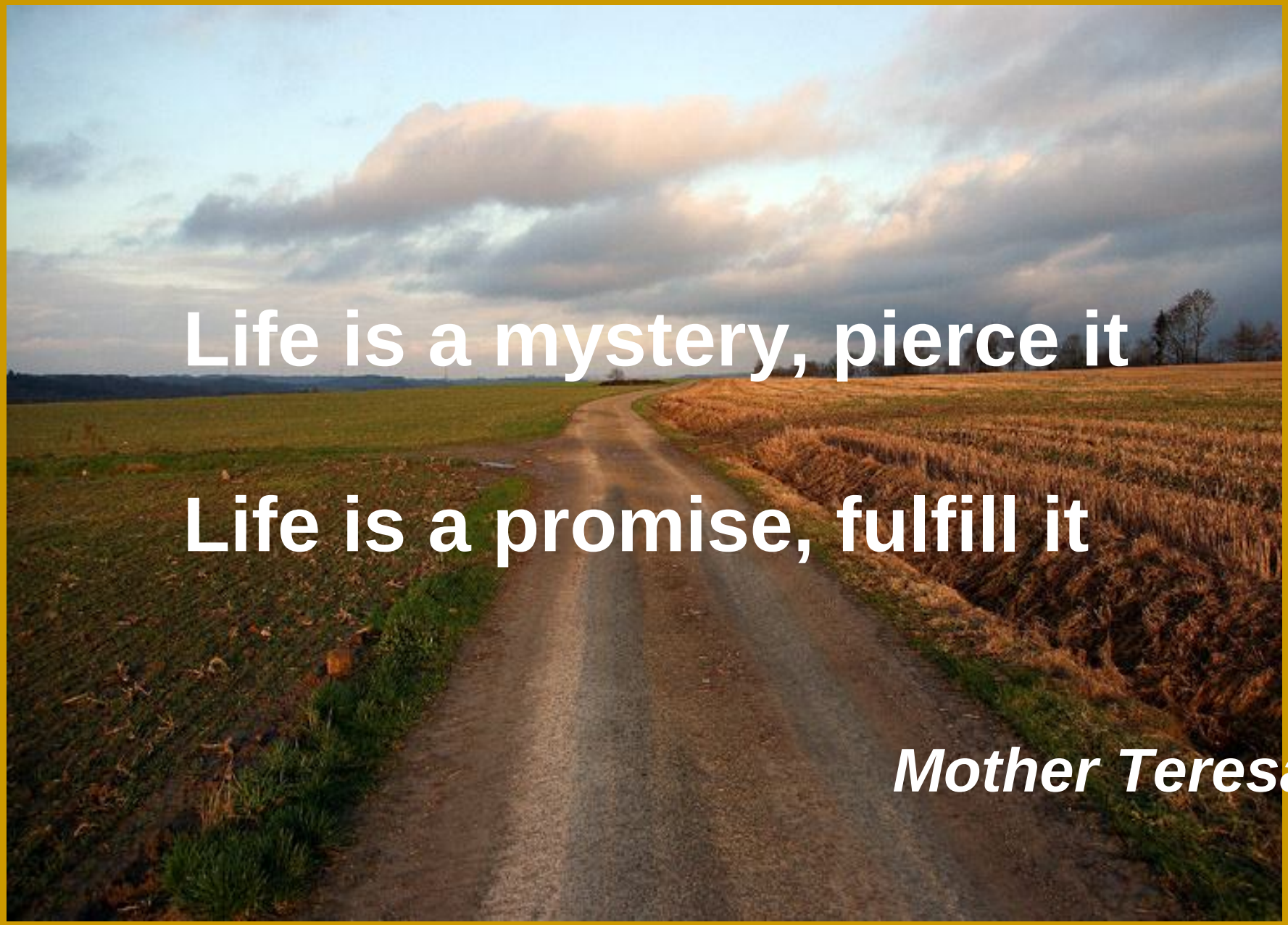
LONG TERM OUTCOME AFTER RENAL Tx IN CHILDREN

BS HOÀNG THỊ DIỄM THÚY


Life is a mystery, pierce it
Life is a promise, fulfill it
Mother Teresa

QUESTIONS

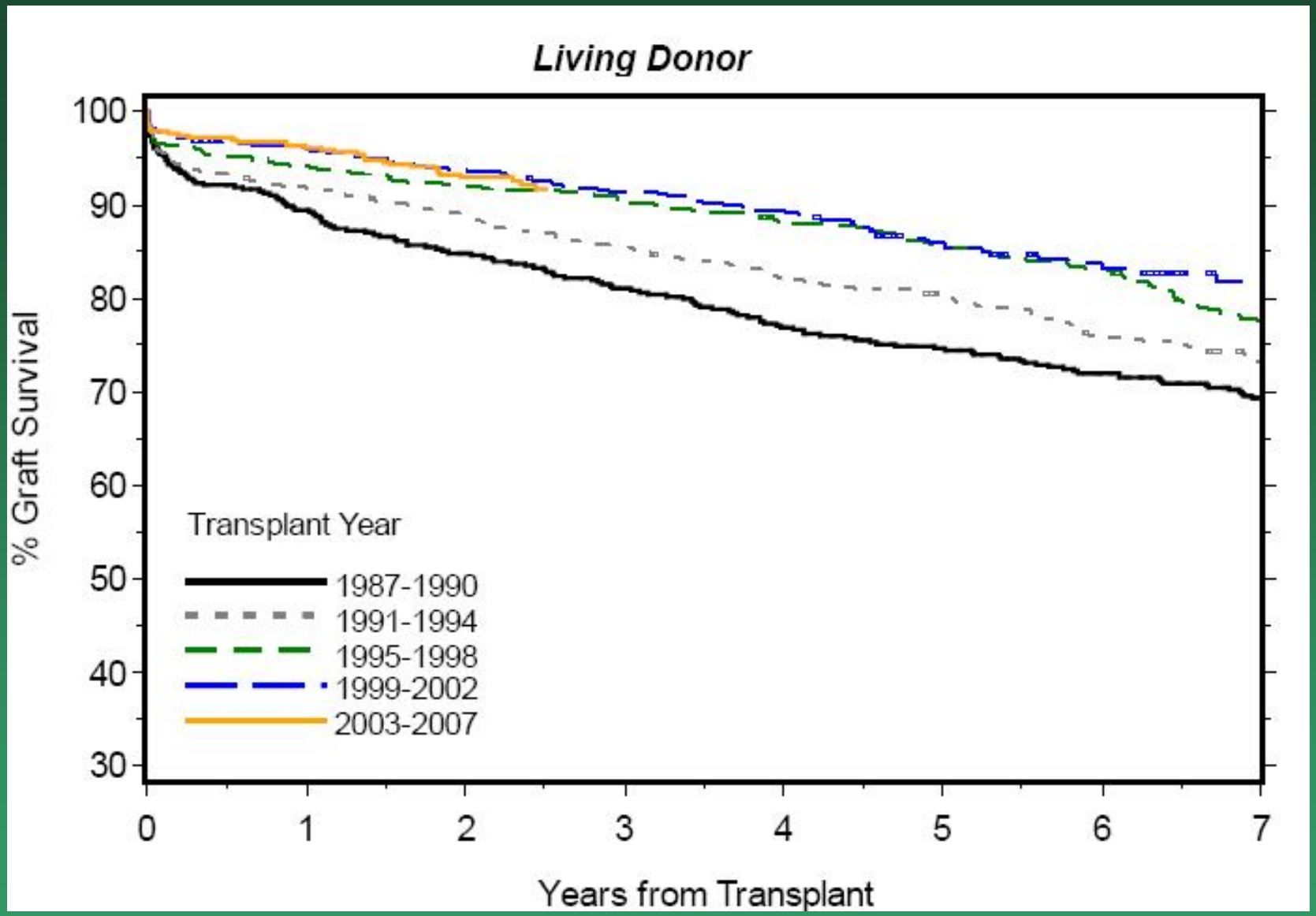
1. What is patient survival overall ?
   - Causes of death ?
   - Comparison of mortality after transplantation with that on dialysis
2. What may be the factors influencing long-term outcome ?
3. How about their life ?

INTRODUCTION

- **The first paediatric renal transplantations took place in the 1970s.**
- **The changes over the years have had both positive and negative influences:**
  - **+ Advances in technical and therapeutic knowledge**
  - **+ Increasing numbers of living donors(LD)**
  - **– More challenging patients :neonates and small children with severe, life threatening, co-morbidity**

OVERALL MORTALITY

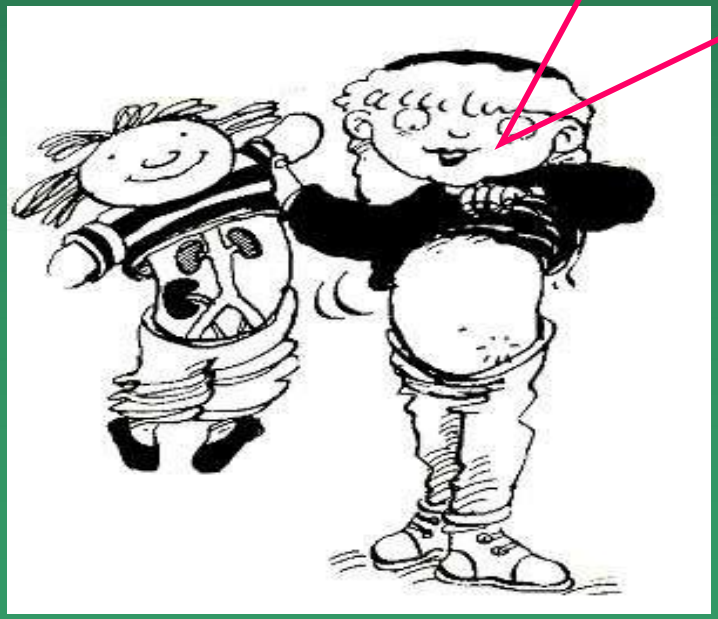
- Relative risk of death after transplantation is 12.7-times higher than that of the age-related general population
- Little sign of improvement since 1995s



NAPRCTS 2005

TARGET : the Tx T/2

LD : 21.6 Y
DD: 13.8 Y



SURVIVAL

- Overall 5-year patient survival varies between 70% and 100% at 5 years
- 75% - 95% at 10 years
- 83% - 94% at 15 years
- 54% - 86% at 20 years

MAJOR CAUSES OF DEATH

1. Cardiovascular disease 30–36% (↓)
2. Infection 24–56% (unchanged)
3. Malignancy 34% (↑)

Malignancy : 10 times more common than expected for age

- Skin cancer : the most frequent 60% of all cancers
- Non-Hodgkin’s lymphoma represents 25% of cases and is the commonest cancer to cause death

- **PTLD** : 10–30-fold increase compared with the general population
- **Kidney cancer** : 15-fold increase .
- **Kaposi's sarcoma**
- **Higher risk of some solid organ tumours** : colon, lung, bladder and larynx cancer : 2–5-fold increase

ADVANTAGES OF Tx/HD-PD

- Survive 5 years
  - 80% patients on HD-
  - 83% on PD
  - 93% of those with a transplant
- Mortality rates are seven-times higher in dialysis than in transplant
- Comorbidity with dialysis is associated with a risk more than four-times

COST-UK

£ 17,500 per patient per year for PD

£ 35,000 per patient per year for HD

£ 17,000 per patient per transplant.

£ 5,000 per patient per year for immuno-suppression.

- The cost benefit of kidney transplantation compared to dialysis over a period of ten years (the median transplant survival time) is £241,000 or £24,100 per year for each year that the patient has a functioning transplanted kidney.

COST

- On the Indian
  - Dialysis cost is about $4,000 per year.
  - Kidney transplantation costs about $5,000
  - Post-transplantation medications cost $2,000 annually -> $ 5000 / 5Y
- THAILAND
- 1st- 6th month: 601 USD/m
- 6- 12th month: 464 USD/m
- After 12th month: 384 USD/m
- US
- Dialysis cost : 43.000 USD per year..
  - Kidney transplantation 14.000

THE MAJOR EFFECTS ON SURVIVAL

1.EFFECT OF RECIPIENT AGE

- Young children and, particularly, in those under 2 years of age at transplantation
- Adolescents: non- observance of treatment

- Until recently, young age was considered to be the most important predictor of outcome principally due to technical difficulties, in those under 2 years of age

- ***UNOS data*** **: OR = 2 risk of graft loss in 2 to 5 year olds in comparison with 6 to 12 year olds**

Causes of graft loss in the youngest children

1. Arterial thromboses
2. Urological problems

-> in the first few months

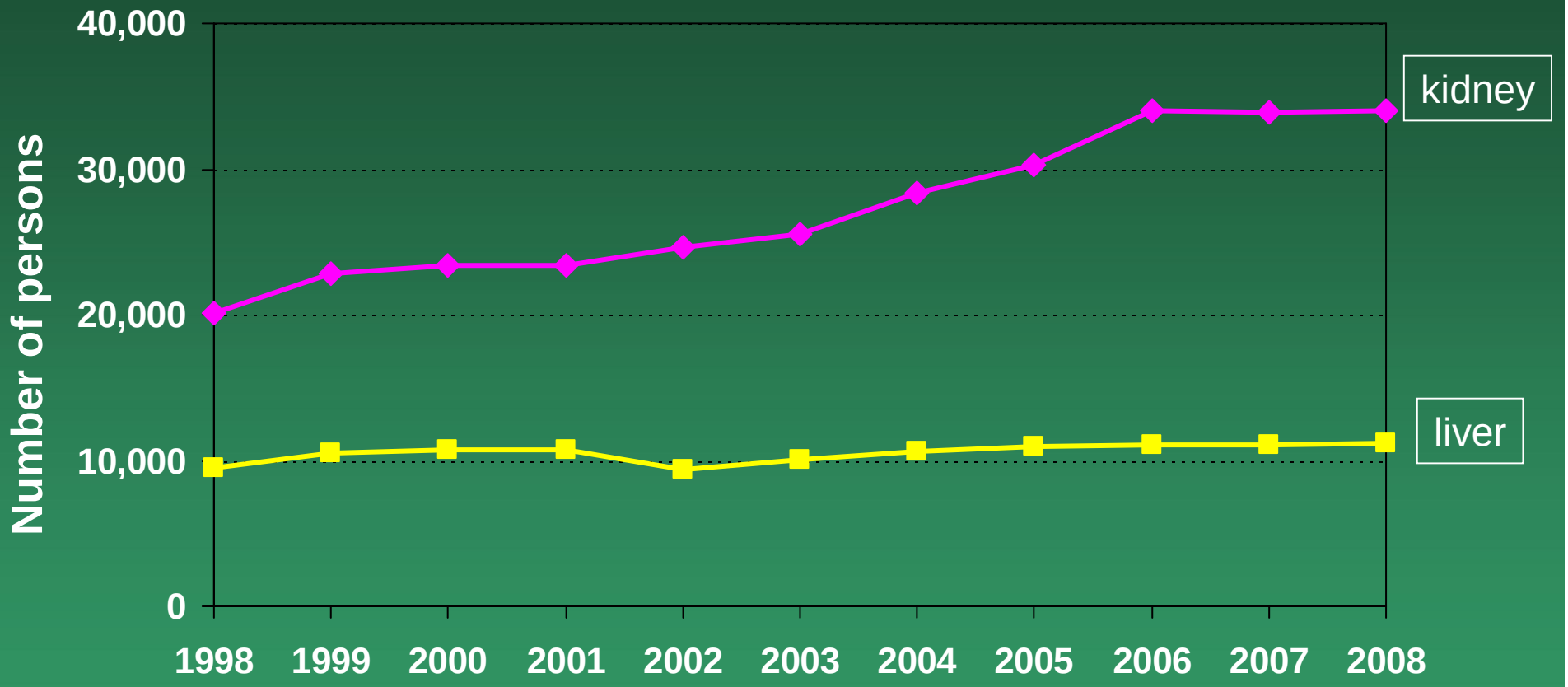
2. EFFECT OF DONOR AGE

- Kidneys from donors aged 11–17 years do best
- young donors < 5 years of age : graft thrombosis
- > 65 years old: CAN

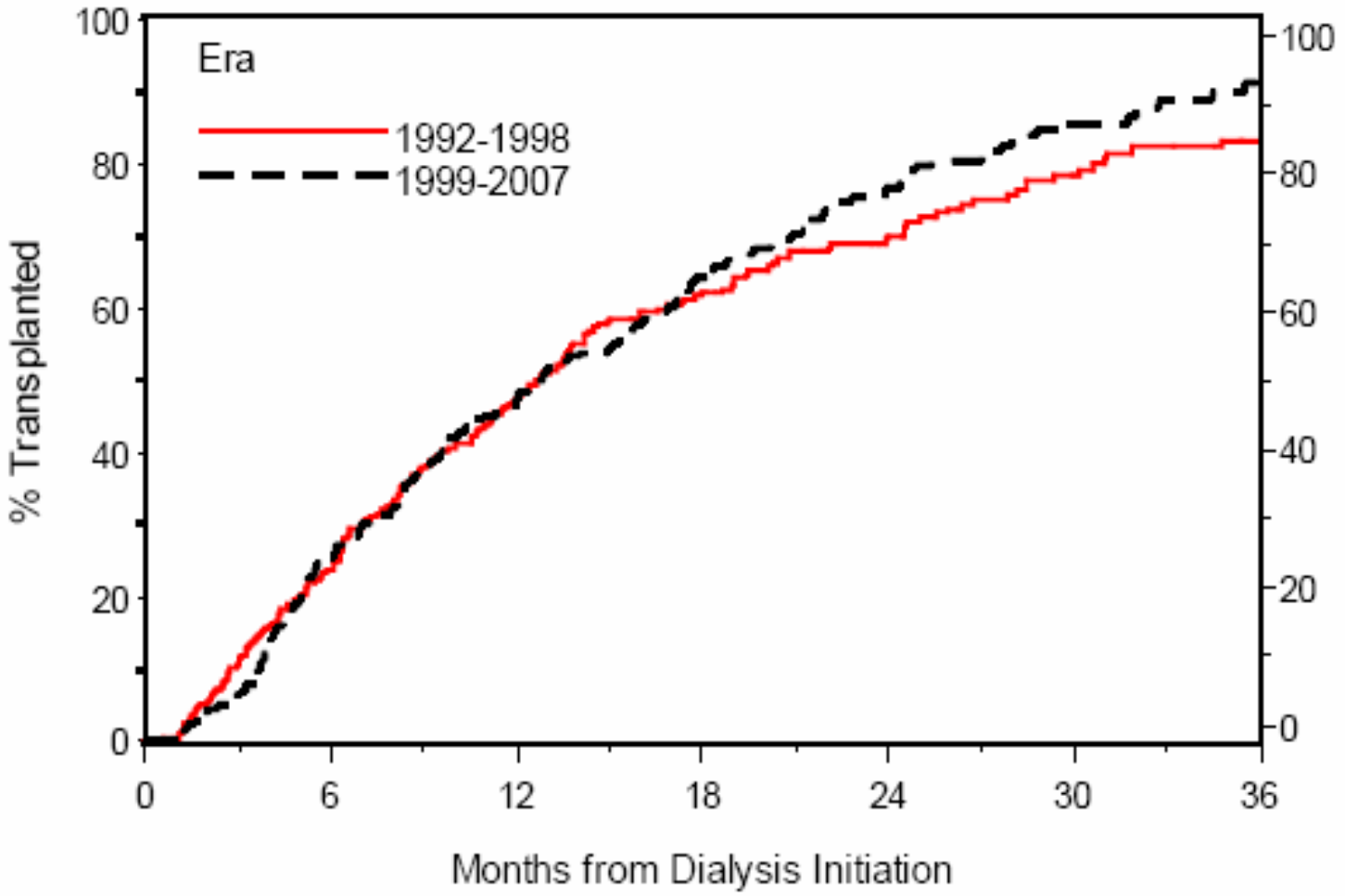
3. EFFECT OF DONOR TYPE

- Living related donation (LRD) has been shown to benefit outcome, with results of 75% and 85% at 10 years, compared to 46% for DDs
- Half-life of 13.1 years from an LRD and 10.8 years from a DD

Waiting list 1998-2008
U.S.



TIME TO TRANSPLANT FOR PATIENTS ON DECEASED DONOR LIST (at 30 days)



LIVING DONOR

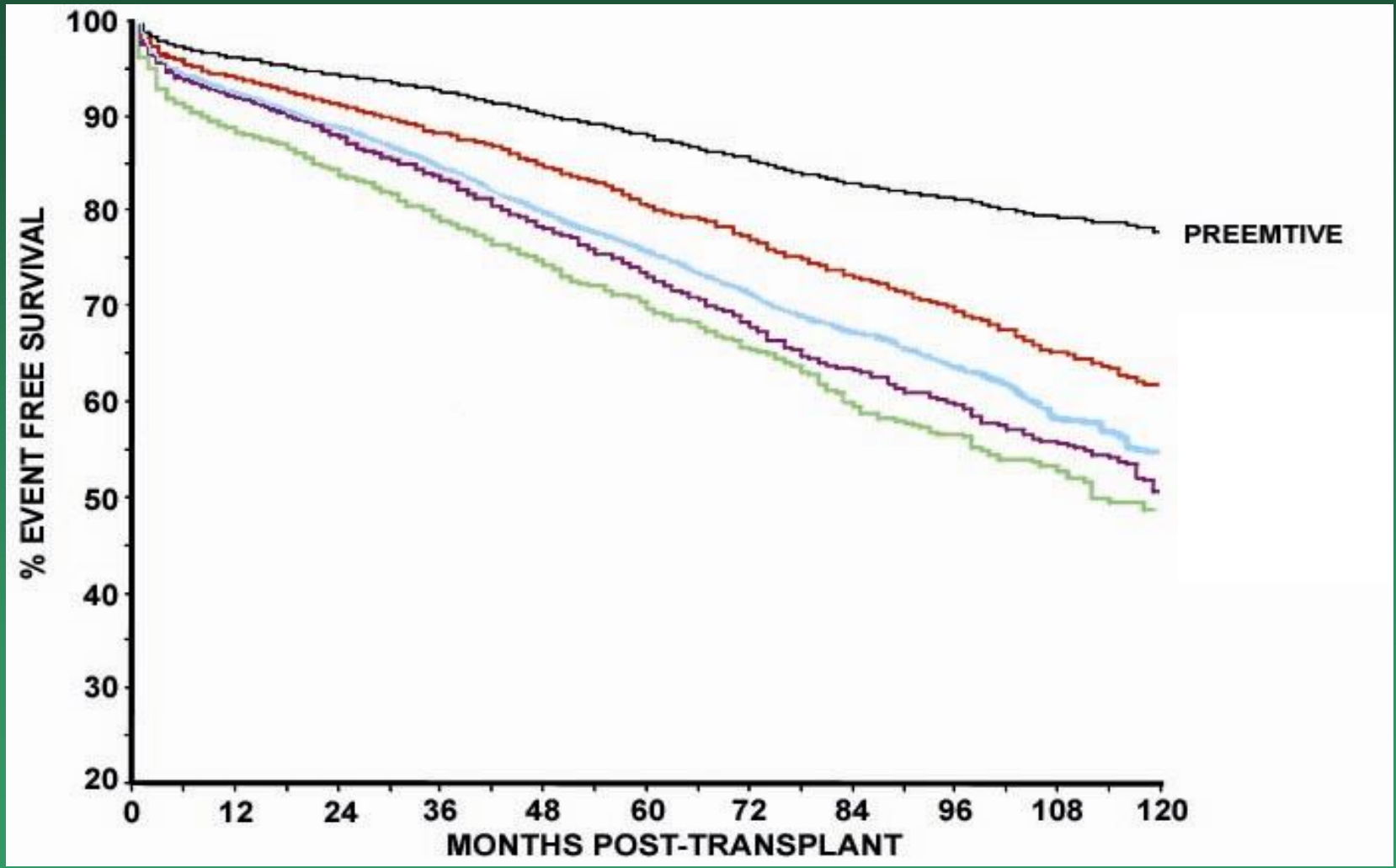
- Countries vary in the size of their LD programmes.
- 1987 and 1991 : 43% (USA)
- Since 1998 : 58%.

  82% were parents (56% mothers, 44% fathers)

4. EFFECT OF RACE

- Poorer outcomes for Afro- Americans than for the white population.(*US registries)*
- Most of this difference can be accounted for by an increased incidence of cardiovascular deaths by approximately 1.6 times.
- Asian ?

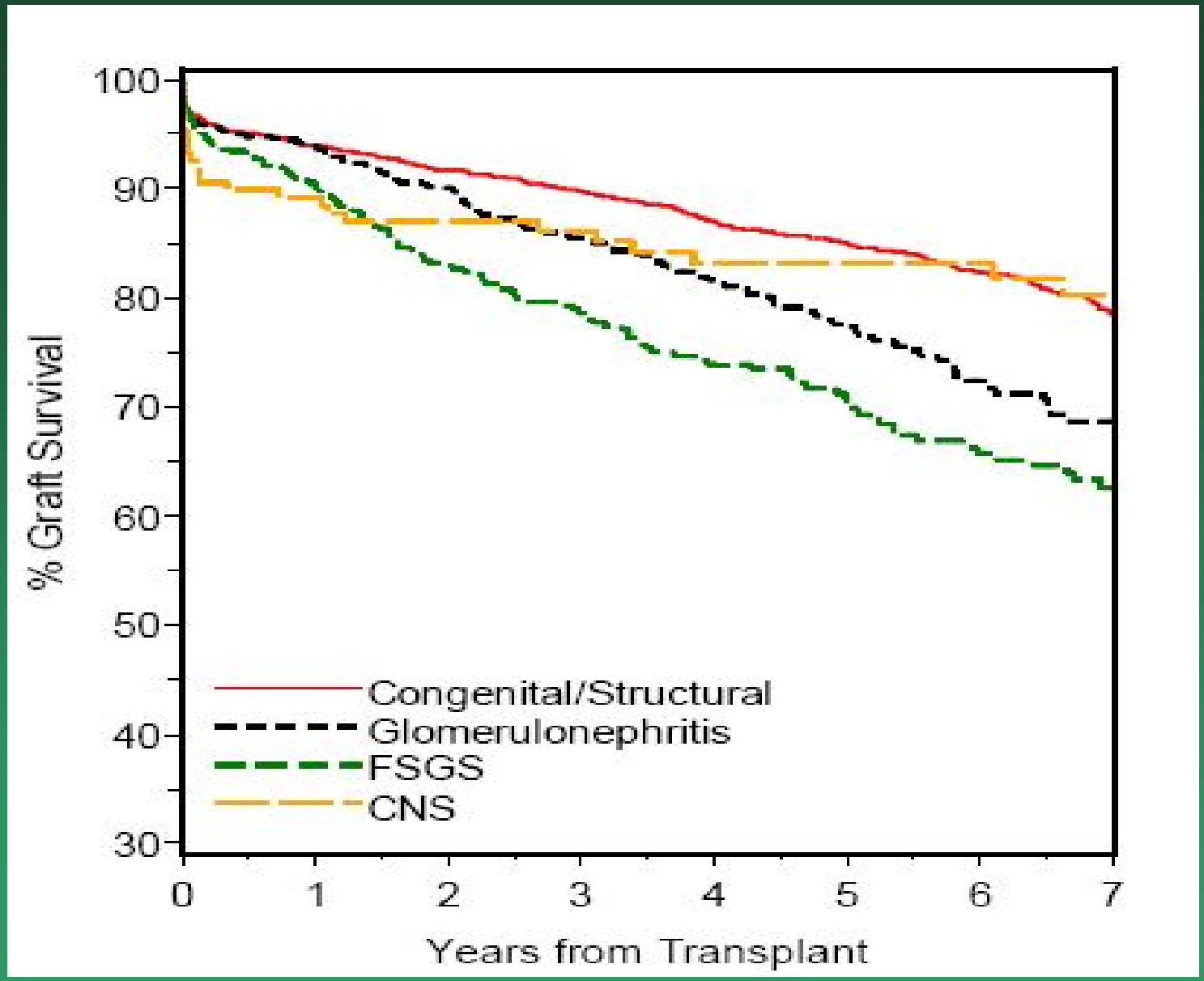
5. EFFECT OF PRE-EMPTIVE Tx



MEIER-KRIESCHE AND KAPLAN. TRANSPLANTATION 74:1377, 2002

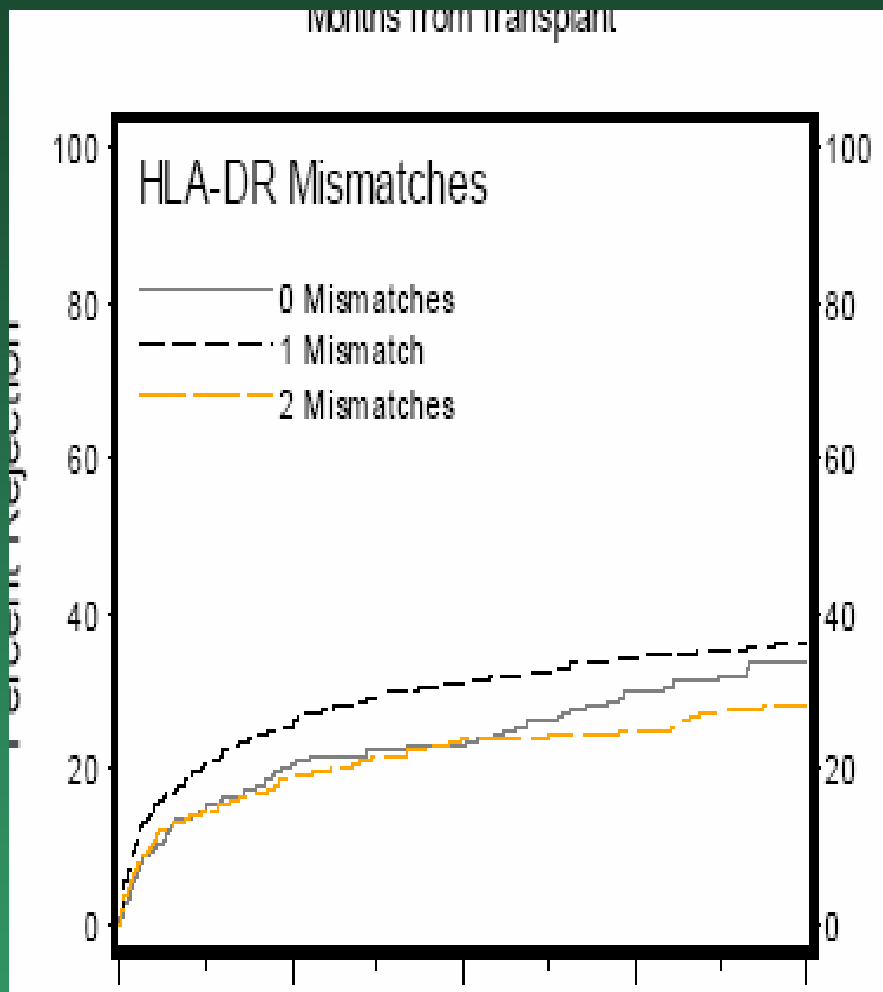
6. EFFECT OF RECURRENT DISEASES

- Include FSGS, membranoproliferative glomerulonephritis (MPGN) and haemolytic uraemic syndrome (HUS)
- Oxalate will continue to be deposited in the transplant if liver transplantation is not undertaken in patients with hyperoxaluria.

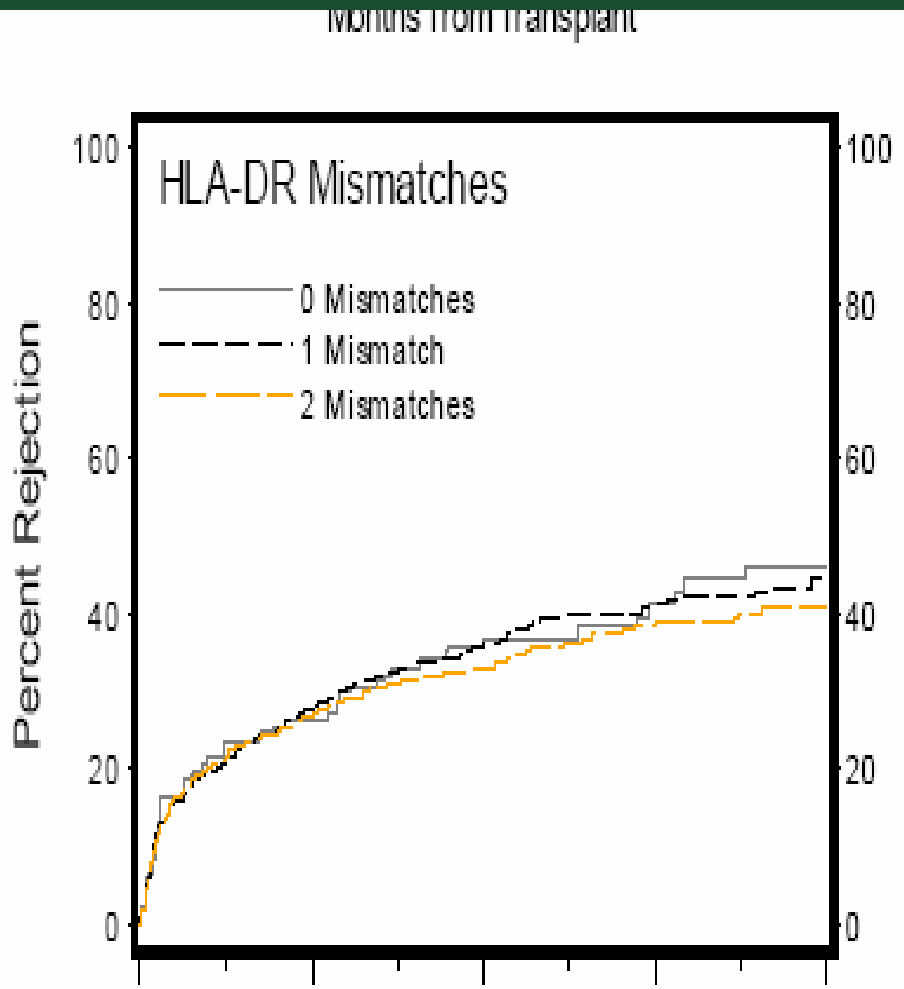

100
90
80
70
60
50
40
30
% Graft Survival
Congenital/Structural
Glomerulonephritis
FSGS
CNS
0
1
2
3
4
5
6
7
Years from Transplant

7. EFFECT OF HLA MATCHING

- Worst outcome : 2 HLA-DR mismatched
- Grafts 000 survived longest
- Sensitised patients (panel reactive antibodies (PRA)>40%) : poorer outcome



LIVING DONOR



DECEASED DONOR

8. Delayed graft function (DGF)

- Defined by the need of dialysis during the first week following Tx -> poor outcome
- Central to the ischemia injury are reactive oxygen species (ROS). Reactive oxygen species are directly toxic to cells inducing apoptosis and/or necrosis.

9. EFFECT OF IMMUNOSUPPRESSION

TACROLIMUS > NEORAL

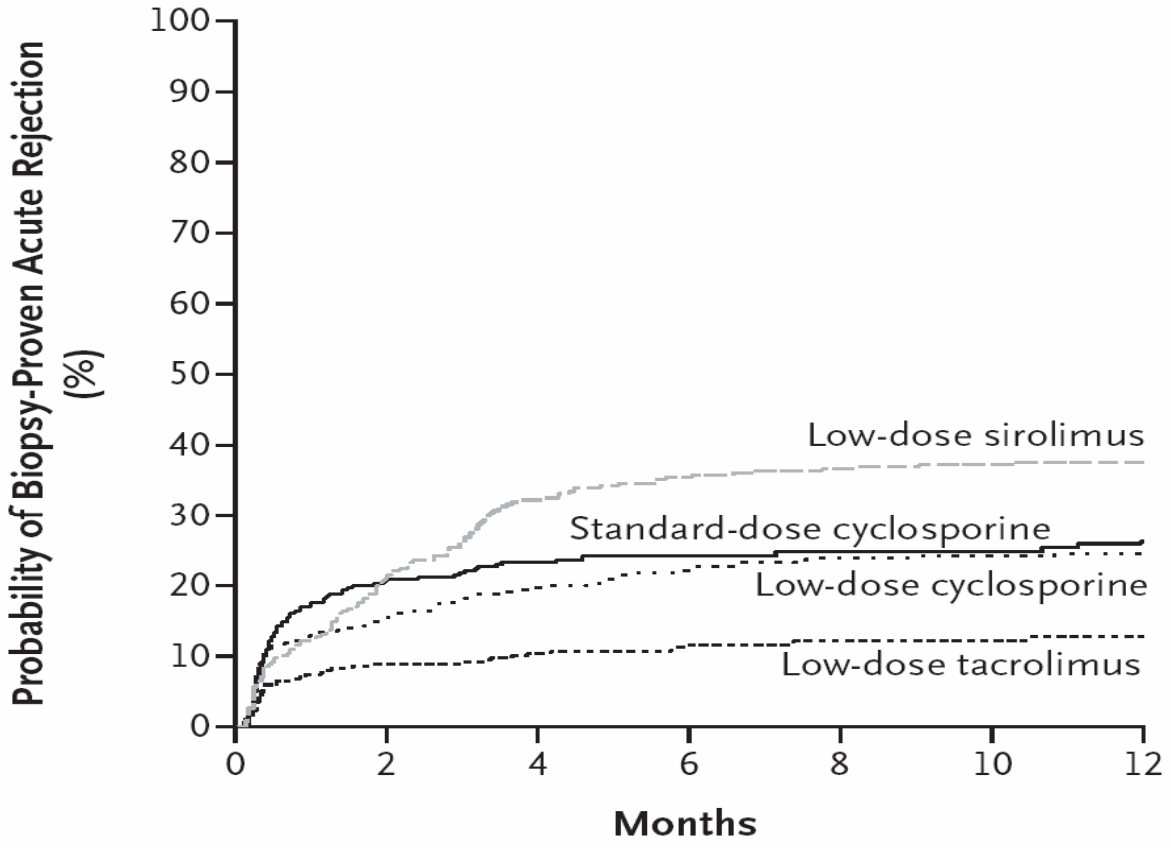
- Tacrolimus is more effective than Ciclosporin
- 4-year transplant survival rate of
  - 86% Tacrolimus
  - 69% Ciclosporine

TROMPETER ET AL. PEDIATR NEPHROL 3:141,2002

MMF > AZA

- 5 years transplant survival's
  - 90.7% for MMF
  - 68.5% for AZA

A



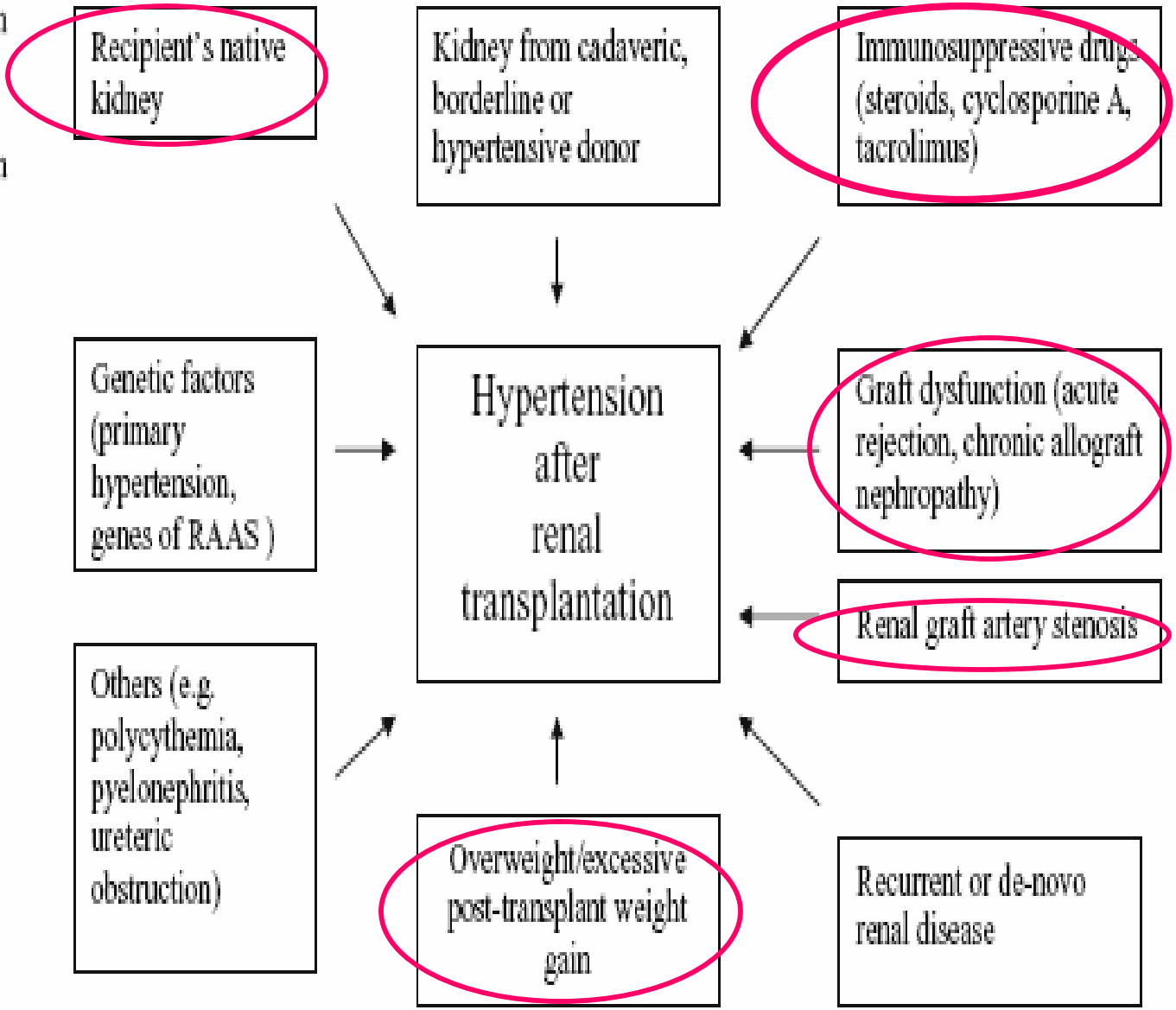
No. at Risk

Standard-dose cyclosporine	390	293	277	272	268	265	257
Low-dose cyclosporine	399	326	308	297	289	283	276
Low-dose tacrolimus	401	350	340	334	328	324	309
Low-dose sirolimus	399	297	252	236	228	225	214

10. EFFECT OF HYPERTENSION

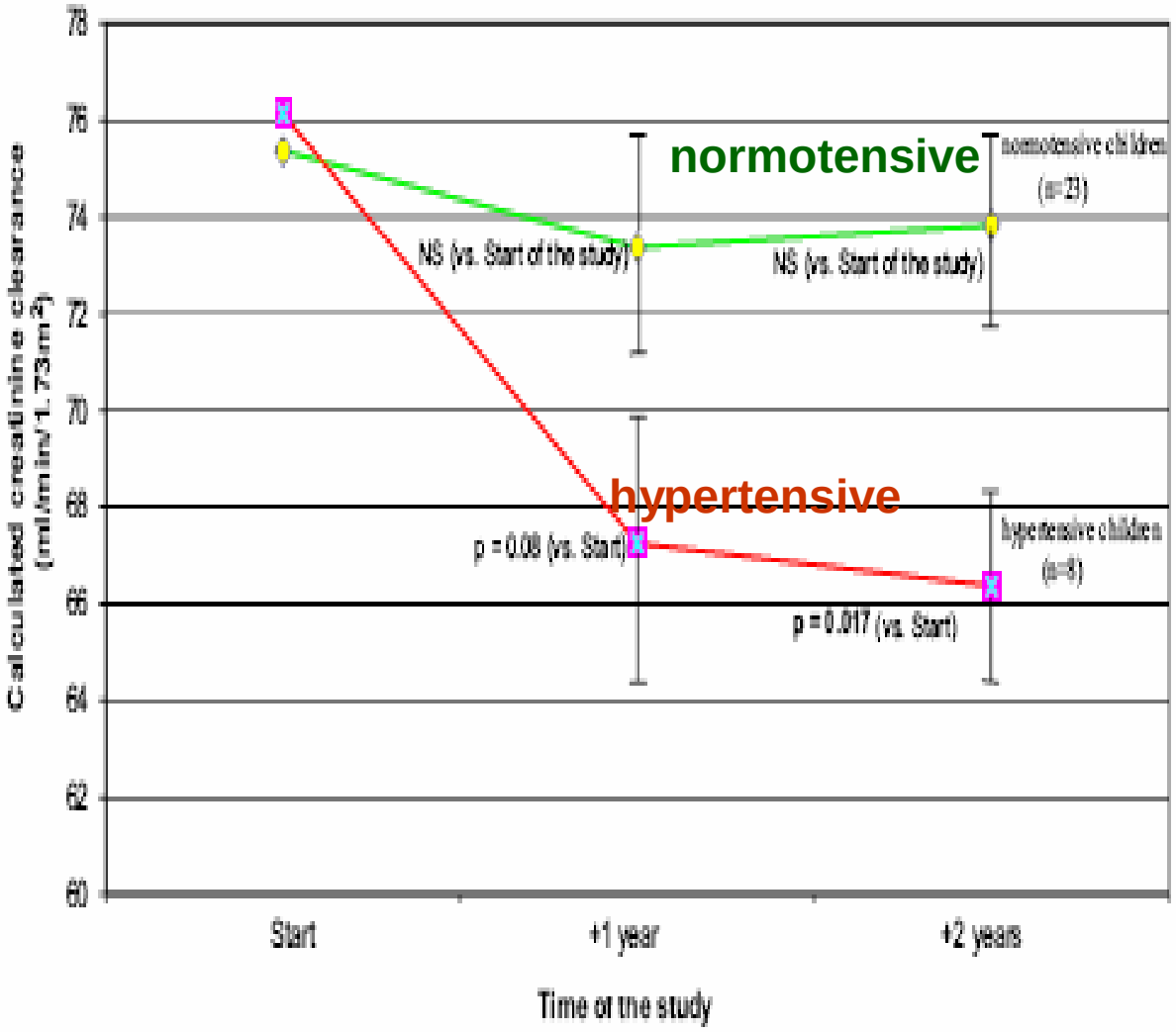
- Incidence varies with time
  - 46% at 1 year
  - 40% at 5 year
  - 66% at 10 year

Fig. 1 Causes of hypertension in patients after renal transplantation. *RAAS* renin-angiotensin-aldosterone system



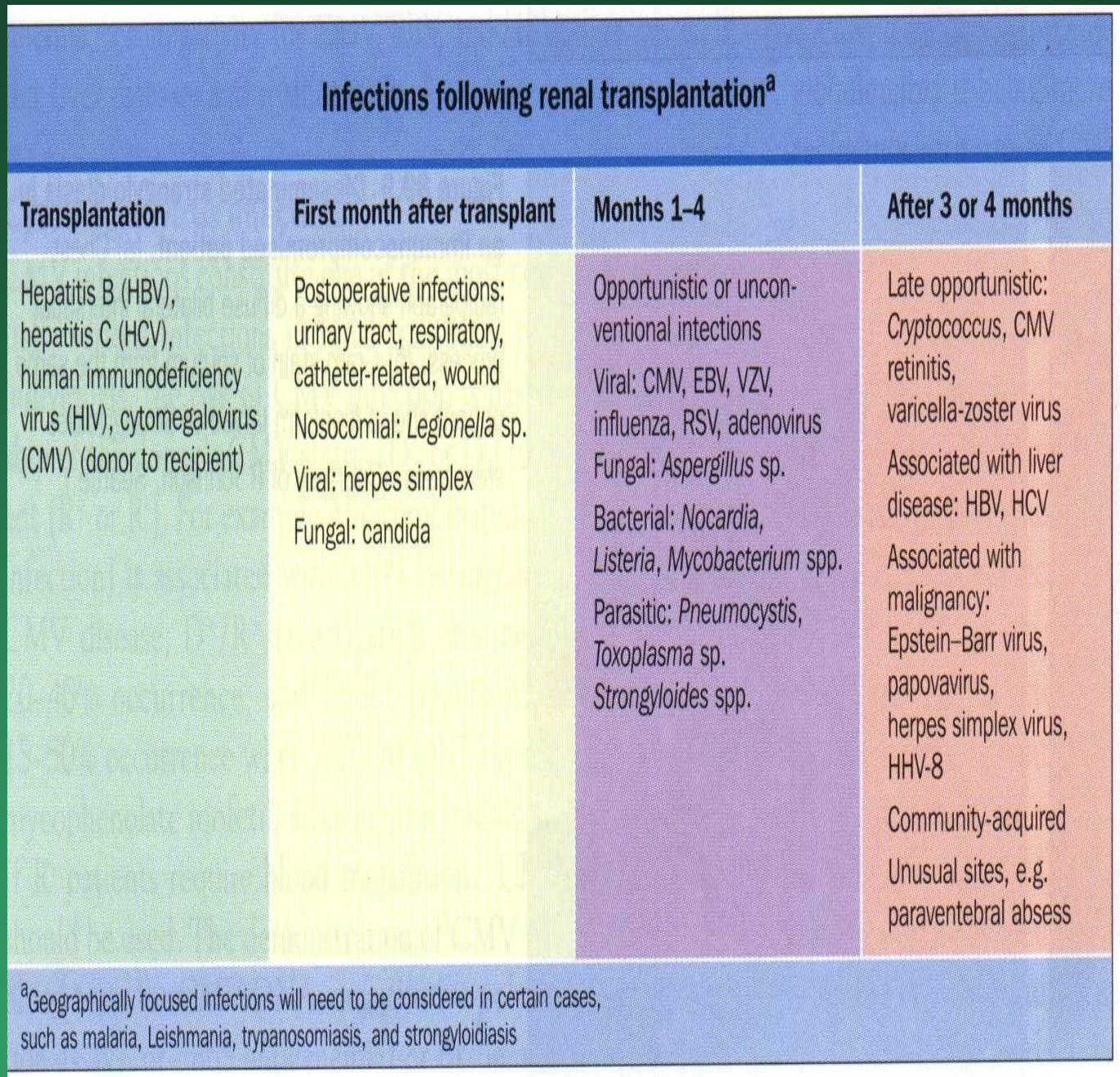
- The presence of hypertension is a significant and independent predictor of poor long-term transplant function

Fig. 3 Graft function in children who where normotensive or hypertensive at 2 years (values of SD in *error bars* are divided by 10)



11. EFFECT OF INFECTION

- T cell depletion
- Opportunistic infection
- May significantly affect graft survival



Infections following renal transplantation[a]

Transplantation	First month after transplant	Months 1–4	After 3 or 4 months
Hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV) (donor to recipient)	Postoperative infections: urinary tract, respiratory, catheter-related, wound Nosocomial: *Legionella* sp. Viral: herpes simplex Fungal: candida	Opportunistic or unconventional intections Viral: CMV, EBV, VZV, influenza, RSV, adenovirus Fungal: *Aspergillus* sp. Bacterial: *Nocardia*, *Listeria*, *Mycobacterium* spp. Parasitic: *Pneumocystis*, *Toxoplasma* sp. *Strongyloides* spp.	Late opportunistic: *Cryptococcus*, CMV retinitis, varicella-zoster virus Associated with liver disease: HBV, HCV Associated with malignancy: Epstein–Barr virus, papovavirus, herpes simplex virus, HHV-8 Community-acquired Unusual sites, e.g. paraventebral absess

[a]Geographically focused infections will need to be considered in certain cases, such as malaria, Leishmania, trypanosomiasis, and strongyloidiasis

Figure 89.6 Types of infections following renal transplantation.

BK VIRUS- PVAN

- PVAN (polyomavirus-associated nephropathy) affects 2–8% of pediatric renal transplants
- Significant graft dysfunction is observed in more than 50% of cases,progressive early graft loss is reported in (9%) of cases.

Table 3 Pediatric renal transplant patients with biopsy-proven human polyomavirus type 1 (BKV) nephropathy

Authors	Center BKV nephropathy rate (%)	Pt. number (<20 years)	Age (years)	Time posttransplant (months)	Treatment
Alexander et al. [14]	7.7	4	N/A	38	↓ ImmunoSup
			N/A	24	↓ ImmunoSup + cidofovir
			N/A	12	↓ ImmunoSup + cidofovir
			N/A	6	↓ ImmunoSup
Araya et al. [35]	N/A	3	8	48	↓ ImmunoSup + cidofovir
			17	19	↓ ImmunoSup + cidofovir
			19	4	↓ ImmunoSup + cidofovir
Comoli et al. [38]	N/A	3	9	32	
			15	3	
			18	1	
Ginevri et al. [15]	3	3	N/A	32	↓ ImmunoSup + cidofovir
			N/A	1	↓ ImmunoSup
			N/A	4	↓ ImmunoSup
Herman et al. [17]	4.3	2	13	6	↓ ImmunoSup + CMV Rx
			8	14	↓ ImmunoSup + cidofovir
Hymes et al. [36]	6.6	8	12±4	22±13	↓ ImmunoSup + cidofovir (7/8) ↓ ImmunoSup (1/8)
Muller et al. [37]	3	1	N/A	N/A	↓ ImmunoSup + leflunomide
Smith et al. [26]	N/A	6	16	14	↓ ImmunoSup
			3	44	↓ ImmunoSup
			8	47	↓ ImmunoSup
			5	4	↓ ImmunoSup
			13	16	↓ ImmunoSup
			13	10	↓ ImmunoSup
Vats et al. [33]	N/A	2	4	22	↓ ImmunoSup + cidofovir
			10	12	↓ ImmunoSup + cidofovir

12. MEAN OF DONOR NEPHRECTOMY

- Laparoscopic donor nephrectomy is associated with a longer operation time and longer warm ischaemia and cold ischaemia times in LDs than is the open approach
- Graft outcome does not seem to be affected .

HOW’S ABOUT THEIR LIFE ?

APPEARANCE

- Final height is influenced by : age of Tx, pre-transplantation management, the decline in steroid dosing.
- < 5.2cm (boy)& 13cm (girl) if Tx before puberty.
- < 12.6cm after puberty.

NISSEL ET AL KI 66:792 2004

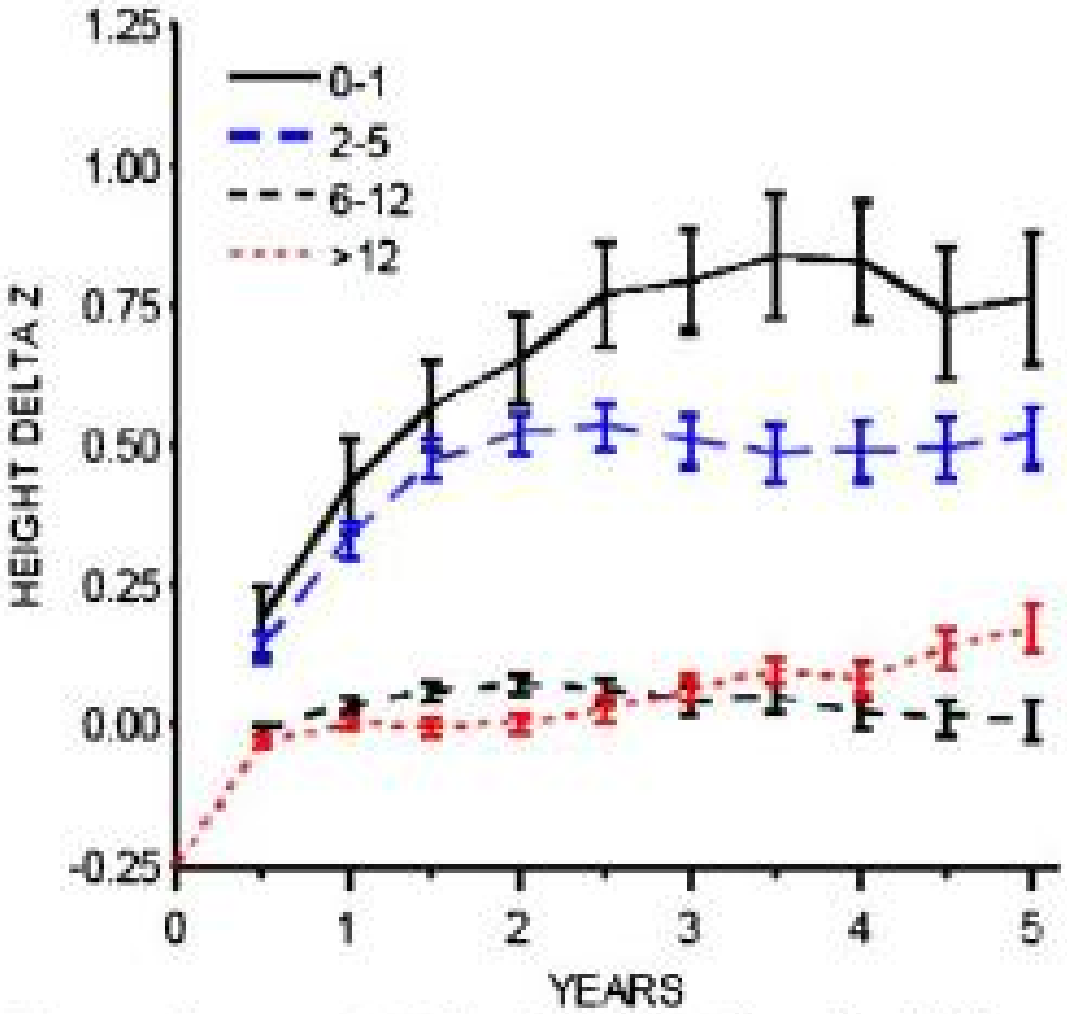


Fig. 1 Mean changes (±SE) from baseline in height standard deviation score (SDS) by age at transplant (data from the NAPRTCS 2006 annual report)

OBESITY

- Obesity, defined by a body mass index (BMI) >95th percentile, is increasing in the transplant population
- Significantly affect on graft survival
- More common in girls

EMPLOYMENT

Satisfactory employment levels

- 81% employed
- 61.5% able to work
- 18.7% receiving a disablement pension

Eur J Pediatr 151:S16–S22

- 73% employed versus 72% in the general population,
- 6.5% unemployed versus 10.5% in the general population

- 91% were satisfied with their ability to perform at work or school
- only 5% were dissatisfied

RELATIONSHIP

- 50% married, and the majority reported satisfaction in their sexual lives
- 50% of women and 27% of men married
- 27% had children

Nephron 105:68–76

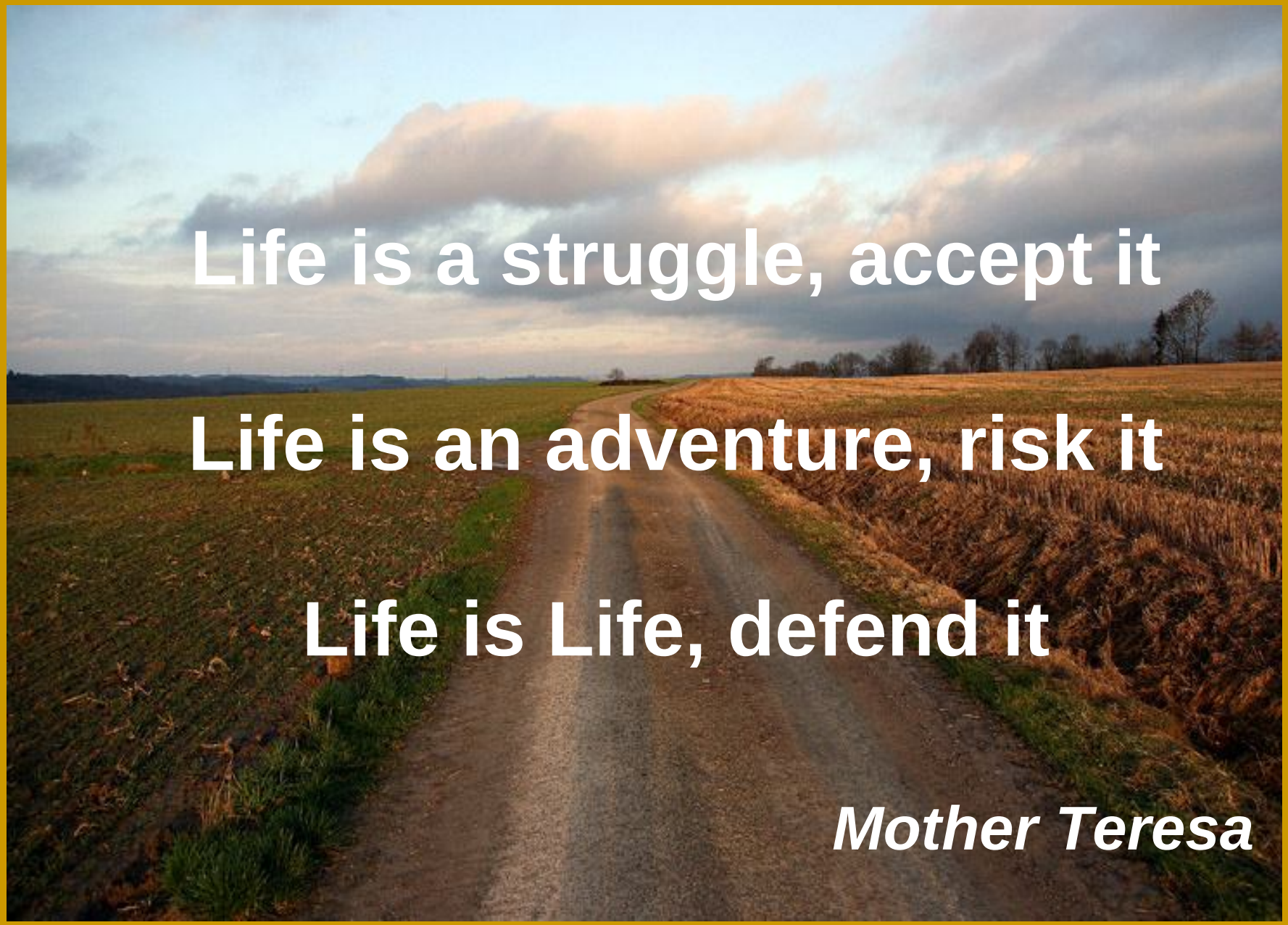
EDUCATION

- The mean intelligence quotient (IQ) was 87
- In the French study, the distribution of educational level was lower than national averages:
  - 27.4% were at the lowest level versus 3% of the general population,
  - 41.4% were at the middle level
  - 31.2% had reached the baccalaureate
  - 11% had followed a university course

Transplantation 77:1033–1037

REFERENCES

1. Philip D. Acott & Hans H. Hirsch.BK virus infection, replication, and diseases in pediatric kidney transplantation. Pediatr Nephrol (2007) 22:1243–1250
2. Robert H. Mak. Recent advances in chronic dialysis and renal transplantation in children. Pediatr Nephrol (2009) 24:459–461
3. Lesley Rees. Long-term outcome after renal transplantation in childhood. Pediatr Nephrol (2009) 24:475–484
4. Tomáš Seeman Hypertension after renal transplantation. Pediatr Nephrol (2009) 24:959–972
5. S. Schmaldienst and W. H. Horl. Bacterial infections during *Nephrol Dial Transplant* (1996) 11: Editorial Comments
6. Broyer M, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, Niaudet P (2004) Long-term social outcome of children after kidney transplantation. Transplantation 77:1033–1037
7. Richard Fine : outcome of renal transplantation in children.


Life is a struggle, accept it
Life is an adventure, risk it
Life is Life, defend it
Mother Teresa


THANK YOU