, worsening heart failure, neutropenia, leucopenia, thrombocytopenia, anaemia, depression, amnesia, agitation, confusion, somnolence, thrombophlebitis, abnormal skin pigmentation, alopecia, bullous eruption
- Rare ≥ 1/10000 to < 1/1000: Demyelinating disease (e.g. MS), GBS, neuropathies, meningitis, pancreatitis, vasculitis, circulatory failure, lymphoma, hepatosplenic T-cell lymphoma, seizure, pancytopenia, opportunistic infections, hepatitis, granulomatous lesions
- Very rare < 1/10000: Reactivation of hepatitis B, transverse myelitis, interstitial liver failure, autoimmune hepatitis, pneumonitis/fibosis, Steven Johnson Syndrome, epidermal necrolysis, TTP, ITP, agranulocytosis

# Natalizumab (Tysabri)



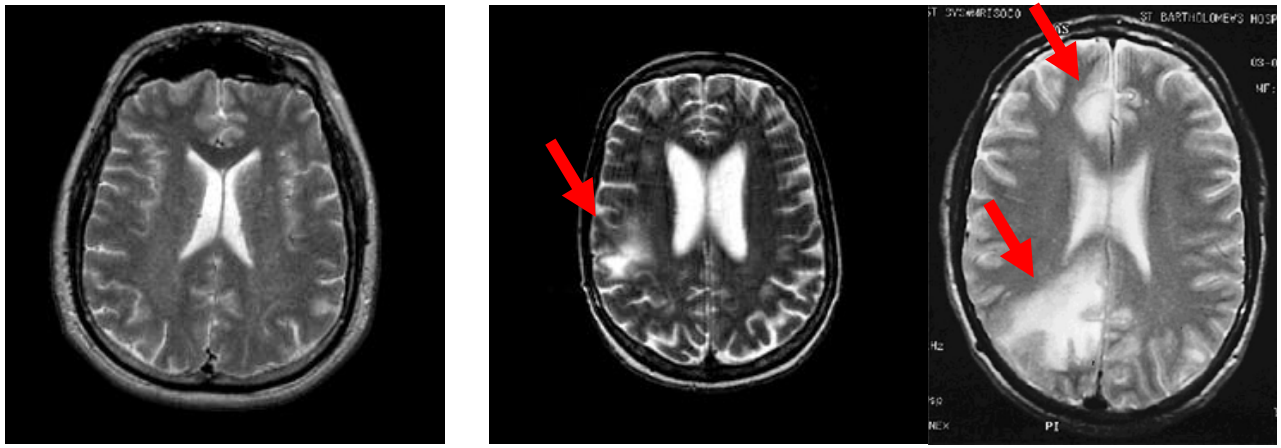

- **Specific bindung: α4-Integrin**
  α4β1- and α4β7-Integrin
  (surface of all leukocytes, except neutrophils)

**=> Block of the interaction with receptor**
(VCAM-1 and MAdCAM-1)

**=> Prevention of adhesion at the endothelium and transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue**

**Indication: Patients with high disease activity despite treatment with a beta-interferon or patients with rapidly evolving severe relapsing remitting multiple sclerosis**

# Natalizumab (Tysabri)



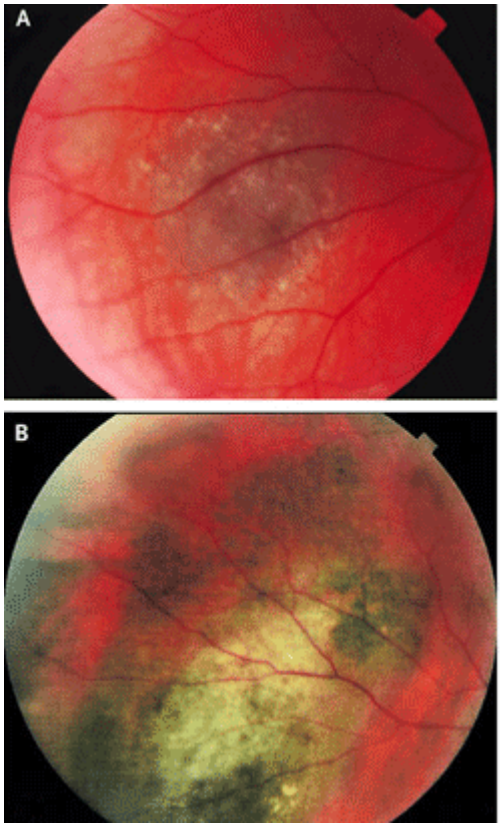
(MRT-Imagies
PML in AIDS)

**3 serious adverse drug reactions**

**Progressive multifokale Leukencephalopathie (PML)**

- **rare, progressive demyelinisation in the brain**
- **caused by JC-virus (polyomavirus)**
- **severe immunocompromised patients**
  - HIV-infektion/AIDS (5% of patients)
  - transplantation
  - tumor patients under chemotherapy  etc.

# Melanoma Complicating Treatment with Natalizumab for MS (Mullen NEJM et al 2008: 358, 647-648)




**Choriod nevus in a 45 old female (stable since 1999)**

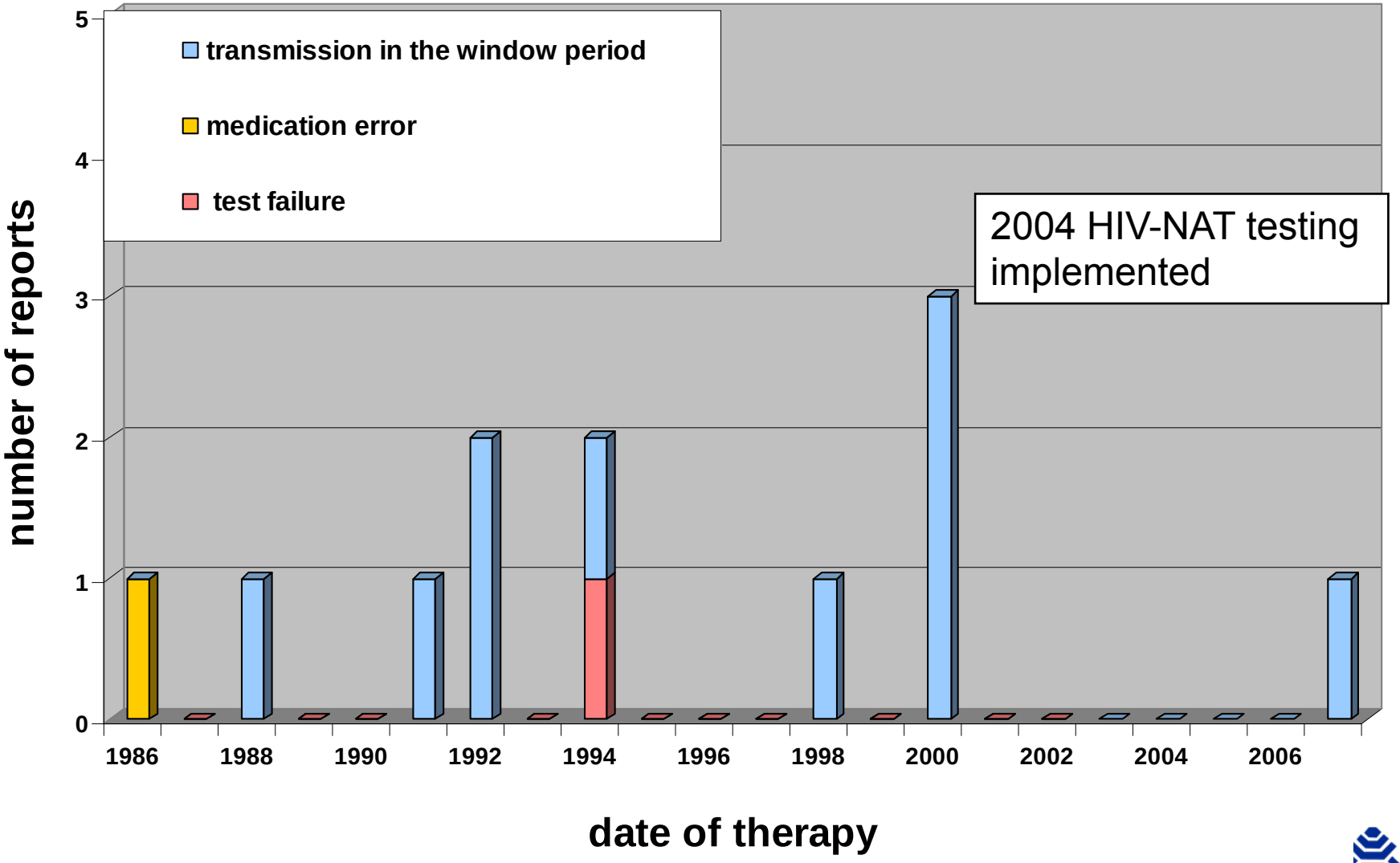
**Melanoma in the same patient after treatment with natalizumab**

# Donor epidemiology (Germany)

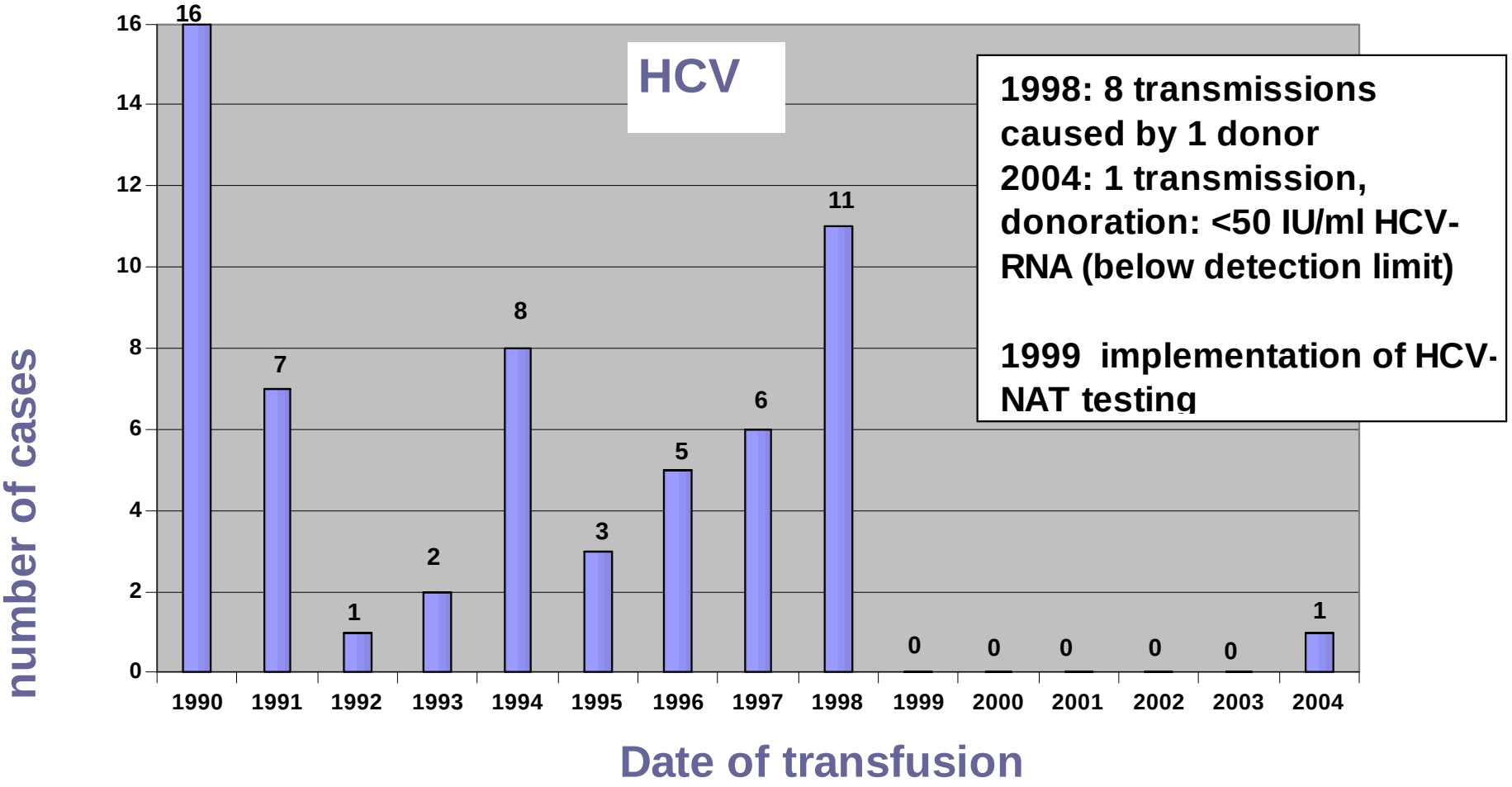
- 2000 – 2006 Average annual number of blood components distributed:
  - RBC 4,412,900
  - PC 404,400
  - FFP 1,227,200
  - Total 6,044,500
- Residual risk rate of undetected donor infections (adjusted incidence/window period model based on data 2000-2002)

| | Without NAT | Minipool NAT |
|---|---|---|
| HIV | 1:2,770,000 | 1:5,540,000 |
| HCV | 1:670,000 | 1:4,400,000 |
| HBV | 1:230,000 | 1:620,000 |

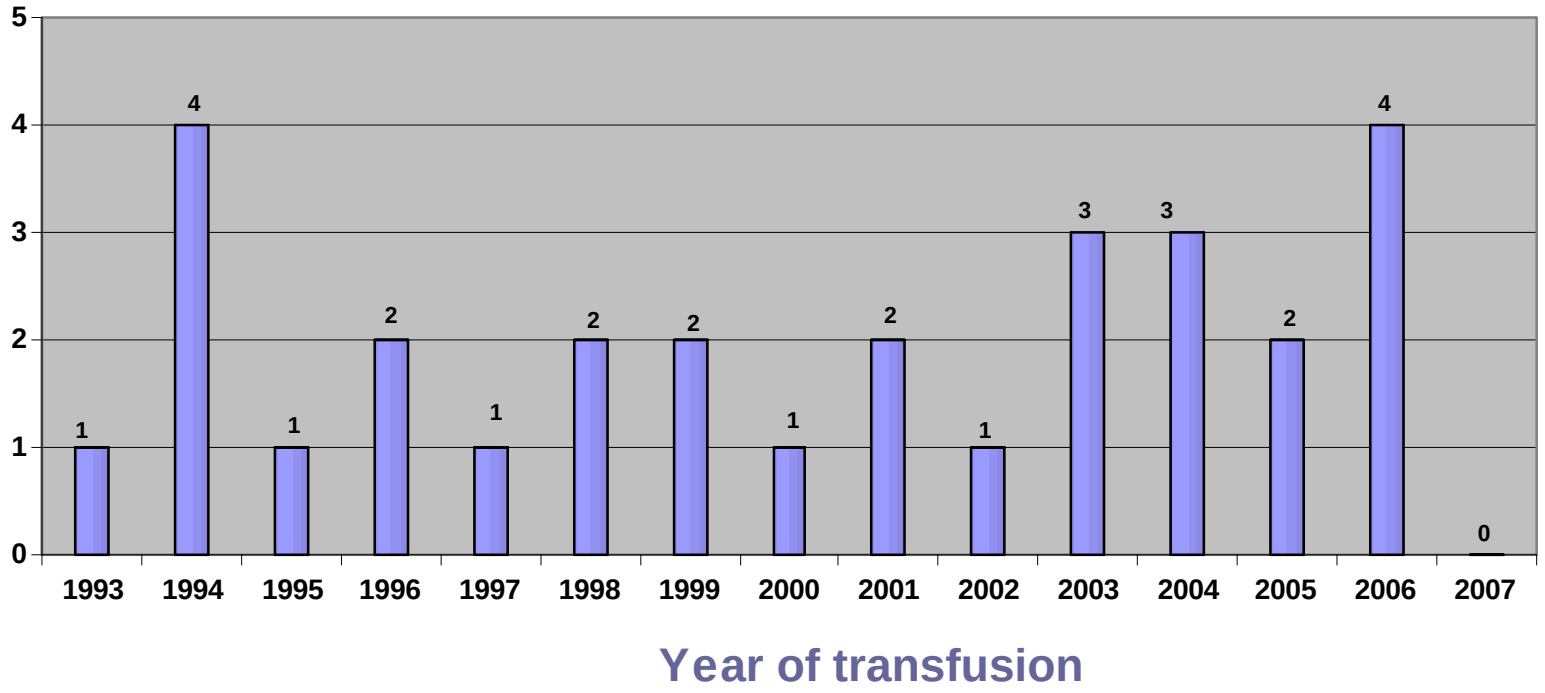
# HIV-transmission (n=12)
# After introduction of HIV-antiboby-testing in donors
# Reports received 1995 – 2007



# HCV transmissions in the window period (n = 60)
# Reports received 1995 – 2007



# HBV-transmissions in the window period (n = 29)
# Reports received 1995 – 2007




**2006 implementation of anti-HBc-testing**

# Serious adverse event
# HIV1 nucleic acid amplification test
# report of under-quantification

- **HIV1 Ab- Screening test: positive**
- **HIV1 NAT- pool test A: negative**
- **HIV1 NAT- single donor test A: 104 cop/ ml**
- **Donor- exclusion**
- **Comparative evaluation of different HIV1- NAT- tests**

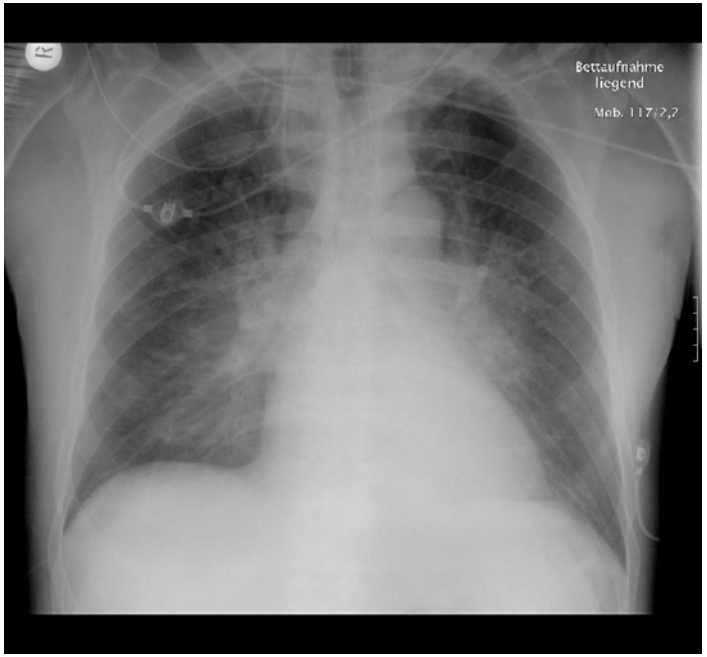
# Comparison of two NAT tests

| Tested sample | 1. HIV1 – NAT test A copies/ ml | 2. HIV1- NAT – test B copies/ ml |
|---|---|---|
| Donor (single test) | 104 | 32.000 |
| Pool of 12 samples | 52 | 2.500 |
| Pool of 48 samples | negative | 850 |
| Pool of 96 samples | negative | 260 |

# TRALI

**Frequency of immunological TRALI 1: 5000 (Popovsy MA, Transfusion 1985)**

**Fequency of non-immunological TRALI 1: 1200 (Siliman CC, Blood 2003)**




TRALI is a rare adverse reaction

# Example USA: Estimated Risk

| | |
|---|---|
| **Bacterial Contamination** [1] | |
| **Random donor platelets** | **1:3000 components** |
| | **(1:500 / 6 pack)** |
| **Apheresis** | **1:2000 components** |
| **Red blood cells** | **1:30,000** |

***RM Lewis, 3rd IABs International Symposium on Advances in Transfusion Safety, Bethesda, MD, June 4-6, 2003***

| | |
|---|---|
| **Erroneous administration 2** | |
| **ABO-incompatible** | **1:38,000** |
| **ABO-compatible** | **1:41,000** |
| **Total (adjusted)** | **1:14,000** |
| **Fatality** | **1:1,800,000** |

[1] Blajchman, IABs Int. Symp. Advanc. Trans Safety, 2003.

[2] Linden, *Transfusion*, October 2000.

# Number of reported and confirmed transfusion transmitted bacterial infections from 1997-2006

| | 1997-2006 |
|---|---|
| Suspected transmitted bacterial infection | 135 |
| Confirmed bacterial transmission | 63 |
| Transmission by PC | 32 |
| Transmission by RBC | 26 |
| Transmission by FFP | 5 |
| Fatal outcome | 9 |
| caused by RBC | 4 |
| caused by PC | 5 |

# Most of the known serious transfusion-related reactions are rare

# Perception of Risk and Benefit