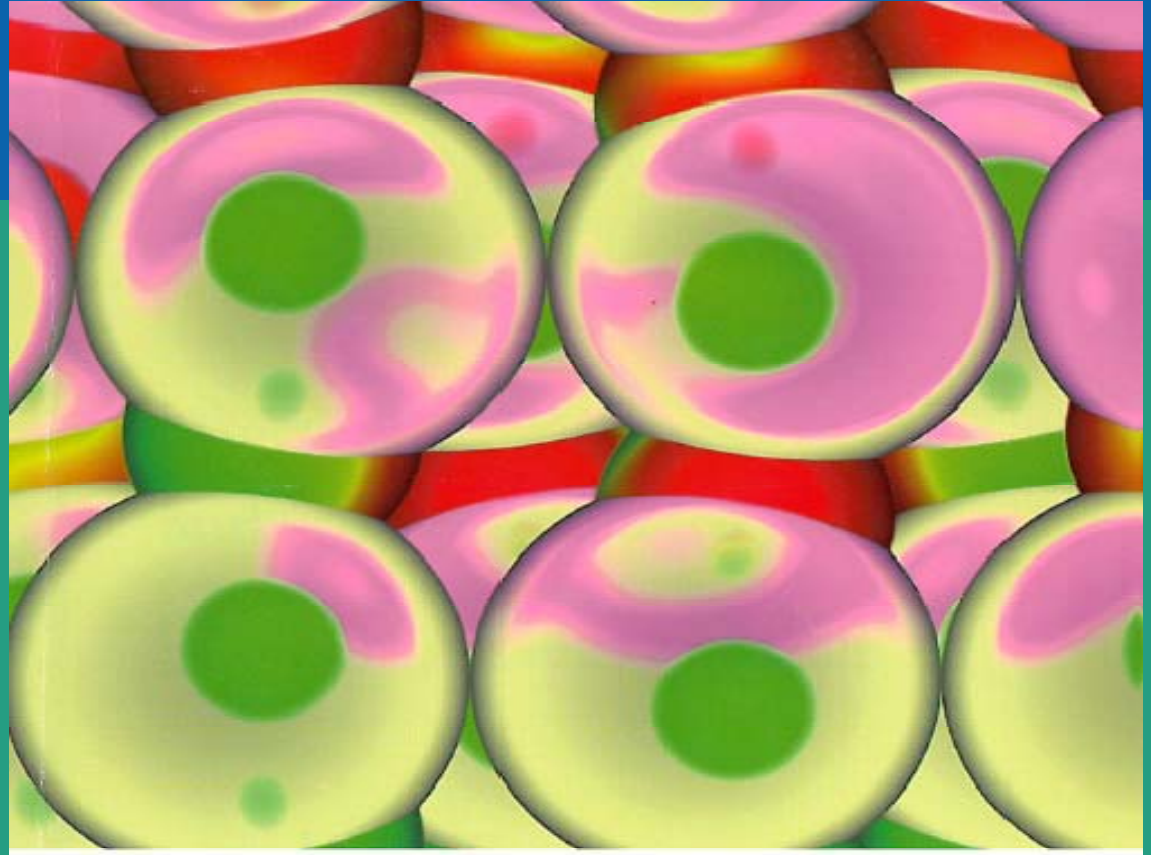
10. European Haemovigilance Seminar (EHS)
of the European Haemovigilance Network (EHN)
Frankfurt, February, 29th, 2008

Safety of organs in Europe

Guenter Kirste
Deutsche Stiftung Organtransplantation

Transfusion / Transplantation

Transfusion	**Safety first!** (PCR, storage)
Transplantation	**Safe lives avoid risks by evaluation of the donor!** - cause of death - anamnesis - travel history



Guide to safety and quality assurance for the transplantation of organs, tissues and cells

3rd edition

Council of Europe Publishing
Editions du Conseil de l'Europe

STATE OF THE ART REPORT ON SEROLOGICAL SCREENING METHODS FOR THE MOST RELEVANT MICROBIOLOGICAL DISEASES OF ORGAN AND TISSUE DONORS

INTRODUCTION

Transmission of virological and bacterial diseases after transplantation of organs and tissues has been reported. Therefore, it is essential to screen all the potential organ and tissues donors for transmissible diseases. It must be noted, however, that testing alone is not considered sufficient screening. Medical and social history are important.

At present all organ exchange organizations require that all organ and tissue donors are tested for HBs Ag (Hepatitis B) and anti- HIV-1 and 2 antibodies as well anti-HCV-antibodies (Hepatitis C) in most countries. Routine donor testing for antibodies against anti- HTLV 1 and II is still a matter of debate, both in the field of blood transfusion as well as in transplantation. No consensus exists with regard to testing for anti-Syphilis and anti-CMV-antibodies.

This document suggests how to handle the screening methods of organ and tissue donors by stating the different screening methods used and the corresponding confirmatory tests. In view of rapid developments in these fields, screening and confirmatory tests should be chosen according to the currently used techniques with respect to sensitivity and specificity with good quality control. All tests should be performed by well equipped and experienced laboratories with sufficient expertise to interpret the results of the tests. It is also important to remember that occassionally screening tests may be rendered negative due to massive blood transfusion, and in such cases tests should be performed on pre-transfusion blood samples. The time taken to do all the tests may render an organ unusable and this factor also needs to be considered.

As indicated before, organ and tissue donors must be tested for a number of viruses i.e. Human immunideficiency virus (HIV-1/2), Hepatitis B (HBs Ag) and Hepatitis C (HCV). The requirement for other tests can vary from country to country, these include CMV, HTLV-1, syphilis, Ebstein-Barr virus, HTLV-2 which may be important for epidemiological reasons. These additional tets may limit the use of organs and tissues across national borders. Furder experience may indicate whether these tests improve the quality and outcome of transplantation.

COMPULSORY TESTS FOR EVERY ORGAN AND TISSUE DONOR.

1. Human Immunodeficiency Virus (HIV 1/2)

Screening of the donor blood for the presence of antibodies against HIV by using a most recent generation Elisa technique.

Cascade (see figure 1)

If the first Elisa test is negative, the donor is suitable for transplantation purposes, if there are no other risk factors. If positive, a second different Elisa test shoul be performed. If the result is negative, a third Elisa test should be done using the same test as in the second test.

The second and third Elisa test can be performed simultaneously. In both second and third Elisa tests are negative, the donor is suitable for transplantation purposes. If the second or the third Elisa test is also positive, the Elisa es considered to be positive and the donor is not suitable for transplantation purposes. (An exception might be when the donor blood was hemolysed and the results of both Elisa tets were just above the cut-off point for positives togheter with a negative Immunoblot and negative PCR-test. A negative Immunoblot-test alone is not sufficient to declare a donor suitable for transplantation purposes).

HIV-O recently described in individuals from Cameroon, appears to be identified by some Elisa tests only. Further information is awaited and the topic needs to be kept under review.

2. Hepatitis B

Screening for the donor blood for HBsAg by using the Elisa or RIA method.

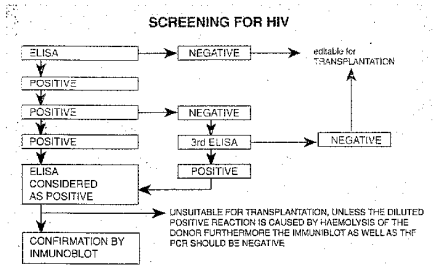


Figura 1. ***Screening for HIV.***

Cascade (see figure 2)

If the first test is negative, the donor is suitable for transplantation purposes. If the test is positive, a second different Elisa or RIA test should be performed, if the result is negative a third different Elisa or RIA test should be done. The second and third Elisa/RIA tests can be performed simultaneously.

If the second or third Elisa/RIA test is also positive, The HBsAg is considered to be positive, and a confirmation test should be performed. If the confirmation test is negative and the Elisa/RIA tests were performed in hemolysed blood, the donor can be used for transplantation purposes. If the second and third Elisa/RIA are negative; the donor is suitable.

3. Hepatitis C (HCV, non-A non B hepatitis)

In some countries all donors are tested for HVC. It is hoped that all donors will be tested in all countries in the near future. The most recent generation Elisa HCV-antibody test should be used for screening.

Cascade (see figure 3)

If the first Elisa test is positive, a second Elisa test should be performed . If the result is negative a third Elisa thest

Note

1. Organs and tissues from high risk donors should not be used even if microbiological tests are negative. However it is conceivable that if life threatening cincumstances organs might be used from such donors. The doctor in charge of such organ recipientsshould have the final decision in such exceptional casesand should inform the patient or the patient´s relatives about this xeceptional situation. The consent must be documented.
2. Preferably, the donors should be tested twice in order to increase the safety and reduce the risk of false negative results. Depending on the rate of false negatives for the relevant test, it may be necessary to use an additional screening test to reduce the possibility of false negatives results.
3. Some experts believe it is important to store always a frozen serun sample and cells of each organ and tissue donor preferably for a period of ten years.
4. Each organ/tissue which is sent to another center for transplantation should be accompanied by a form on which the most relevant donor data and results of the screening tests are given. If possible and avaible, a donor serum sample could be included to make re-screening possible.
5. There are a number of transplant centre who have vaccinated their potential recipients againts Hepatitis B. However, it should be stressed the efficacy of HBV-vaccination in some organ transplant candidates has been show to be rather low. In some countries, the rules allow, while others they do not, for the doctor in charge of the potential recipient to decide to accept or to refuse the organ offer, taking account of all the relevant circumstances.
   Tissues of a Hepatitis B positive donor should not be offered for transplantation.
6. It must be known that a negative HBs antigen does not eliminate the risk of transmitting HBV disease with the graft. Detection of donors with negative HBs antigen, negative HBs antibody, but positive anti HBc antibody is recommended. Use of tissues from such donors should be prohibited. Use of organs from such donors should be restricted to urgent cases.

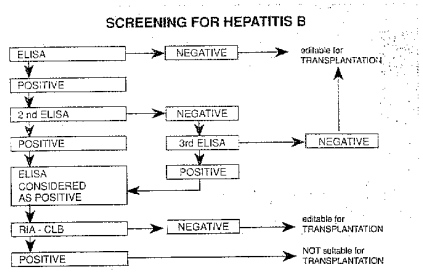


Figura 2. ***Screening for hepatitis B.***

should be done. the second and third Elisa tests can be performed simultaneously. If both second and third Elisa test are negative, the donor is suitable for transplantation purposes. If the second or third Elisa test is also positive, the Elisa is considered to be positive. In some countries were the rules allow, the doctor in charge of the potential *organ* recipient in the transplant centre decides whether to accept or to reject the *organ* offer from positive donor, for his/her patient. *Tissues* of such donor should neither be used nor offered. An exception might be when the donor blood as hemolysed and the results of both Elisa tests were just above the cut-off point for positives together with a negative immunoblot test *and* a negative PCR-test. A negative Immunoblot test alone is not sufficient to declare a donor suitable for transplantation purposes.

The following test are optional and dependent on differente donor-related factors. From a epidemiological point of view it might be, however, very important and relevant to test for these microbiological disease.

1. Cytomegalovirus (CMV)

In some countries donors are tested for the presence of IgG and IgM antibodies againts CMV. It is helpful to know the CMV status of the donor, either by Elisa or by Immunofluorescence technique in the case of organ transplantation, specially when the recipient is CMV-negative. For cornea donation the CMV-status of the donor seems to be unimportant and so testing is not routinely performed.

Bone donors are usually tested for the CMV-status although this is only important in immunosuppressed recipients.

2. Human T-leukemia virus (HTLV-1 and HTLV-2)

Recently, blood banks in some countries have started or are planning to start testing blood donors for the presence of HTLV-1/2 antibodies by using an Elisa technique and a test

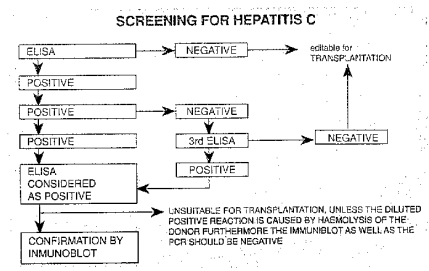


Figura 3. ***Screening for hepatitis C.***

cascade comparable of that of HIV. Organ and tissue donors are also tested for HTLV-1/2 in some countries. If the Elisa test is repeately reactive the donor organs and tissue should not be used. The incidence is very low in Europeans but is much higher in Afro-Caribbeans and people from S.W. Japan.

3. Syphilis

In most countries donor blood is screened for syphilis by using TPHA-test

Cascade (see also figure 4)

If the TPHA test is negative, the donor is suitable for transplantation purposes. If the TPHA test is positive, a second TPHA test should be performed. If the result is negative, a third TPHA test should be done. The second and third test can be performed simultaneously. If both second and third TPHA tests are negative, the donor is suitable for transplantation purposes. (If the second or the third TPHA test is positive, the TPHA is considered to be positive and, other tests such as VDRL and FTA-abs. tests should be carried out). When these tests are positive, the decision to accept organs from this donor is up to the doctor in charge of the organ recipient, where national laws allow this. (Confirmatory cascades may differ from laboratory to laboratory).

Instead of the TPHA test the VDRL test can also be used for screening.

4. Creutzfeldt Jacob disease (CJD)

Although there are not serological screening tests available for this disease, most countries require additional information on the possibility or likelihood of transmitting this disease.

All individuals who have in the past been treated with extracts derived from human pituitary glands and/or who have clinical signs which may be caused by CJD or who have a family history of CJD are debarred from donation.

5. Other diseases

Some countries require additional microbiological tests if available or possible. Among these are the following:

- Tuberculosis (specially when there is s a positive history of the donor of tuberculosis.
- Epstein-Barr virus;
- Toxoplasma (specially for hearth transplantations);
- Neurotropic viral diseases (Rabies).

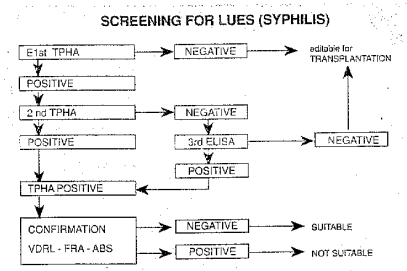


Figura 4. ***Screening for Lues (syphilis).***

Note:

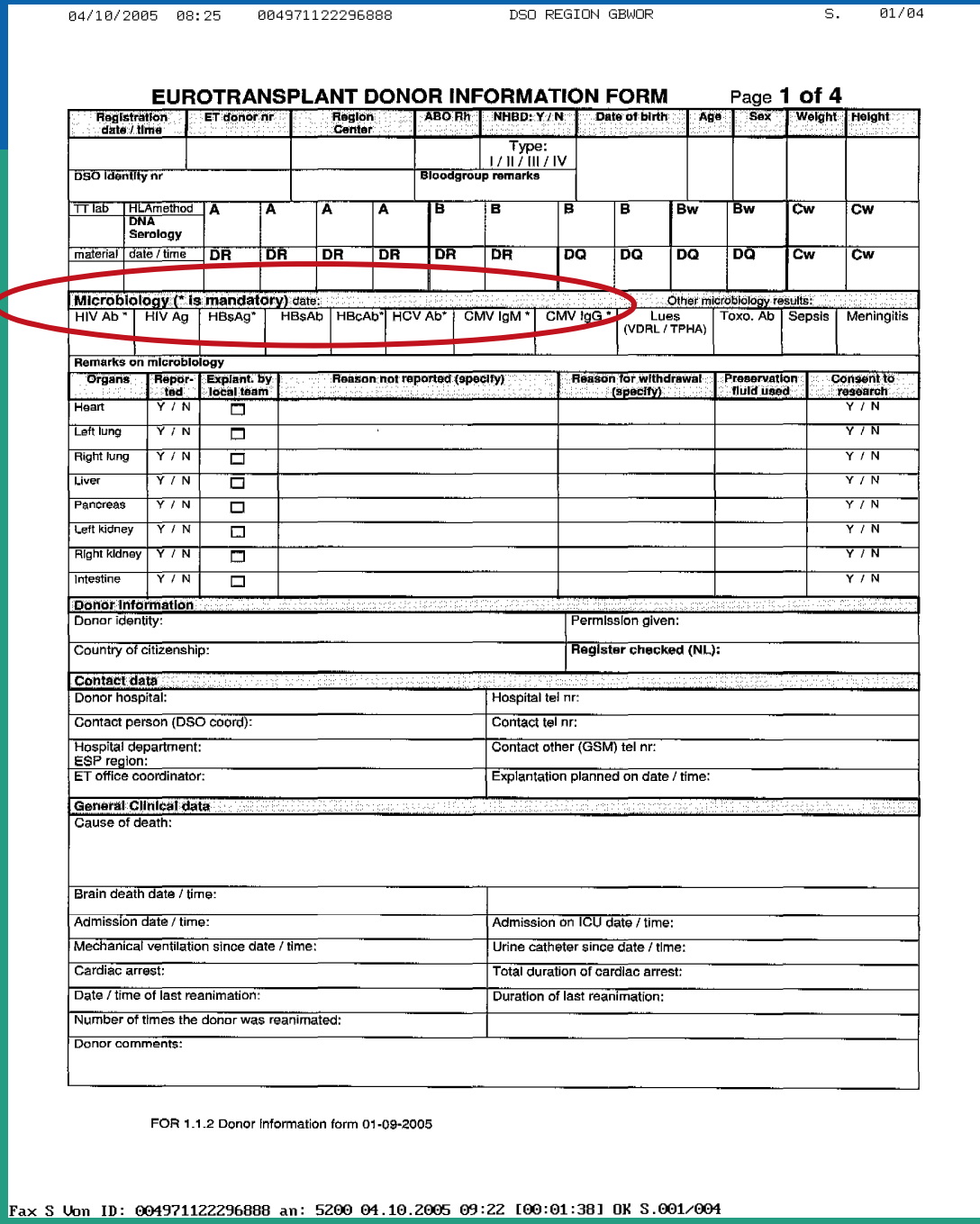
7. The American Association of Tissue Banks has recently decided that all potential tissue donors should be tested for HTLV-1. At the moment there exists no reliable ecreening test for HTLV-2. However, the ELISA-test used for HTLV-1 cross-reacts with most types of HTLV-2.

Donor Information Form ET

Microbiology (mandatory):

- HIV Ak
- HBs Ag
- HBc Ak
- HCV Ak
- CMV Ak (IgM/IgG)

- Lues Ak
- EBV Ak
- Toxoplasmose Ak



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EUROTRANSPLANT DONOR INFORMATION FORM Page **1 of 4**

Registration date / time	ET donor nr	Region Center	ABO Rh	NHBD: Y / N	Date of birth	Age	Sex	Weight	Height
				Type: I / II / III / IV					
DSO identity nr			Bloodgroup remarks						

TT lab	HLAmethod DNA Serology	A	A	A	A	B	B	B	B	Bw	Bw	Cw	Cw
material	date / time	DR	DR	DR	DR	DR	DR	DQ	DQ	DQ	DQ	Cw	Cw

Microbiology (* is mandatory) date: Other microbiology results:

HIV Ab *	HIV Ag	HBsAg*	HBsAb	HBcAb*	HCV Ab*	CMV IgM *	CMV IgG *	Lues (VDRL / TPHA)	Toxo. Ab	Sepsis	Meningitis

Remarks on microbiology

Organs	Repor-ted	Explant. by local team	Reason not reported (specify)	Reason for withdrawal (specify)	Preservation fluid used	Consent to research
Heart	Y / N	☐				Y / N
Left lung	Y / N	☐				Y / N
Right lung	Y / N	☐				Y / N
Liver	Y / N	☐				Y / N
Pancreas	Y / N	☐				Y / N
Left kidney	Y / N	☐				Y / N
Right kidney	Y / N	☐				Y / N
Intestine	Y / N	☐				Y / N

Donor Information

Donor identity:	Permission given:
Country of citizenship:	Register checked (NL):

Contact data

Donor hospital:	Hospital tel nr:
Contact person (DSO coord):	Contact tel nr:
Hospital department: ESP region:	Contact other (GSM) tel nr:
ET office coordinator:	Explantation planned on date / time:

General Clinical data

Cause of death:

Brain death date / time:	
Admission date / time:	Admission on ICU date / time:
Mechanical ventilation since date / time:	Urine catheter since date / time:
Cardiac arrest:	Total duration of cardiac arrest:
Date / time of last reanimation:	Duration of last reanimation:
Number of times the donor was reanimated:	

Donor comments:

FOR 1.1.2 Donor Information form 01-09-2005

Fax S Von ID: 004971122296888 an: 5200 04.10.2005 09:22 [00:01:38] OK S.001/004

Infectious Diseases Reported to Have Been Transmitted by Organ Allografts

- Rabies
- CJD
- HIV
- Hepatitis B & C
- CMV, EBV
- Parvovirus
- Toxoplasmosis
- Chagas' Disease
- Malaria
- Bacteria
- Tuberculosis
- Hepatitis B & C
- HHV-8
- Strongylodiasis
- West Nile Virus
- Lymphocytic choriomeningitis

Extended Donor Criteria (ECD)

- **Virushepatitis**
  (HBsAg+, anti-HBc+ or anti-HCV+)
- **Sepsis with positive blood culture**
- **Meningitis**
- **Malignant Tumor in the medical history**
- **Drug abuse**

Richtlinie der BÄK zur Organtransplantation gemäß § 16 TPG

Safety for organ recipients

Goals:

1. **Detect classic parenteral transmitted infections**
   - HIV 1 / 2
   - HBV
   - HCV

2. **Avoid complications due to transmission of**
   - „opportunistic“ Virus
   - CMV
   - EBV

Safety for organ recipients

DSO

Goals

3. **Exclude donors with suspicion of**

   West Nile Virus

   LCMV

   Rabies **absolute contraindication**

4. Avoid donors with rare parenteral infections

   HTLV 1/2

   HHV 8

   Others **relative contraindication**

Donor screening

Donor screening

- bacterial infections
- mycobacterial infection
- fungal infection
- parasitic infection
- viral infection

Bacterial infection

- Respiratory tract
- Urinary tract
- Systemic infection

No contraindication for organ donation

→ blood culture

→ specific treatment

Syphilis

- Rarely transmitted by transplantation
- Post transplant treatment with penicillin

No contraindication

Mycobacterium tuberculosis

Transmitted from the donor in 4 % of post TX TB cases

Tine test in donors (LD)

- X-ray
- Sputum culture

No contraindication for cadaveric donation

If Tine test is known to be positive
→ Isoniazid prophylaxis

Fungal infections

Contraindication for donation

- Most post transplant cases are reactivations in the recipient

Parasitic infections

Toxoplasmosis	Lymphadenopathy
Cryptosporidium	Diarrhoea
Isospora belli	Diarrhoea (tropical disease)
Leishmaniasis	Cutis
Amoebiasis	Colitis
Malaria	Periodic fever
Chagas disease	Myocarditis

Toxoplasma gondii

75 % from the population is seropositive

- IgG positive 2 weeks after infection
- IgM acute infection (specificity?)
- PCR (sensitivity?)

No contra indication for organ donation

But:

Prophylaxis

D+ R -

Toxoplasma gondii

75 % from the population is seropositive

- IgG positive 2 weeks after infection
- IgM acute infection (specificity?)
- PCR (sensitivity?)

No contra indication for organ donation

But:

Prophylaxis

D+ R -

Alliance-O
Work Package 4
INCREASE SAFETY AND QUALITY IN ORGAN TRANSPLANTATION

Deliverable 4.1
STATE OF THE ART OF SAFETY PROCESSES, EXCHANGE OF BEST PRACTICES

WP partner representatives	
Alessandro Nanni Costa	CNT
Francesco Gabbrielli	CNT
Sante Venettoni	CNT
Guenter Kirste	DSO
Daniela Norba	DSO
József Borsi	Hungarotransplant
Peter Borka	Hungarotransplant
Bernard Loty	Agence Biomedecine
Thanh Le Luong	Agence Biomedecine
Luisa Taveira	OPT
Manuel Abecassis	OPT
Blanca Miranda	CENATMER
Steve Bell	UKTransplant

Alliance-O-project

Table 4: type of test not performed	
Anti HBsAg	HT
AntiHBcAg	HT
HDV (if patients HBsAg positive)	DSO, ABM, OPT, HT
HSV-1(IgG)	DSO, ABM, OPT, HT, ONT
HSV-2(IgG)	DSO, ABM, OPT, HT, ONT
EBV (anti VCA and anti EBNA antibody)	HT, ONT
VZV (IgG)	ABM, UKT, OPT, HT, ONT
Toxoplasma (antibody)	OPT, HT

On the other side all countries require the following fundamental tests:

- Anti HIV,
- Anti HCV,
- HBsAg,
- Syphilis (TPHA/VDRL),
- Anti CMV (IgG and IgM).

Definition of risk levels

Unacceptable risk (absolute contraindication). It includes all cases listed in the next paragraph (B). In these cases the donor is not suitable for transplantation.

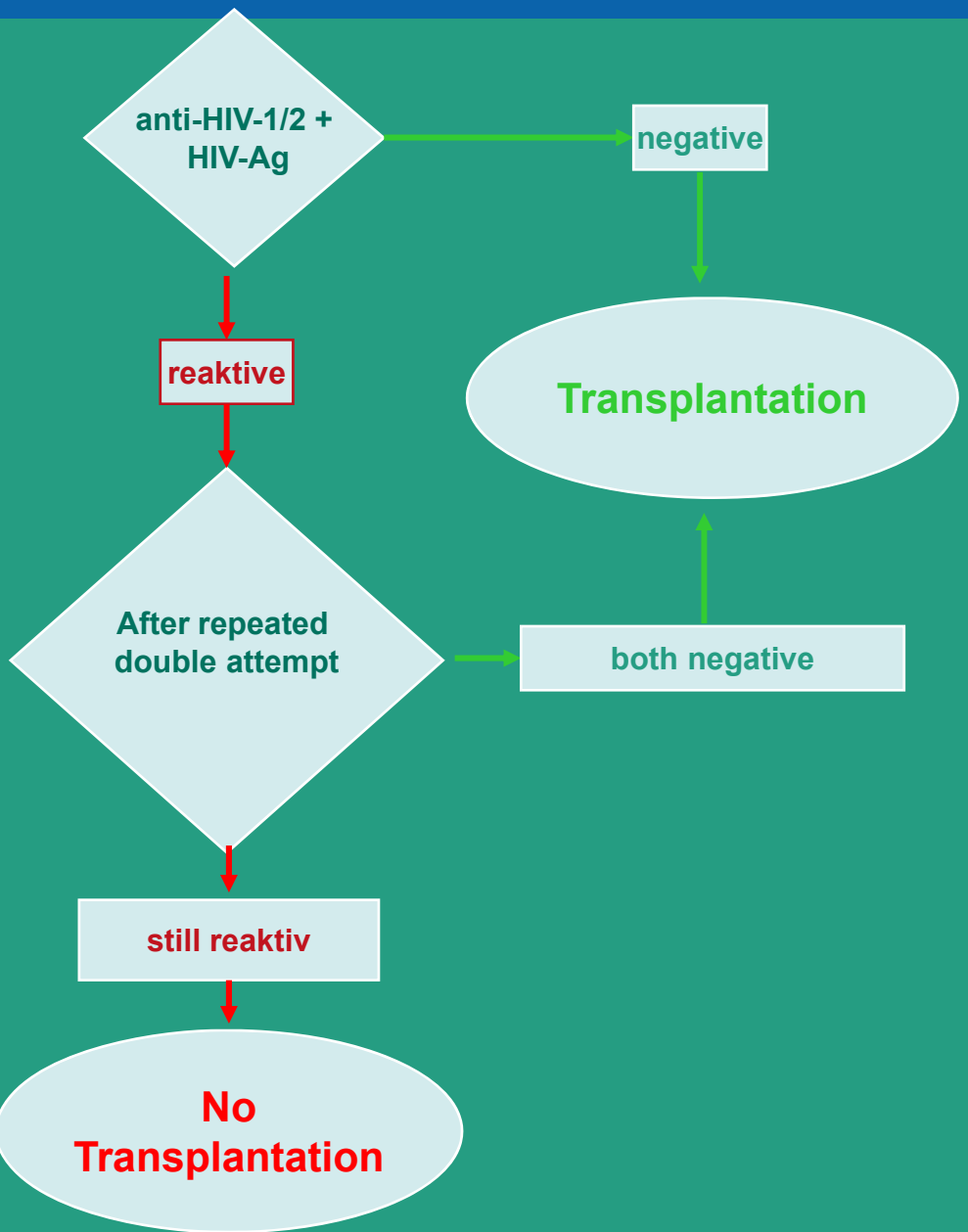
Increased but acceptable risk. It includes cases where transmissible organisms or diseases are identified during the evaluation process of the donor, but organ utilization is justified by the recipient specific health situation or by the severity of his/her clinical conditions.

Definition of risk levels

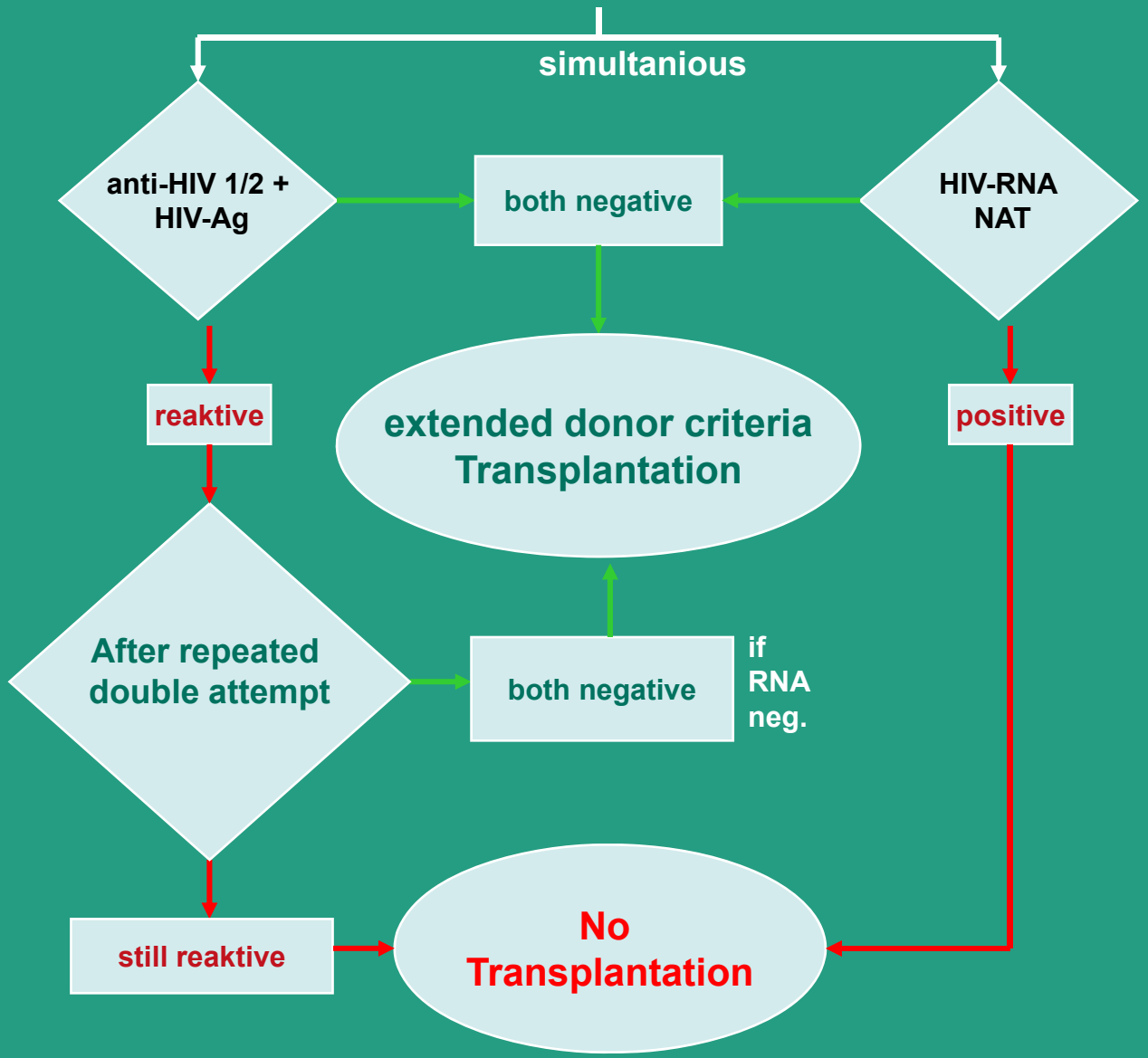
Not assessable risk: It includes cases where the evaluation process does not allow an appropriate risk assessment for transmittable diseases.

Standard Risk: It includes cases where the evaluation process did not identify any transmittable disease. Experts could be consulted if any doubt arises (second opinion).

HIV, no risk constellation



HIV, positive risk constellation

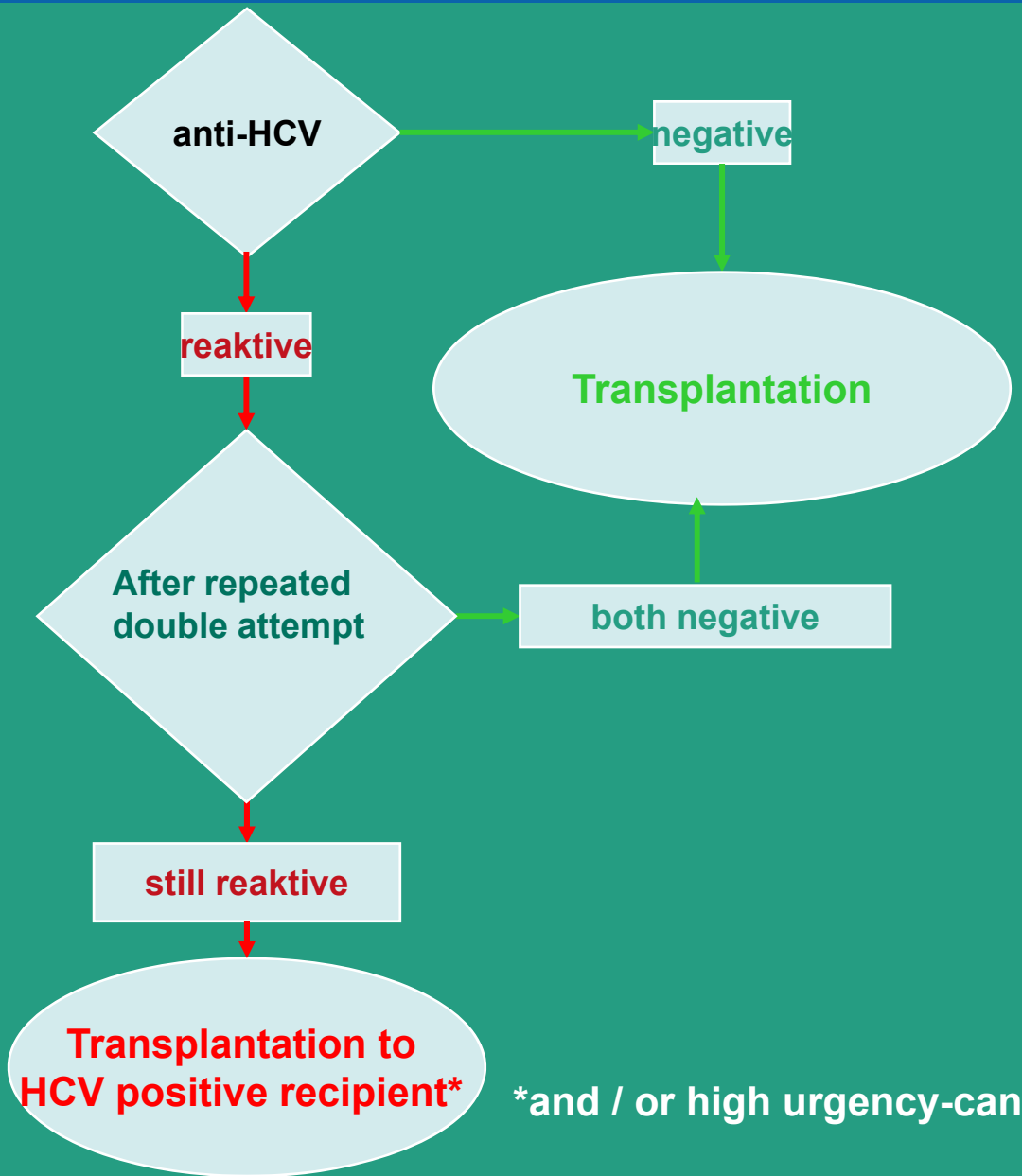


Risk constellation:
i.v.-drug abuse, prostitution, MSM, HWG

Blood sreening and NAT simultanious

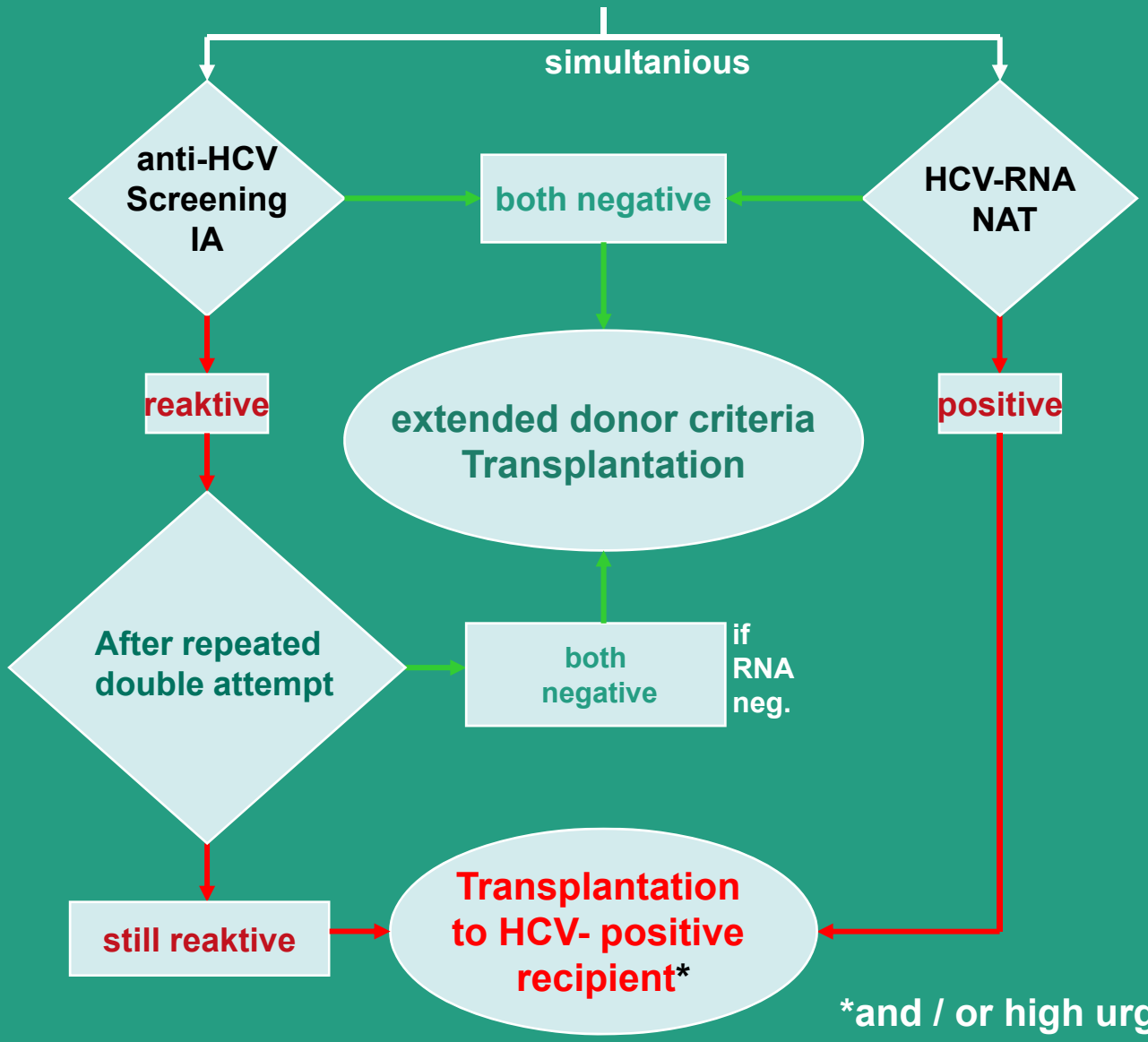
Transplantation:
extended donor criteria

HCV, no risk constellation



*and / or high urgency-candidate (liver exempted)

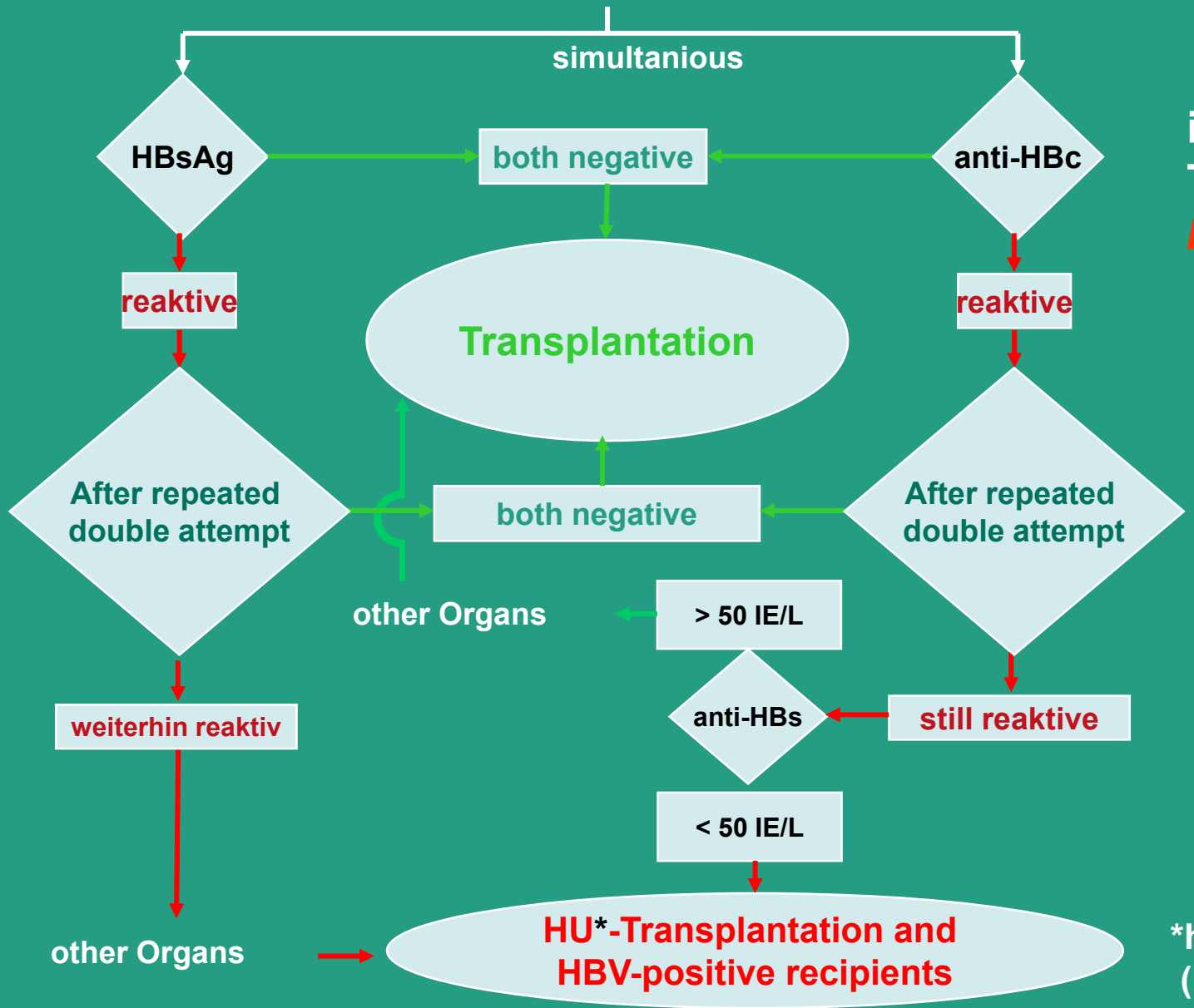
HCV, positive risk constellation (i.v. drug abuse)



Transplantation:
extended donor criteria

*and / or high urgency-candidate (liver exemted)

HBV



if risk constellation Transplantation:
Extended donor criteria

*high urgency-recipients (liver exempted)

Viral infections

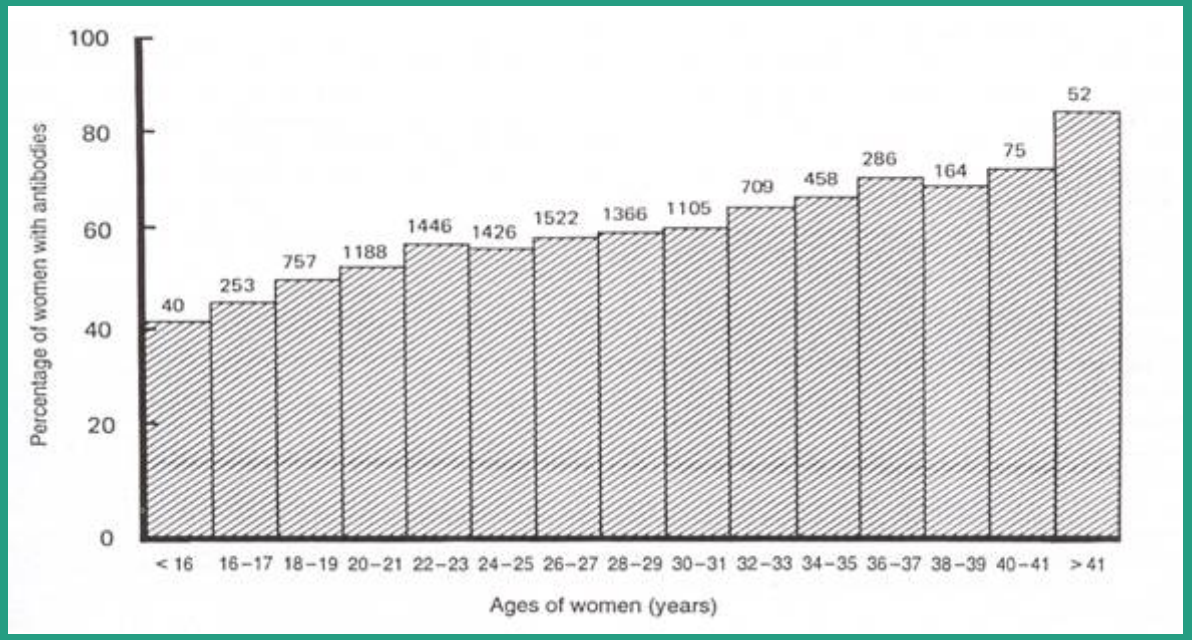
CMV
EBV
Herpes Virus
- HSV 1-2
- VZV
- HHV 6
- HHV 8

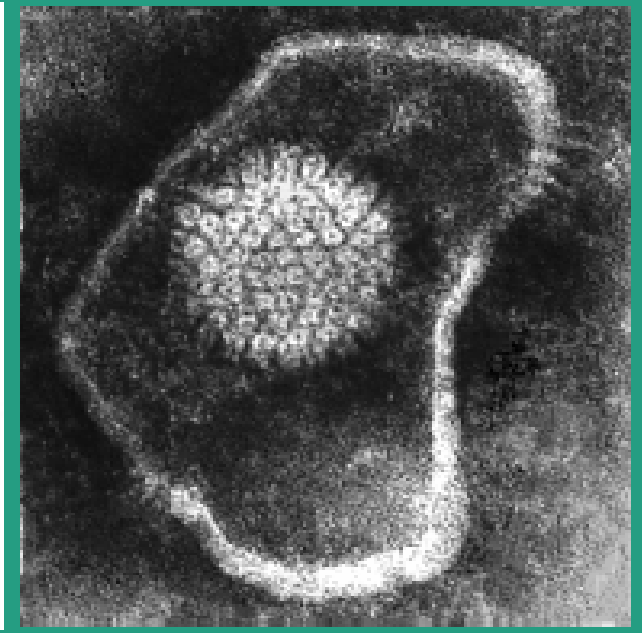
HBV
HCV

HIV
HTLV I/II
West Nile Virus
SARS
LCMV
Rabies

Avoid complications in transplant recipient

- HSV, CMV, EBV
- No contraindications for organ donation





West Nile Virus

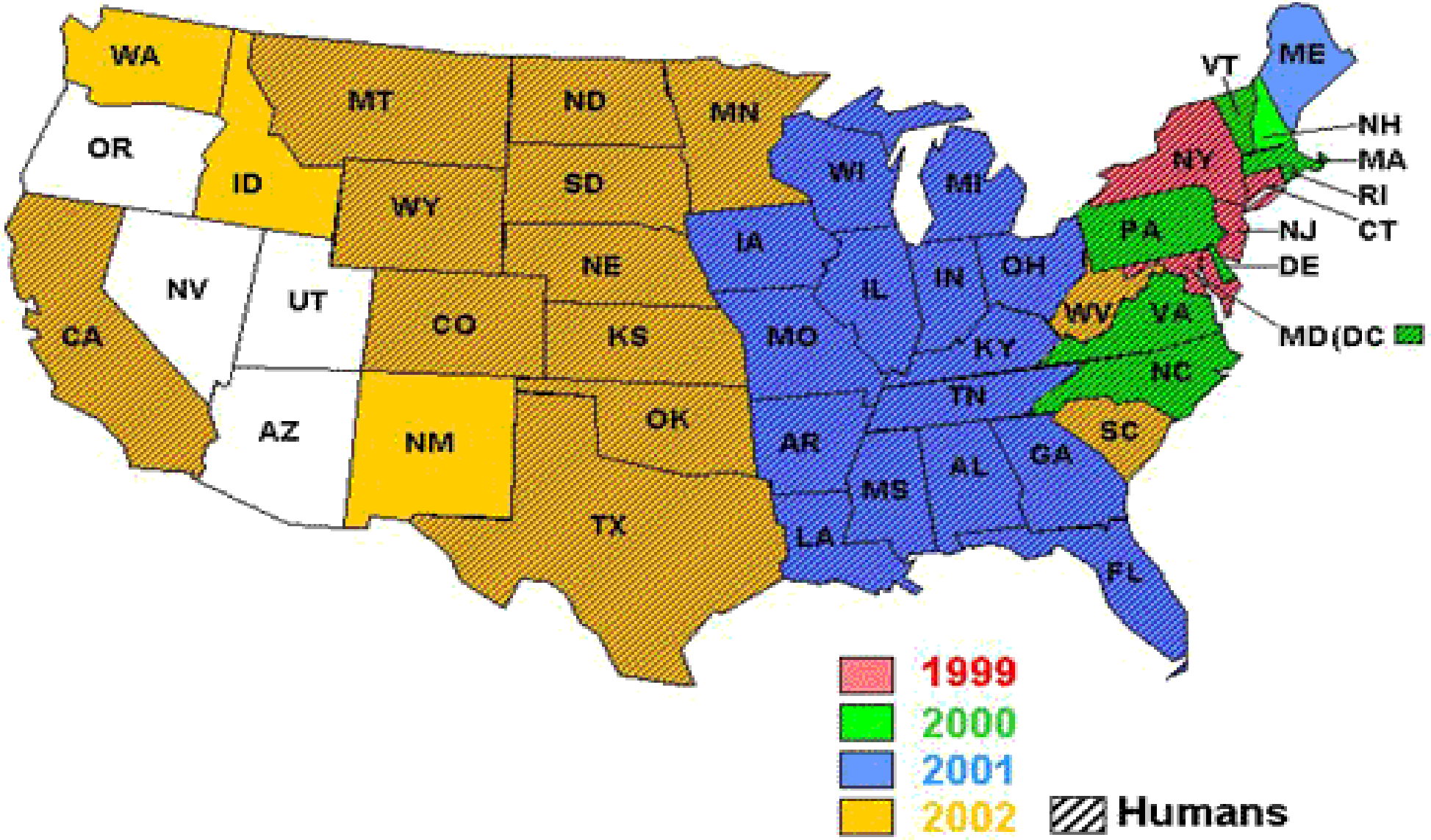
1937 Uganda

Till 1999 Only Africa, Asia, Middle East

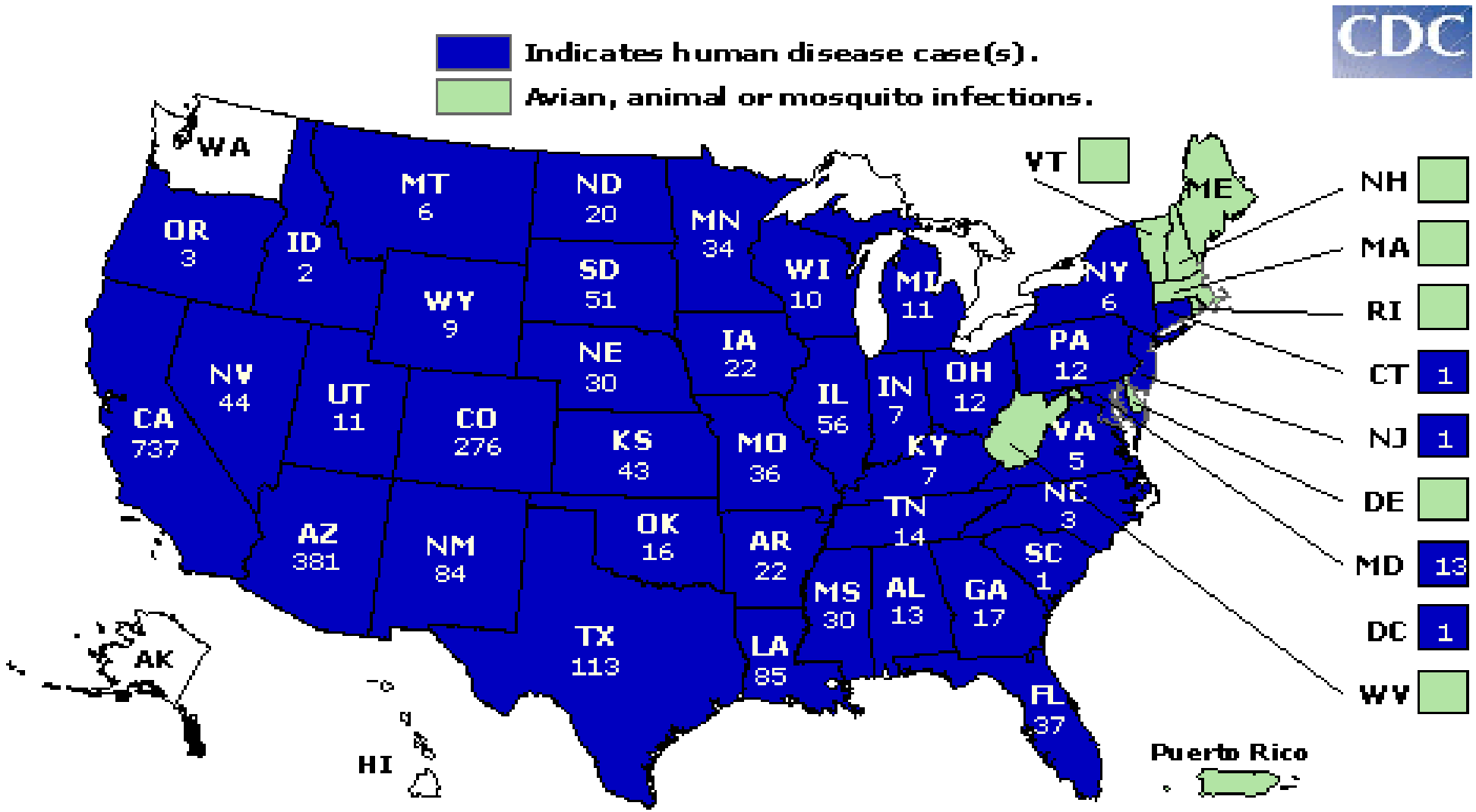
1999 North America

2002 3737 cases resulting in 201 deaths
- Infections through mosquitoes
- Incubation 3 – 14 days
- High fever, meningitis, encephalitis
- Treatment: Ribavirin, Interferon - α

West Nile Virus in the United States, 1999 - 2002



2004 West Nile Virus Activity in the United States
(reported to CDC as of November 8, 2004)



Rare Viral Infections

Definition: rare – currently not endemic in central Europe

No routine diagnostic

- high rate of false positive
- no testing possible
- no experience
- no qualified test

High costs

Avoid risk - donors

26 year old female organ donor with rabies infection 2004 / 2005

12-20-2004	Headache
12-21-2004	Visit to a small country hospital seen by Neurologists and specialists in ENT-doctor
12-23-2004	Visit to neurological Department of district hospital with severe headache complete neurological diagnostic with CT-Scan, EEG, NMR and cerebro-spinal fluid punction. She referred having visited India on a round trip in October 2004, the trip which lasted several weeks. She further reported having used oral drugs such as speed and LSD the night before being taken to hospital. She neglected having used any i. v. drugs; temperature was measured 37.8 °C, laboratory values normal,

26 year old female organ donor with rabies infection 2004 / 2005

She got a medication with Diazepam and was sent back home.

12-25-2005 She was brought to a Psychiatric Department of another hospital with anxiety and psychiatric disorders. Drug screening was negative except Diazepam. She was kept in hospital until the following day

12-26-2005 She developed fever of 38°C, Chest X-ray showed pneumonia, she was sent to another general hospital.

Blood values:
Natrium 114 mg %
Kalium 2,9 mg %
Leukocytosis 21.5000
CRP normal

Complete bacteriological and virological screening →negative
Whole body CT-Scan, cerebro-spinal fluid punction, blood culture,
Malaria, Leishmaniase, Toxoplasmose → negative

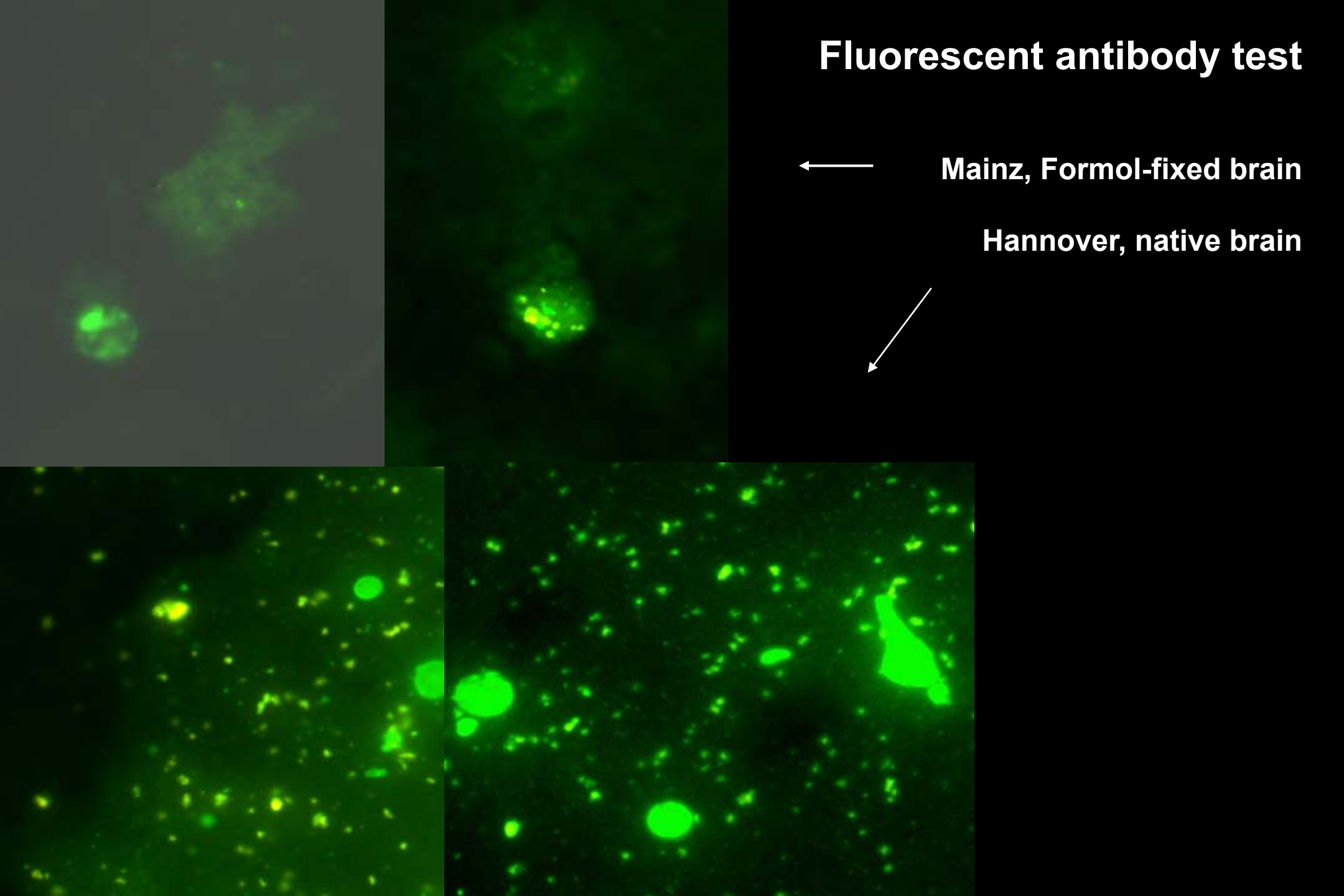
26 year old female organ donor with rabies infection 2004 / 2005

12-26-2004	6.00 p.m. cardiac arrest She was found laying in front of her bed immediate resuscitation was performed duration of cardiac arrest unknown She was referred to ICU
12-27-2004	transmission to ICU of University Hospital, Mainz, cerebral oedema, again cardiac arrest followed by resuscitation, cerebral CT-Scan with severe oedema, cerebro-spinal fluid punction
12-28-2004	Patient developed signs of brain death
12-30-2004	Brain death diagnosis confirmed brain death at 6.20 p.m. Diagnosis was performed with clinical investigation and evoqued cerebral potentials

Transplantation-associated Rabies infections in Germany

Rapid diagnosis and virological follow-up

Christian Drosten, Bernhard Nocht Institute


Fluorescent antibody test
Mainz, Formol-fixed brain
Hannover, native brain

Genome

N

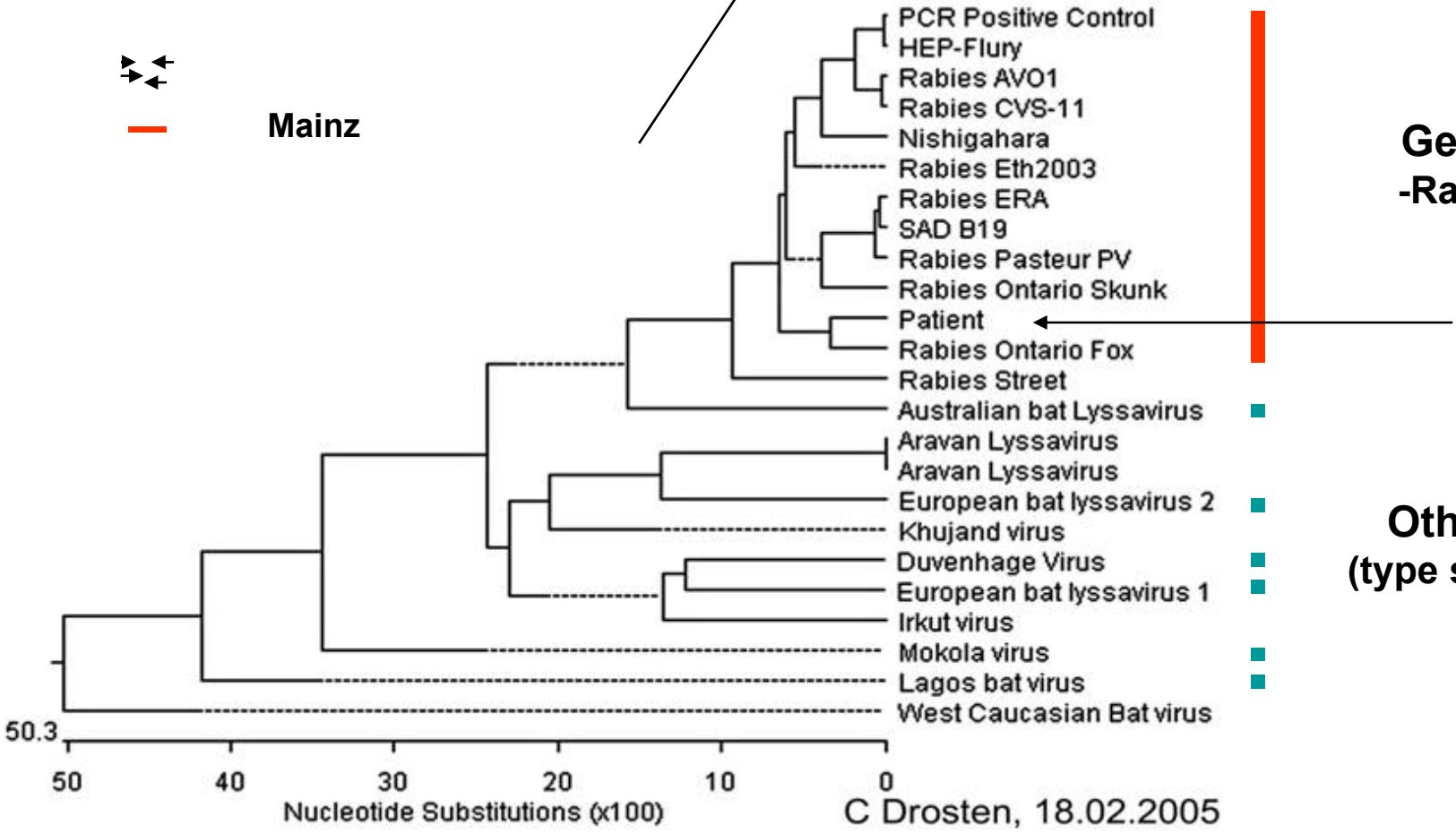
Marburg

Hannover

Hannoversch Münden

Mainz

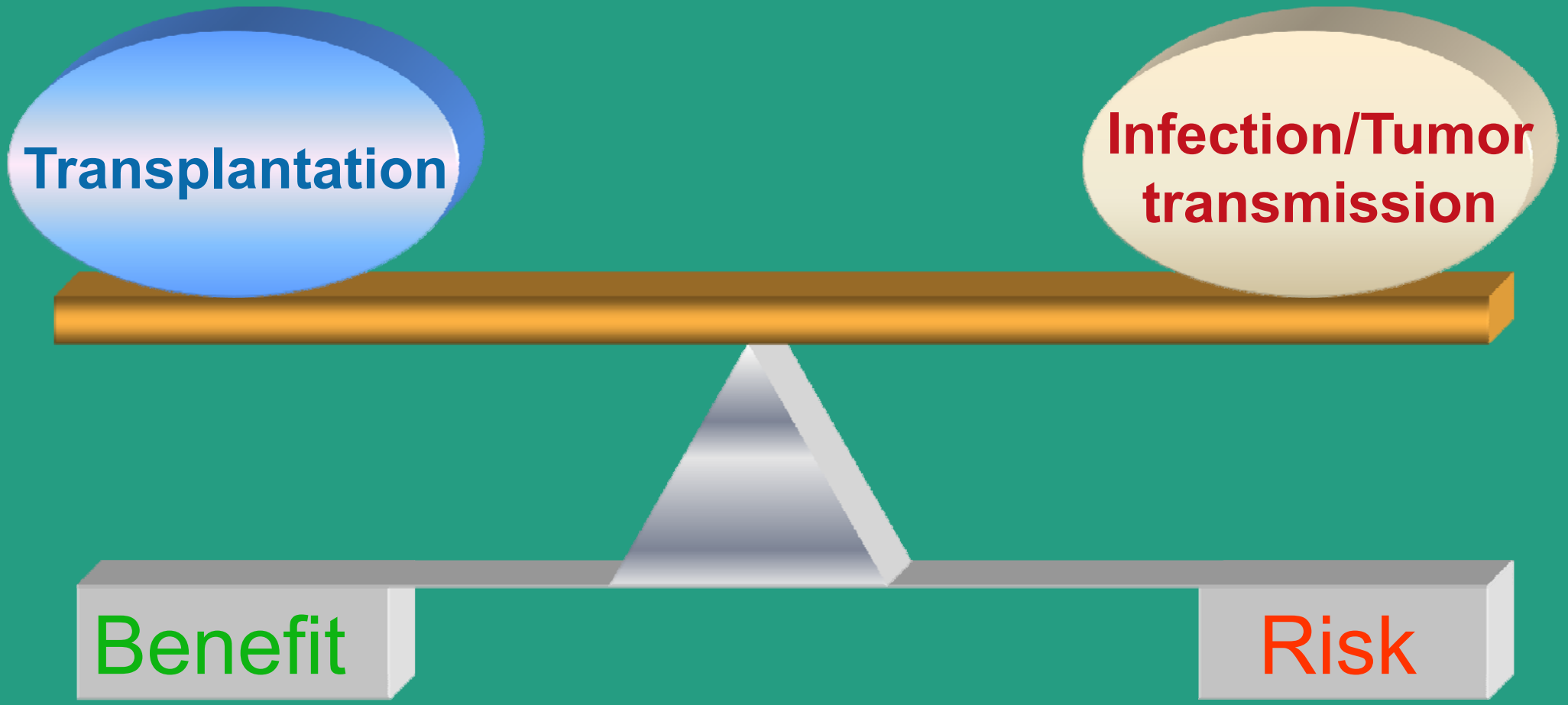
Sequencing: all 100% identical



Genotype 1
-Rabies virus-

Other 6 genotypes
(type strains highlighted)

Calculation of risks



Summary

- Risk consideration in all individual cases:
  → „risk to die without graft“
- Extended donor criteria
- Personal criteria of acceptance (patients-profile) – notification to ET
- Special education and acceptance of patient/ recipient of graft

Syphilis Treponema pallidum

- VDRL-reaction
  (venereal disease research lab)
- TPHA – test
  (trep. pall. hemagglutination antibody)
- FTA – Abs – Test
  (fluorescent trep. antibody absorption)

VDRL	TPHA	FTA-Abs	
-	-	-	No disease or early state (3 weeks)
-	+	+	Post treatment or early state
+	+	+	Treatment necessary