

# DEPRESSION AND HIV

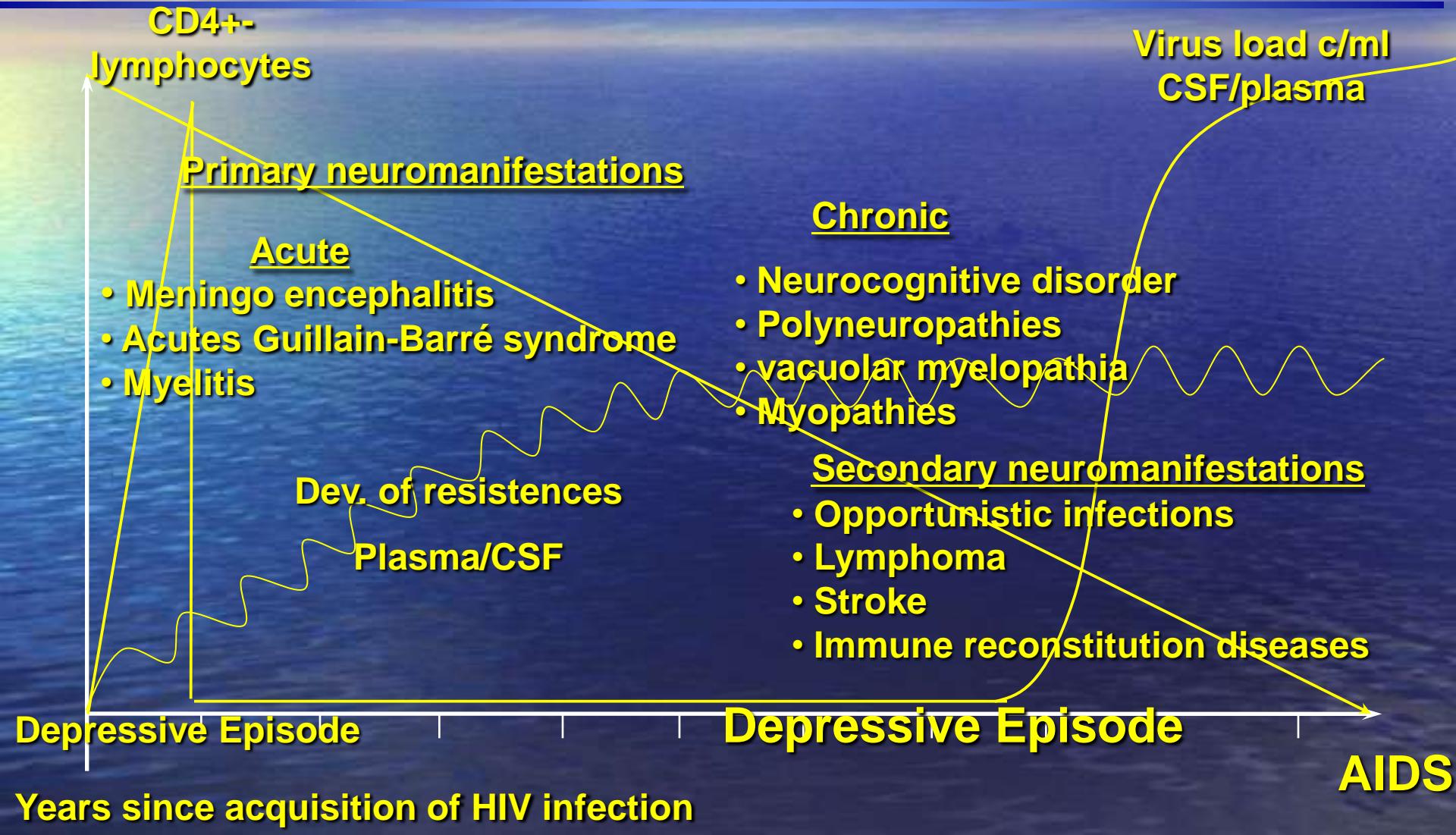
I W Husstedt

University Hospital Münster  
Germany

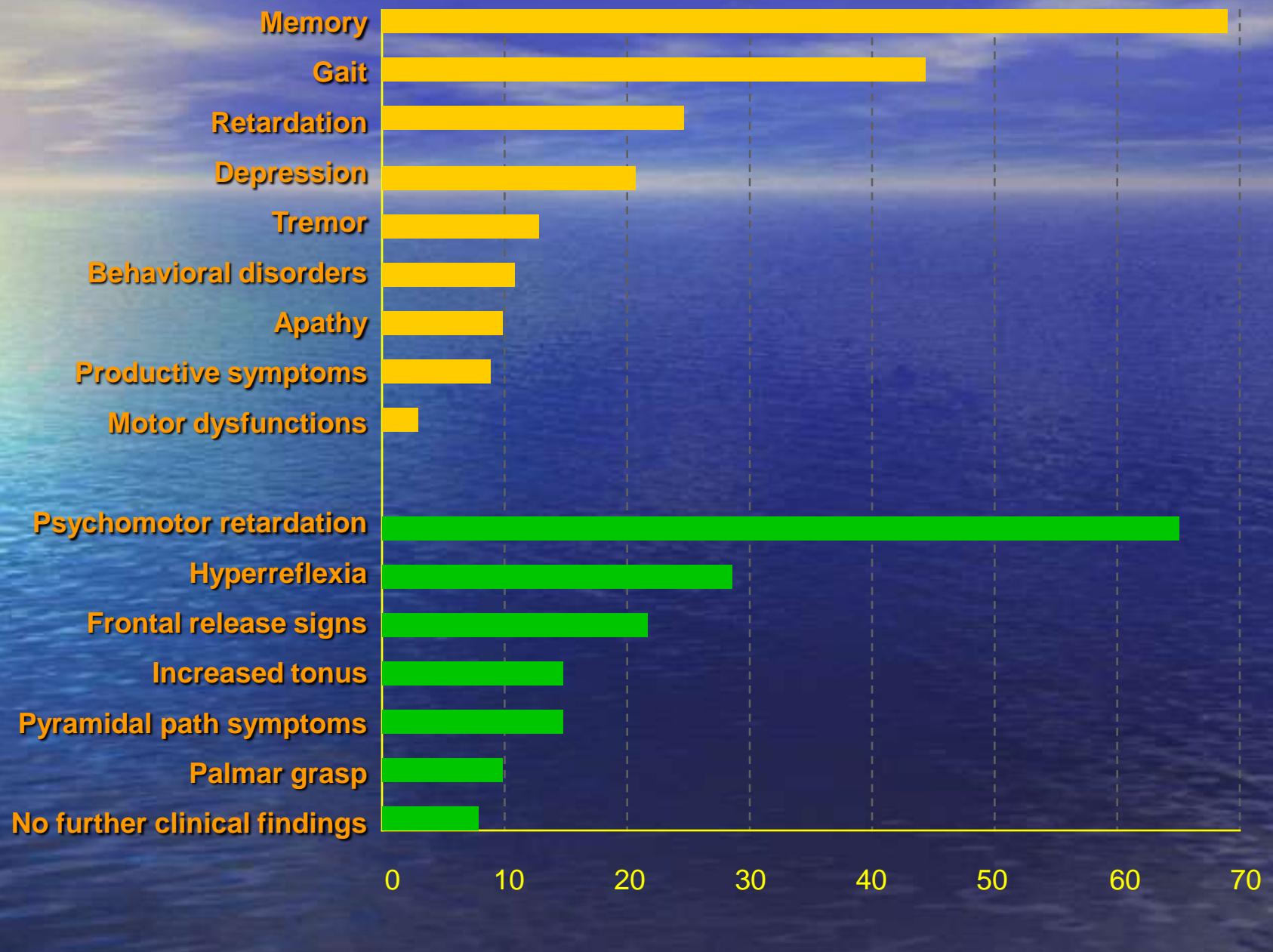
Townhall of Münster 13. Cent.,  
Gothic style



# Natural Course of HIV Infection and Time Correlation of Primary and Secondary Neuromanifestations



# Symptoms and Findings with HIV-Associated Neurocog. Disorder %, (n=299) Brew et al.1997



# Depression – General Epidemiology

First appearance usually between age 35 and 40; > 60 yrs. only approx. 10 % develop depression. Lifetime prevalence for men is 12 %, whereas for women it is 20 %. Lifetime risk is around approx. 17 %. In only 50 % of the cases, depression is diagnosed correctly, and only 10 % receive sufficient treatment (Germany).

# HIV and Depression Forms

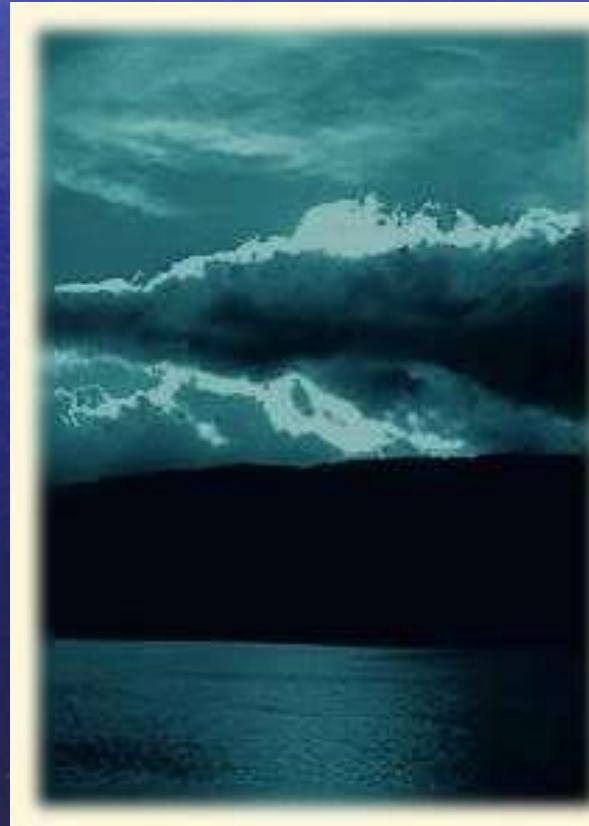
	<b>HIV-infected patients</b>	<b>Control group</b>
<b>Major depressive disorder *</b>	10 – 36 %	5 – 17 %
<b>Dysthymia *</b>	4 – 7 %	2 – 4 %
<b>Anxiety disorders</b>	11 %	-----
<b>PTSD</b>	11 %	-----
<b>Acute psychosis</b>	2 – 9 %	-----

\* Crisla et al.: Am J Psych (2001)  
(n=2596)

Tarrina et al.: J Aff Dis (2001) (n=132)

# HIV and Depression Epidemiology

- Depression after having been diagnosed to be HIV infected
- - 50 % go through a depressive episode
  - - 5 % have suicidal thoughts for a short while
  - - 2 % attempt to commit suicide
- Incidence of suicidal crises is higher for HIV-infected patients as compared to patients with malignoma



# Epidemiology of depression (D)



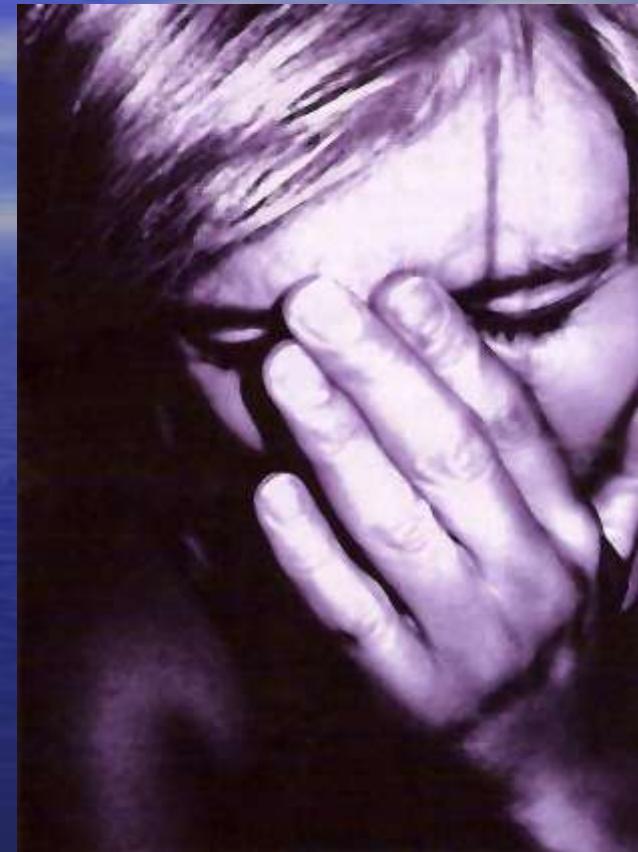
- 20–37 % of HIV-infected patients have diagnosable D (Jia et al. 2004)
- One third scored 14 or higher on Beck Depression Inventory, indicating mild or moderate D during HIV (Ciesla et al. 2001)
- 54 % with D in a patient collective during HIV-infection (Williams et al. 2005)
- 2-fold increase in rate of D compared with HIV-individuals (Ciesla et al. 2001)

# HIV and Depressive Episodes

**Key questions about  
depressive episode:**

**Do you feel...? / Are you still  
able to...? Do you get stuck  
in...? Do you have ...?**

- **Sad?**
- **Be happy?**
- **Brooding?**
- **Self-confidence?** Difficulties
- **Self-blame?**
- **Guilty?**
- **Energy?**
- **Suicidal thoughts?**
- **Purpose in life?**
- **Sleep disorders?**
- **concentrating?**
- **Wake up frequently?**
- **Pessimistic future  
prospects?**



# WHO Well Being Index

	<i>Over the last two weeks</i>	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
<b>1</b>	<b>I have felt cheerful and in good spirits</b>	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
<b>2</b>	<b>I have felt calm and relaxed</b>	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
<b>3</b>	<b>I have felt active and vigorous</b>	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
<b>4</b>	<b>I woke up feeling fresh and rested</b>	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
<b>5</b>	<b>My daily life has been filled with things that interest me</b>	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0

The score ranges from 0-25 representing worst possible and best possible quality of life < 13 strong sign for depression

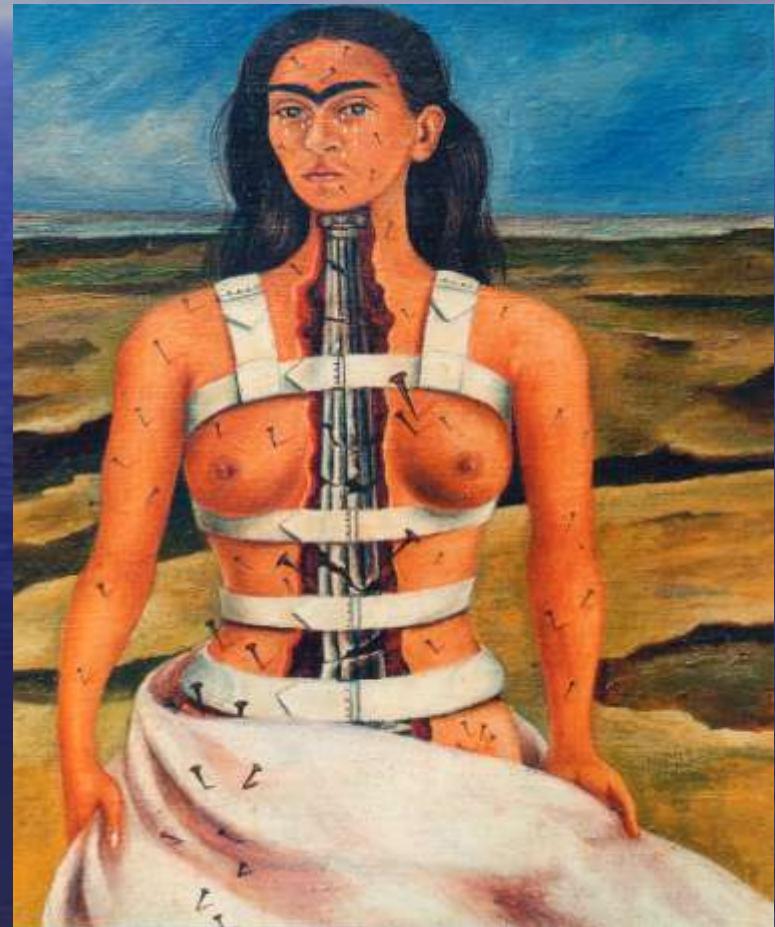
# Symptoms of Depressive Episode ICD 10

- The patient suffers from lowering of mood, reduction of energy and decrease in activity.
- Capacity for enjoyment, interest and concentration is reduced
- Marked tiredness after even minimum effort is common
- Sleep is usually disturbed and appetite diminished
- Self-esteem and self-confidence are almost always reduced
- Even in the mild form, some ideas of guilt or worthlessness are often present
- The lowered mood varies little from day to day, is unresponsive to circumstances
- May be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings
- Waking in the morning several hours before the usual time, depression worst in the morning,
- Marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido
- Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe

# HIV and Depressive Episode

## Common Unspecific Symptoms

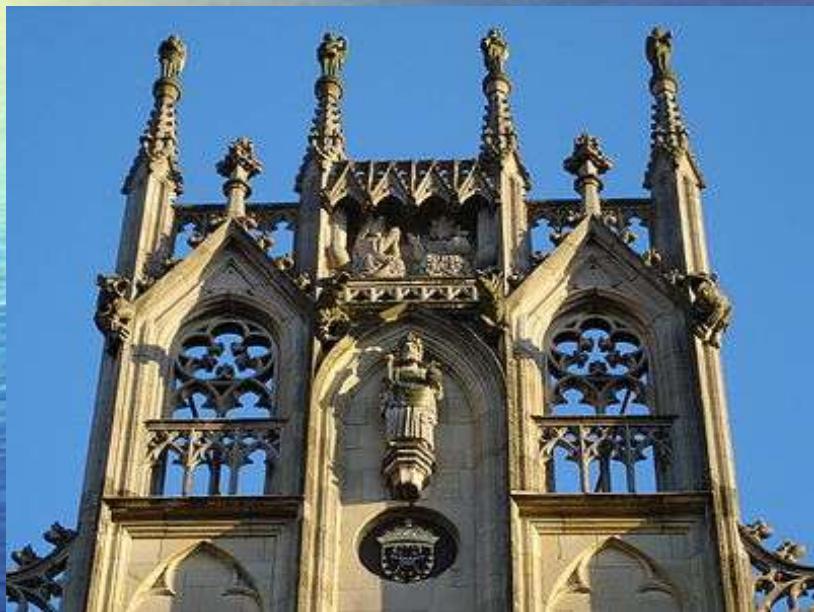
- 83 % of patients with depressive episodes primarily mention physical complaints
- Reduced physical performance
- Diffuse, difficult-to-localize pain in the abdomen, thorax, head (58%)
- Digestive disorders
- Diffuse muscle and joint complaints
- Sleep disorders
- Dizziness
- Fatigue



# Depressive Episode

## Differential Diagnosis of secondary depression

- An exact neurological and internal examination, including MRI and CSF analysis
- HIV-associated neurocognitive disorder
- Mood disorders caused by Cocaine, Sedatives, Alcohol,
- Internal: Hepatitis C, HIV-associated nephropathy, Cirrhosis of liver
- Endocrine disorders: Hypothyroidism, Diabetes, Hypotestosteronism, Adrenal insufficiency, vitamin lack
- Side effect of medication, e.g. HAART, amprenavir, delavirdine, efavirenz, saquinavir, stavudine, zidovudine



Gable of the Townhall of Münster  
13. Cent., Gothic style

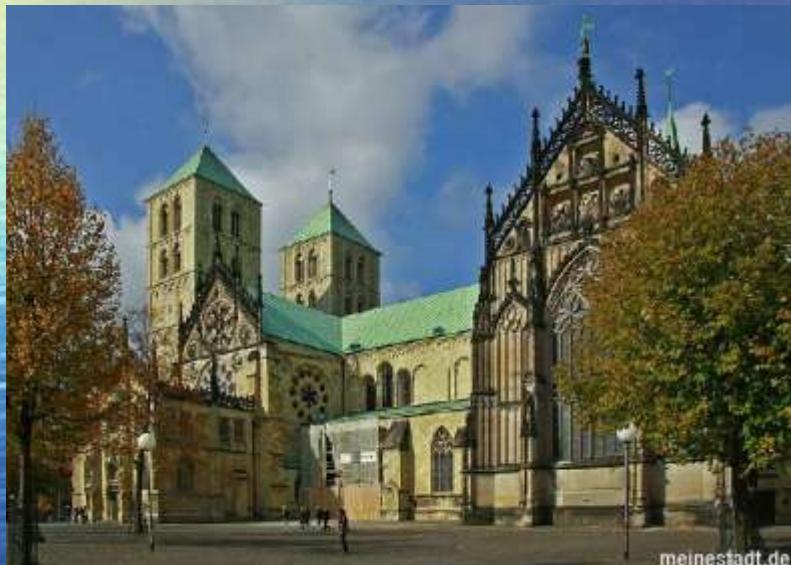
# HIV and Depression

## Reasons for Poor Adherence

### Why patients with HIV-infection fail to take their medication:

- Simply forgot 66 %
- Busy with other things 53 %
- Fell asleep before taking their dose 46 %
- Taking them regularly is difficult 40 %
- Feel depressed 24 %
- Would like to avoid side effects 18%
- Need to take too many remedies 14 %
- Don't want others to know about medication 14 %

# **Impact of Depression (D) on HIV Progression**



Cathedral of Münster - Roman style 14. cent.

- Women with D are 2x more likely to die from AIDS (Ickovics et al. 2001)
- Women with more positive psychological resources (e.g. positive affect) have lower Aids-related mortality (Ickovics et al. 2001)
- D at initial HAART use is associated with 5x risk of progression to AIDS (Bouchnik et al. 2005)
- D with and without somatic symptoms is correlated with progression to AIDS during 6.5.years (Bouchnik et al. 2005)

# **Stressfull life events, Trauma and their impact on HIV-disease progression**

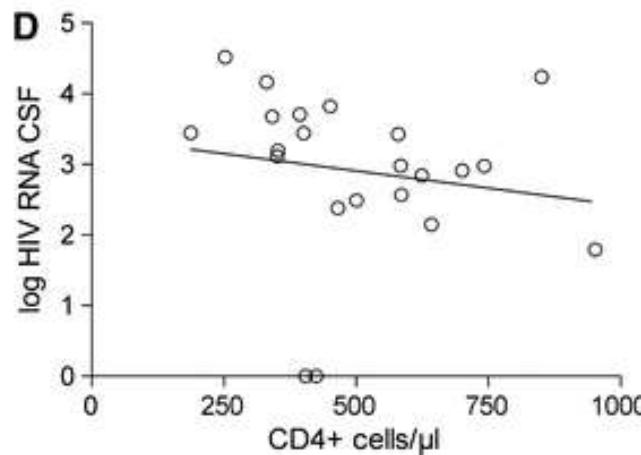
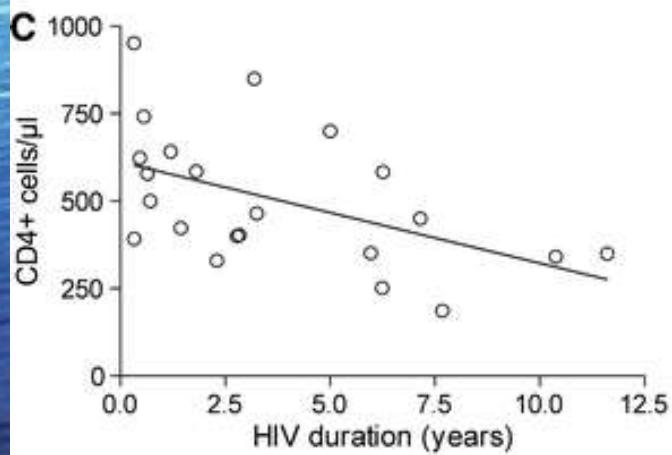
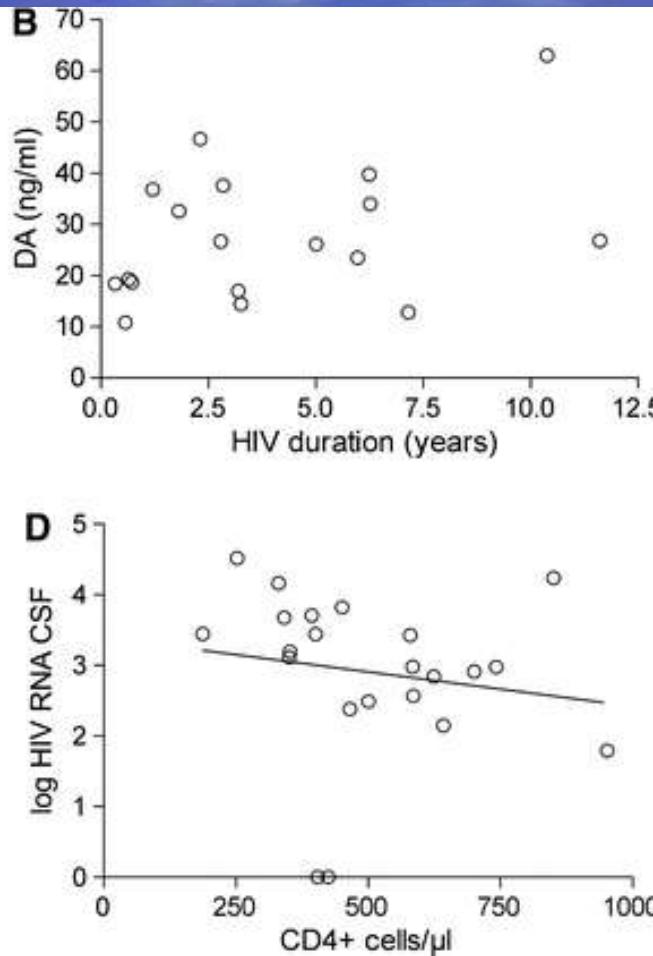
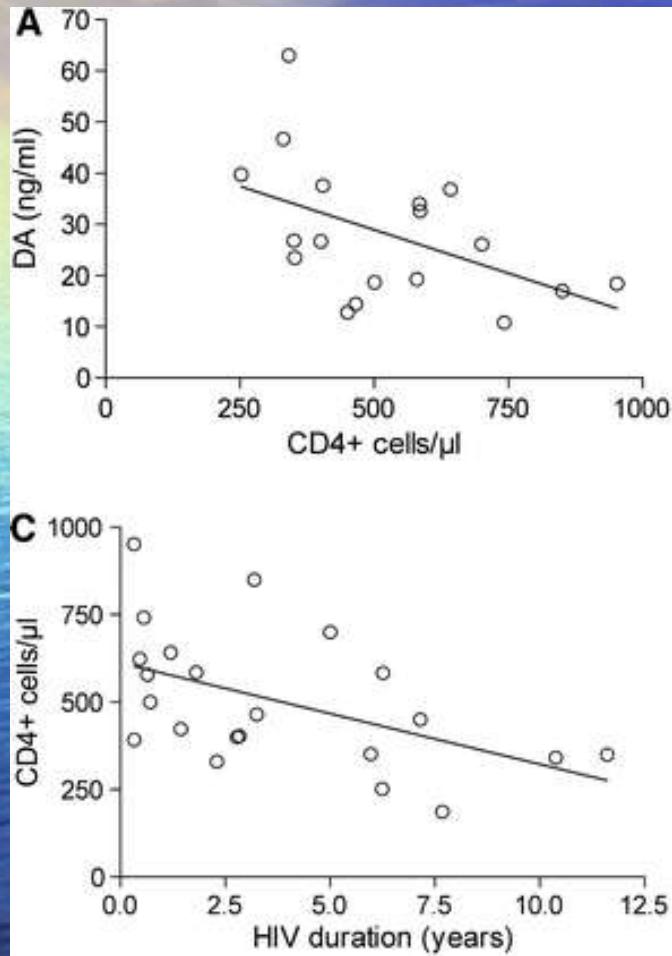


House „Rüschhaus“, Site of the poetess A. von Droste-Hülshoff, one of the the most famous german poetesses (1797-1848)

**Stressfull life events are e.g. major illness of parents, death, lost employment, housing change, desertion**

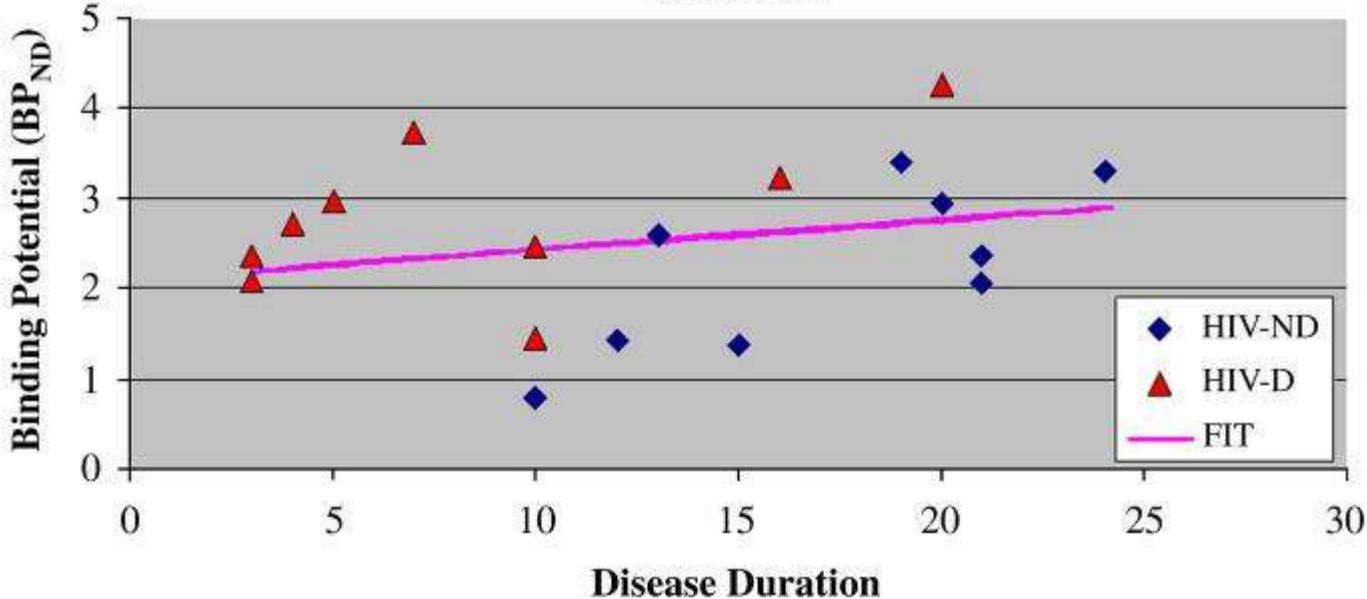
- **Higher stressfull event score is predictive of faster progression to AIDS during 5 –7-and 9 year follow up (Lesermann et al.2002)**
- **Increase in cumulative –average stress equivalent doubles the risk of Aids (Lesermann et al.2002)**
- **74 of the patients above the median in stress progressed to AIDS compared to 40 % below the median (Lesermann et al.2002)**

# Pathologic dopaminergic neurotransmission during HIV-infection

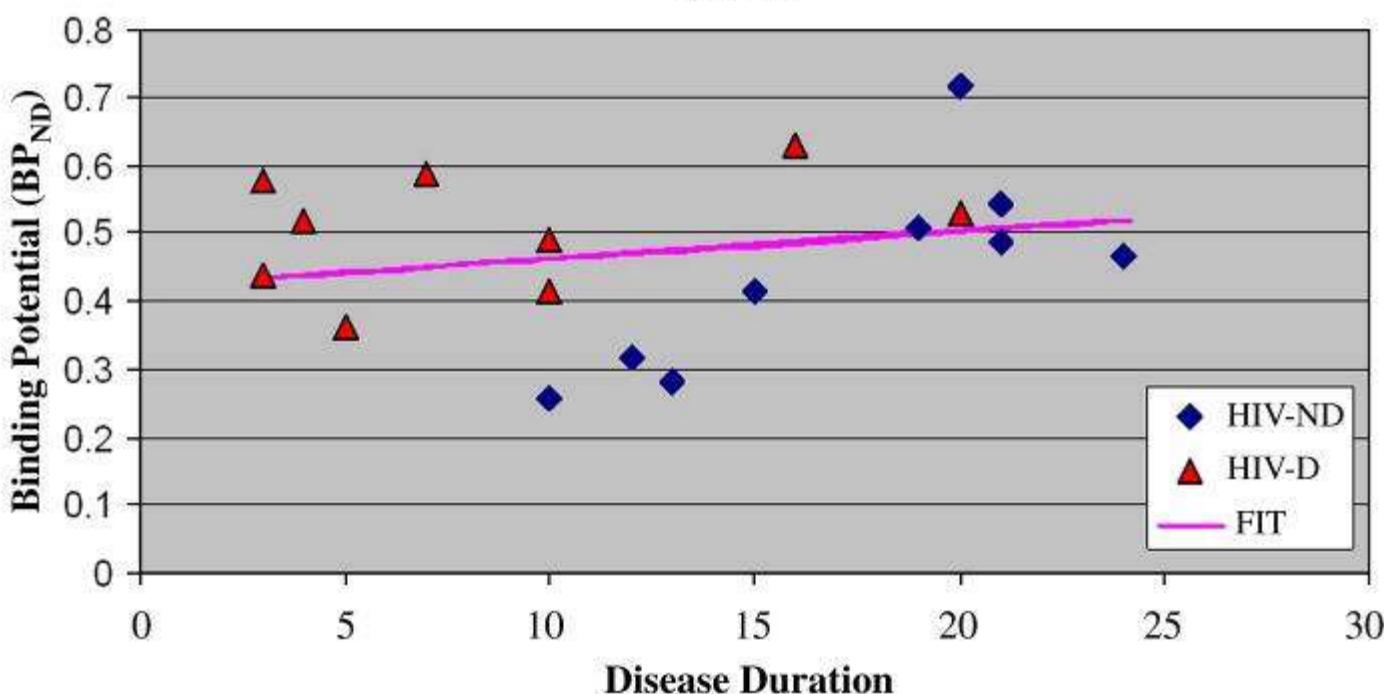


- A: significant correlation of dopamine and CD4+-cells ( $p<0.02$ )
- B: correlation between DA and HIV-du-duration
- C: linear regression between CD4+ and HIV dura-tion ( $p<0.02$ )
- D: linear regres-sion between HIV RNA in CSF and CD4+.

## Midbrain



## Insula



Pathogenesis of  
HIV- associated  
depressive  
episode

Higher binding of 5-HTT leading to increased clearance of serotonin from the synapse, which could in part account for depressive episode in HIV-infected individuals

# When Is IT Necessary to Use Antidepressants?

- If the neurologist/psychiatrist/physician has clearly diagnosed a depressive episode
- Fights disturbed neurotransmission directly
- Early initiation results in easier and faster remission
- The earlier treatment starts, the faster the depression will leave and the patient will have his/her normal life back.
- To improve adherence

# In case of doubt therapy is recommended

- Traditionally, depression tended not to receive treatment for fear of side effects
- Depression is often experienced as a stigma
- Current recommendation: "In case of doubt take the risk to opt for treatment!"
- Many patients, many of whom had been suffering for months, feel much better when treated
- After a long time, patients are able to participate again in everyday life and can go back to work
- Improvement of adherence.

# **Studies of pharmacologic treatment**

- **Mirtazapine, nefazodone, venlafaxine in small studies with response rate of 70%**
- **Zisook et al.;1998; Fluoxetine 20-60 mg/5.7 weeks, n=47, BDI mean change 5.9, Placebo1.2**
- **Rabkin et al.,1999; Fluoxetine 20-40 mg/8 weeks, n=120, HAM-D mean change 13.1, Placebo10.2**
- **Elliott et al.,1998; Paroxetine 33.9 mg vs. Imipramine 162.5 mg, 12 weeks, n=25, HAM-D full responer P 55%, I 80 %**
- **By depression and low testosterone were 58 % responders compared to 18 % with placebo(400 mg im biweekly)**

# HIV and Depression - Therapy

- AIDS support organization - in Germany AIDS-Hilfe
- Cognitive behavioral approaches (25 – 80 h)
- Psychodynamic approaches (25 – 80 h)
- Antidepressants
- Duloxetine (Cymbalta) (30-120 mg) resp.
- Venlafaxine (Trevilor) (75-375 mg)
- Citalopram (Cipramil) (20-60 mg, 40mg 6 w.) 70 % resp.
- Fluoxetine (Fluctin) (20-80, 40 mg/d, 4 m.) 89 % resp.
- Imipramine (Tofranil) (25-150 mg, 150 mg 3 m.) 74 % resp.

# Antidepressants and Their Interactions with HAART

Substance	1A2	2C9/10	2C19	2D6	3A3/4
Paroxetine (Tagonis) SSRI	•	•	•	+++	•
Duloxetine (Cymbalta) SSNRI	•	•	•	++	•
Venlafaxine (Trevilor) SSNRI	•	•	•	•	•
Bupropion (Zyban)	?	?	?	+++	?

Increase of plasma levels for other medication depending on the cytochromeP450 system

•minimal (<20%), +mild(20-50%), ++moderate (50-150%),+++significant(>150%)

# Antidepressants and Their Interactions with HAART

Substance	1A2	2C9/10	2C19	2D6	3A3/4
Citalopram (Cipramil)	•	•	•	++	•
Escitalopram (Cipralex)	•	•	•	++	•
Fluoxetine (Fluctin)	•	++	++	+++	+
Fluvoxamine (Feverin)	+++	+++	+++	•	++
Sertraline (Zoloft)	•	•	•	+	•

Increase of plasma levels for other medication depending on the cytochromeP450 system

•minimal (<20%), +mild(20-50%), ++moderate (50-150%), +++)significant(>150%)

# Interactions between Antidepressants and HAART

Substance Preparation Dose	Citalopram (Cipramil) 20-60 mg	Fluoxetine (Fluctine) 20-80 mg	Paroxetine (Tagonis) 10-20 mg	Amitriptylin (Sarotene) 25-150 mg	Doxepine (Aponal) 50-150 mg	Cymbalta (Duloxetine) 30-120 mg
Lopinavir	C ↑	L ^	L ↑	L ↑	L ↑	
Ritonavir	C ↑	F ↑	R ↑	A ↑	D ↑	C ↑
Amprenavir		A ↑				
Delavirdin		D ↑				C ↑
Efavirenz		E ↑				C ↑
Indinavir		I ↑				C ↑
Lopinavir		L ↑				
Nelfinavir		N ↑				
Saquinavir		S ↑		A ↑	D ↑	C ↑
Nevirapin						C ↑

# St. John's wort lowers HAART levels



- Indinavir 49-99 %
- Nelfinavir
- Ritonavir
- Saquinavir
- Efavirenz
- Nevirapin
- Tenofovir
- Atazanavir

St. John's wort

Even Hippocrates knew this plant to be an antidaemonium!

# HIV-Infection, Hepatitis C, Interferone alpha and Depressive Episodes

- HIV-infection and chronic hepatitis C  
n=113
- 45 patients had a depressive episode
- For 31, a depressive episode developed in the first 3 months after initiating therapy
- 20 were treated with Citalopram
- Early diagnosis and treatment of the depressive episode will improve therapy adherence significantly and increase life quality

# HIV and Depression

## Treatment Tips

- Patients must be made aware of unpleasant side effects
- Also, patients need to be educated that the treatment will last 2-3 weeks to show effects
- It is practical to limit substances to indications of which the medical practitioner is very familiar with.
- Modern serotonin reuptake inhibitors tend to have little effect with regard to neuropathic pain therapy (approx. 8%) (e. g. fluoxetine).
- In case of additive painful HIV-neuropathy prefer e.g. duloxetine, amitriptyline, imipramine.

# Depression Treatment Tips

- Often it makes sense to administer the first dose before patients go to bed if the substance permits, since this will enable them to sleep through any unpleasant side effects thus restoring better sleep at night.
- Therapy is to be continued for 3-6 months beyond the end of the depression, slowly to be phased out over several weeks.



Modern Art in Münster

D. Judd „Balls“

# **How can the patient's family or partners help? 1**

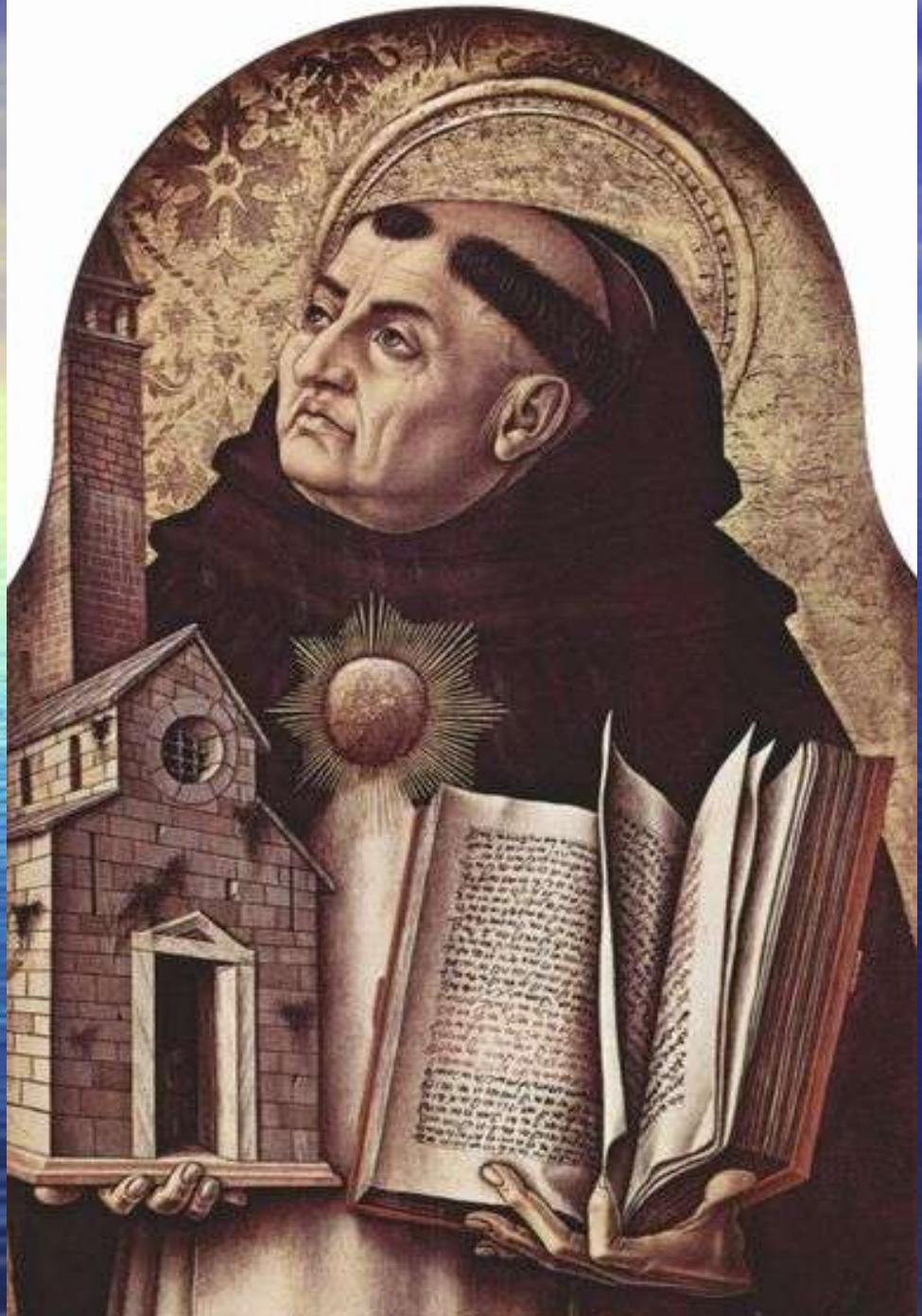
- **By absolutely refraining from telling them to pull themselves together**
- **By not leaving them alone**
- **By being understanding and careful not to ask too much from them**
- **By providing them with stimuli on a regular basis**
- **By ensuring that they can experience the positive side of things again**

# How can the patient's family or partners help? 2

- **Depressive patients are more accessible in the evening than in the morning**
- **By helping them to once again relate to emotions and to participate in life**
- **The motto is to find some words of comfort every day until the scientific treatment methods start to be effective**



Christmas Market



„Among all passions of the soul, depression represents one of the most severe damages on the body“

(Thomas von Aquin 1225-1274)

# VIPs and celebrities afflicted by depression

- Sebastian Deisler (born 1980)
- Marilyn Monroe (1926-1962)
- Ernest Hemingway (1899-1961)
- Vincent van Gogh (1853-1890)
- Abraham Lincoln (1809-1865)
- Leo Tolstoi (1828-1910)
- Franz Kafka (1883-1924)
- Edvard Munch (1863-1944)
- Kurt Cobain (1967-1994)
- Anthony Hopkins (born 1937)



# **HIV and Depression ESSENTIALS**

- HIV-infection disturbs metabolism eg. serotonin
- Depression is found in 20-30 % during HIV-infection
- Women are more frequently affected
- Treatment of depression helps to improve therapy adherence
- Partners/family must be included in therapy
- Unclear symptoms and pain may be a sign of depression
- Adequate therapy improves quality of life
- Adequate antidepressant therapy helps to cut expenses associated with HIV-infected patients by approx. 4,300 € per year and individual

Filippo Moeller aka J.W.von Goethe from Italy in a letter to Duke Carl August in Weimar on Febr. 3, 1787: The young women surrounding the painters as models are adorable and most willing to be looked at and enjoyed. It would be a very comfortable pleasure, if it was not for the French influence which makes this paradise unsafe, too!!



1. Description of syphilis in 1440  
Pathogene detection 1905 by Schaudin & Hoffmann, therapy with silver-salvarsan 1909 by Hoffmann
2. Description of AIDS in 1970  
Pathogene detection 1983 by Montagnier & Gallo, therapy with AZT since 1988



**Thank you for your attention!**

# Prevalence and Localization of Pain in Patients in the AIDS Stage

	Prevalence and localization of pain %	Prevalence/Localization of pain impacting the patient %
<b>% of all patients</b>	<b>74</b>	<b>51</b>
<b>Extremities</b>	<b>35</b>	<b>23</b>
<b>Neuropath. pain</b>	<b>20</b>	<b>15</b>
<b>Upper gastroint. tract</b>	<b>22</b>	<b>12</b>
<b>Lower gastroint. tract</b>	<b>18</b>	<b>13</b>
<b>Head</b>	<b>23</b>	<b>7</b>
<b>Muscles/joints</b>	<b>20</b>	<b>7</b>

# Thermic Hypalgesia and Mechanical Allodynia Caused by HIV-gp120

- CNS infection with the HI-virus induces increased sensitivity to pain
- Since retrovirustatics lead to lower levels in the liquor/CNS than in the blood , glia activation will not be treated sufficiently
- Research on the mechanisms which will lead to increased pain sensitivity caused by the HI-virus might contribute significantly to expanding our knowledge on algotransmission and on developing new pain therapies



# **General Considerations concerning EFV Therapy and Its Side Effects**

- Routine screening for depressive episodes
- Ongoing patient education and support
- Close patient follow-up
- Ensure that patients receive support
- Provide patients with a phone number to call if problems arise
- Call patients for follow-up on day 1 or 2 / first week
- Do not initiate therapy before a weekend or holiday, since then the patients would only be able to contact you with some delay or not at all in the event of problems

# HIV and Depression

## Therapy (1)

- AIDS support organization
- Cognitive behavioral approaches (25 – 80 hrs)
- Psychodynamic approaches (25 – 80 hrs)
- Antidepressants
  - - Fluoxetine (40 mg/d, 4 months)
  - 89 % responders
- Rabbin et al. A J. Psych (1999)
  - - Imipramine (~ 260 mg/d, 3 months)
  - 74 % responders

Rabbin et al. A J. Psych (1994)

# HIV and Depressive Episodes

## Differential Diagnoses

- HIV-associated neurocognitive disorder: (asymptomatic, mild, dementia) (most significant DD of all): exclusion of other diagnoses based on NMR, liquor, neurophysiology, neuropsychology, also see [www.dnaa.de](http://www.dnaa.de)
- Depressive episode triggered by drug, alcohol, tranquilizer, medication abuse
- Depressive episode arising from deficient vitamins, e.g. B-12-avitaminosis
- Depressive episode as a side effect of HAART medication, e.g. for amprenavir, delavirdin, efavirenz, saquinavir, stavudine, zidovudine

# HIV and Depression

## Differential Diagnosis of the Depressive Episode

- **Reaktive:** After significant life events
- **Endogene:** Repeated occurrence of long, severe depressive phases
- **Neurotic:** Repeated occurrence in conflict situations
- **Organic:** e.g. HIV-associated neurocognitive disorder, stroke, Alzheimer's disease
- **Side effect** of medication



# Potential Organic Causes for Depressive Episodes

- **Thyroid diseases:** hyper-/hypothyroidism
- **Neurological diseases:** HIV-associated neurocognitive disorder, Alzheimer's disease, Parkinson's disease, stroke, brain tumors
- **Serious physical diseases:** cardiac infarction, severe asthma, liver diseases
- **Infections:** pneumonia, Lyme disease
- **Tumors**
- **Drugs and alcohol:** cannabis, opiates, stimulants
- **Medication:** antibiotics, cardio-vascular medication, oral contraceptives, cortisone

# Depression (D) and HIV Progression before HAART

- Depressive patients at study entry progresse to AIDS 1.4 years earlier ( Page et al. 1996)
- D is related to decline in CD4+-lymphocytes without progression to AIDS (Burack et al. 1993)
- Men with D at every visit have 67 % higher risk of mortality compared to men without D (Mayne et al. 1996)
- Positive items given by the patient of the depression scale (e.g. happy) are better predictors of survival than negative ones (e.g. sad) (Moskowitz et al. 2003)



meinestadt.de

Palace of Münster - Main building of the University; Baroque style 18. cent.

# HIV/AIDS and Depressive Episodes

- 50 % correct diagnosis
- 10-15 % false-positive diagnoses
- Only 10 % received adequate treatment
- 83 % of patients with depressive episodes primarily mention physical complaints
  - 58 % various physical complaints
  - 25 % pain
  - 7 % depression
  - 4 % anxiety



# Depressive Episode

## Typical Symptoms of Depressive Episodes:

- Loss of interest
- Joylessness
- Listlessness
- "Sense of numbness"
- Difficulties concentrating
- Guilt
- Reduced self-confidence
- Pessimistic view of the future
- Suicidal thoughts
- Social withdrawal
- Reduced appetite, sleep disorders
- Irritability and anxiety



# Symptoms of Depressive Episode

- Depressed mood most of the day, nearly every day
- Reduced /loss of interest or pleasure in almost all activities
- Significant weight loss or gain without dieting
- Insomnia or hypersomnia
- Feelings of lethargy or restlessness
- Fatigue or loss of energy
- Psychomotor retardation or agitation
- Feeling of worthlessness or excessive guilt
- Reduced ability to think or concentrate
- Recurrent thoughts of death or suicide



# HIV and Depression Epidemiology

- 85 % of those treating AIDS in the US have indicated that their patients suffer from depression (telephone alert 2006)
- Depression after having been diagnosed to be HIV infected
- - 50 % go through a depressive episode
  - - 5 % have suicidal thoughts for a short while
  - - 2 % attempt to commit suicide
- Incidence of suicidal crises is higher for HIV-infected patients as compared to patients with malignoma
- Incidence and severity of depressive episodes: **minor: 25 %, severe: 14 %**



# Prevalence of Psychiatric Diseases in HIV-Infected Patients

(n = 1744)

- Psychiatric diseases
  - Depressive episode 57 %
  - Anxiety disorder 34 %
  - Psychosis 9 %
  - Personality disorder 10 %
- Substance abuse
  - Alcohol 29 %
  - Cocaine 18 %
  - Amphetamine 17 %
  - Opiate 12 %







Abb. 1 Typische Lokalisation der HIV-DSP 2-3 Jahrzehnte nach laborchemischer Feststellung der HIV-Infektion. Die schwarze Markierung zeigt die Grenze der schmerzhaften DSP aufsteigend zu den Zehenspitzen in einem typischen Fall. © IWH

Abb.2 Applikation des Capsaicin-Gels. © IWH

Abb. 3 Applikation der Capsaicin-haltigen Qutenza-Folie. © IWH

Abb.4 Fixierung der der Capsaicin-haltigen Qutenza- Folie mit Mullbinden zur besseren Haftung über die Einwirkdauer von 30 Min. © IWH







# **Efavirenz Side Effects Procedure**

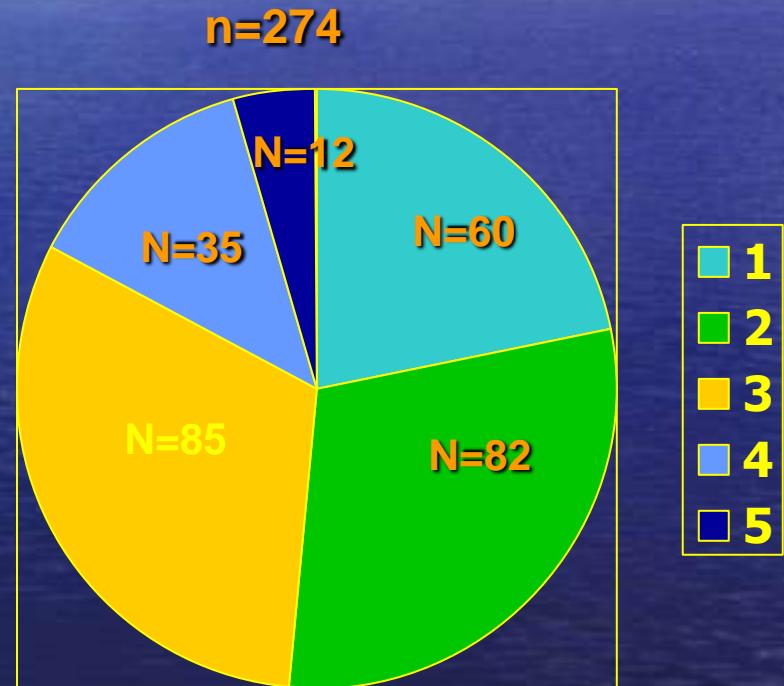
- Medication withdrawal in the event of psychotic episodes
- Therapeutic drug monitoring in the event of depressive episodes
- Examination of other determined etiology
- For patients with major depressive disorder consultations with neuro-psychiatric specialists before initiating treatment
- Exclusion of cerebral neuromanifestation

# **Barriers Preventing Pain Therapy of HIV-Infected Patients from the Perspective of Medical Practitioners**

- Insufficient knowledge 52 %
  - Reluctance to prescribe opioids 52 %
  - Lack of training 50 %
  - Concern about medication abuse 50 %
  - Too little experience 38 %
  - Lack of equipment 15 %
  - Concern about negative impact of opioids on HIV infection 8 %
- \* Breitbart et al. 1999

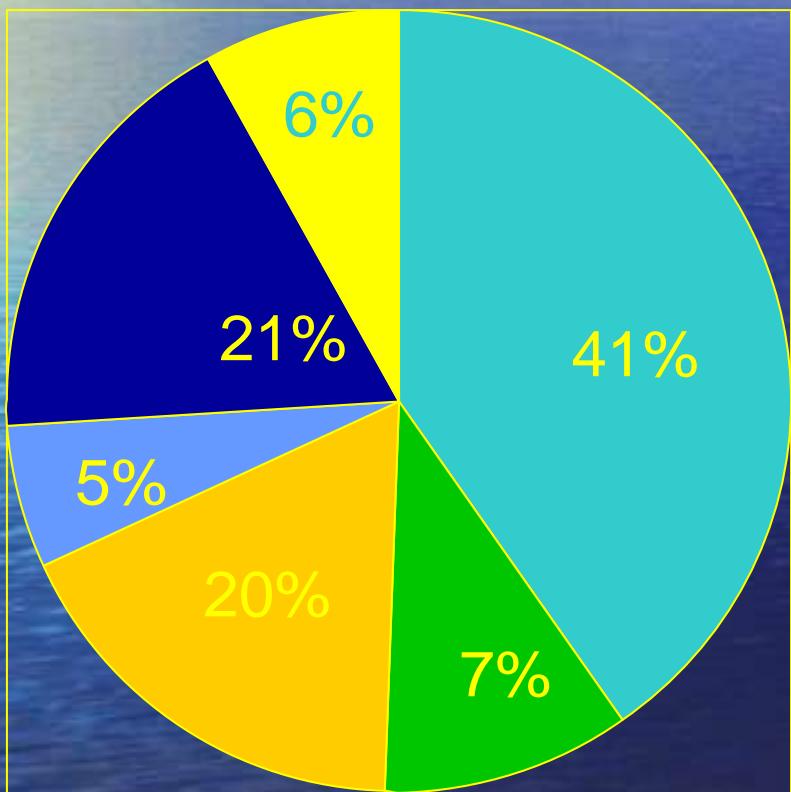
# Pain Intensity for HIV-Infected Out-Patients

- **mild (1-4/10) 19 %**
- **moderate (5-7/10) 64 %**
- **strong (8-10) 17 %**
- **mv pain intensity 5.4**
- **2.5 diff. types of pain on average**



**Number of different kinds of pain per patient**

# Pain Therapy with HIV-Infected Outpatients—Administered Analgetics in %



Total group affected by pain

n=226

- NSAID
- methadone
- no medication
- strong opioids
- weak opioids
- co-analgetics

# Efavirenz Side Effects

Minor

Severe

---

Dizziness

Psychosis (manic,  
schizophrenic)

Sleep disorder

Catatonia

Depression

Severe depression

Restlessness

Attempted suicide

Nightmares

Somnolence

Table 1. Efficacy and Safety of SSRIs in Adults with HIV

Reference	Therapy	n Pts. Completing (N Enrolled)	Duration of Therapy (wk)	Efficacy (%)	Adverse Events
<b>Controlled studies</b>					
Rabkin et al. (1999) <sup>9</sup>	fluoxetine 37 ± 14 mg/day <sup>a</sup> placebo	87 (120)	8	74 47	somnolence, diarrhea, insomnia, GI upset
Zisook et al. (1998) <sup>10</sup>	group psychotherapy + fluoxetine 36 mg/day group psychotherapy + placebo	37 (47)	7	64 23	nausea, dry mouth, headache, diarrhea
Targ et al. (1994) <sup>11</sup>	group psychotherapy + fluoxetine 20 mg/day group psychotherapy + placebo	18 (20)	12	100 100	not stated
Schwartz et al. (1999) <sup>12</sup>	fluoxetine 20 mg/day desipramine 100 mg/day	8 (8) 4 (6) (females only)	6	75 50	dizziness, palpitations with desipramine; tremor with fluoxetine; dry mouth, sedation, poor memory, nausea with both
Elliott et al. (1998) <sup>13</sup>	paroxetine 34 ± 9 mg/day <sup>a</sup> imipramine 163 ± 53 mg/day placebo	11 (25) 10 (25) 13 (25)	12	55 80 23	greater incidence of dizziness, dry mouth, and palpitations with imipramine than placebo ( $p < 0.05$ )
<b>Open-label studies</b>					
Currier et al. (2004) <sup>14</sup>	citalopram 34 ± 10 mg/day <sup>a</sup>	14 (20)	6	50	insomnia, nausea, dry mouth, rash
Levine et al. (1990) <sup>15</sup>	fluoxetine 20–40 mg/day	8 (8)	4	100	anxiety, insomnia, GI upset, decreased appetite
Judd et al. (1995) <sup>16</sup>	fluoxetine 18 ± 4 mg/day <sup>a</sup>	16 (20)	6 mo	94	rash, nausea
Grassi et al. (1995) <sup>17</sup>	fluvoxamine 100 mg/day	6 (16)	several months	100	insomnia, GI upset, anorexia, aggressive and impulsive behavior, somnolence
Grassi et al. (1997) <sup>18</sup>	paroxetine 20 mg/day	14 (15)	6	100	sexual dysfunction, nausea, constipation, psychomotor agitation, insomnia
Rabkin et al. (1994) <sup>19</sup>	sertraline 120 mg/day	20 (28)	8	70	nausea, diarrhea, agitation, sexual dysfunction, overstimulation, dizziness, insomnia
Ferrando et al. (1999) <sup>20</sup>	fluoxetine 21 mg/day sertraline 56 mg/day	14 (21) 4 (9) (females only)	8	78 for all	anxiety, overstimulation, insomnia
Ferrando et al. (1997) <sup>21</sup>	sertraline 50–150 mg/day paroxetine 20–40 mg/day fluoxetine 20–40 mg/day	7 (11) 10 (11) 7 (11)	6	83 for all	insomnia, agitation, anxiety, headache, nausea, diarrhea, sexual dysfunction
Rabkin et al. (1994) <sup>22</sup>	fluoxetine 36 mg/day ± dextroamphetamine 5–25 mg/day	27 (31)	12	83 100	sweating, sexual dysfunction, hyperactivity

GI = gastrointestinal; SSRIs = selective serotonin-reuptake inhibitors.

<sup>a</sup>Mean ± SD.

SIZE ON HAMILTON DEPRESSION SCALE				
HDS effect size	p value	Dropouts	Intent to treat vs. completers	Intent to treat
0.44	NS	30%	Intent to treat	
0.97	.001	17%	Completers	
1.28	.01	45%	Intent to treat after 4 weeks	
0.51	.05			
0.16	NS	29%	Completers	
0.95	0.05	21%	Intent to treat	
0.30	NS	27%	Completers	
-0.04	NS	10%	Completers	

TABLE 1. CONTROLLED TRIALS OF ANTIDEPRESSANTS AMONG HIV-POSITIVE INDIVIDUALS WITH DEPRESSION: METHODOLOGY, EFFECT SIZE ON HAMILTON DEPRESSION SCALE

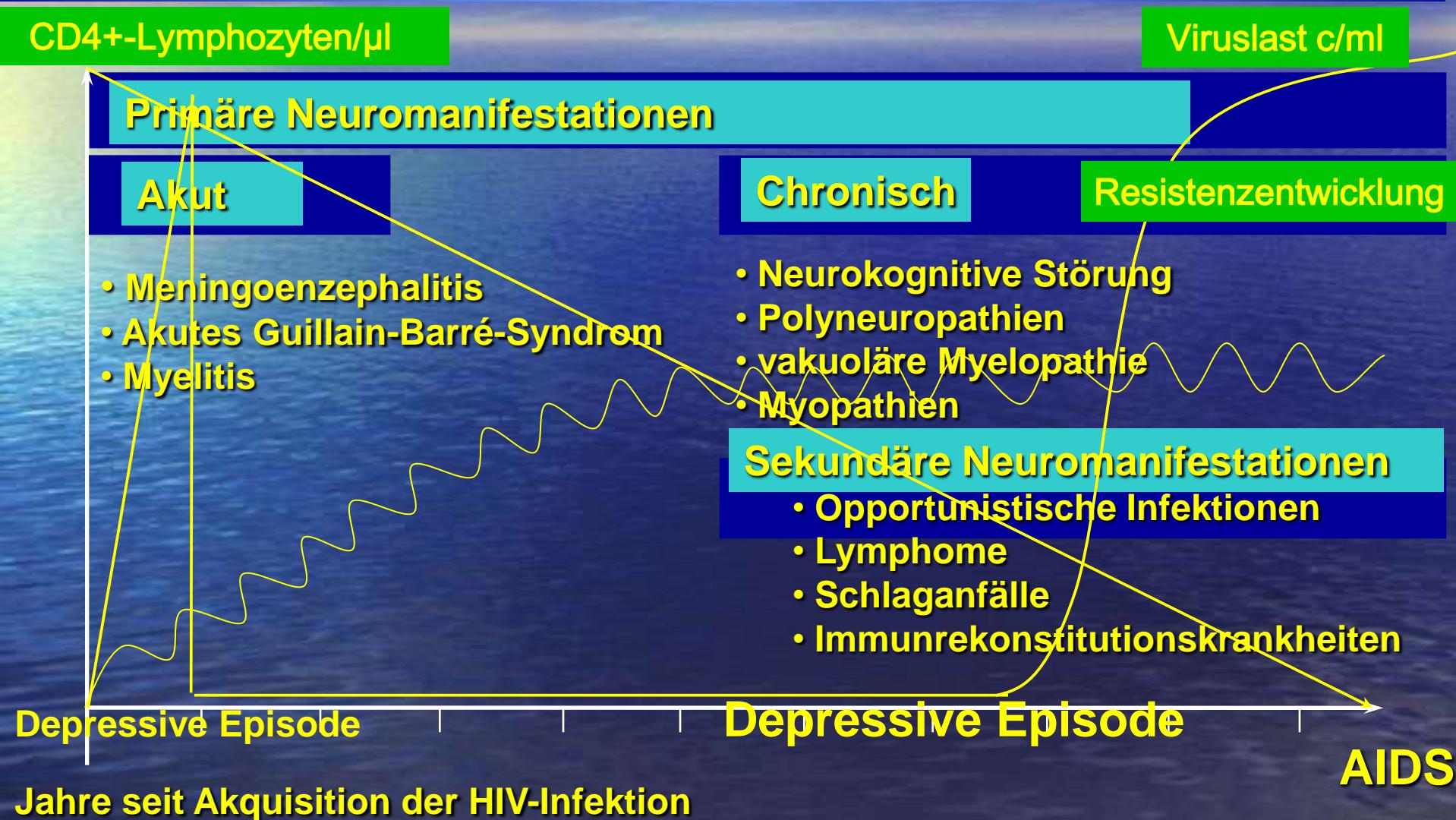
Source	# Randomized	Mean age	White %	Men %	CD4 count mean (SD)	Diagnostic criteria	Baseline HDS Mean (SD)	Medication and mean dose	No. of treatment weeks	Concurrent psychotherapy	Placebo response	HDS effect size	p value	Dropouts	Intent to treat vs. completers
Markowitz (1998)	50	36.9	58	85	280 (222) NA	≥ 15 on HDS (24) & clinical judgment	15.1 (4.0)	Imipramine 210 mg	16	Yes	26% <sup>a</sup>	0.44	NS	30%	Intent to treat
Rabkin (1994)	97	38.0	65	95	301 (202) 23	≥ 14 on HDS (21) & DSM-III-R	16.8 (4.1)	Imipramine 241 mg	6	No	33%	0.97	.001	17%	Completers
Elliot (1998)	75	36.0	93	93	368 (307) 45	≥ 18 on HDS (21) & DSM-III-R	24.3 (5.7)	Paroxetine 34 mg Imipramine 162 mg	12	No	27.3%	1.28 0.51	.01 .05	45%	Intent to treat after 4 weeks
Rabkin (2004)	85	41.0	29	100	455 (324) 37	DSM-IV	16.9 (3.7)	Fluoxetine 34 mg	8	No	60%	0.16	NS	29%	Completers
Zissok (1998)	47	35.5	NA	100	NA	DSM-III-R	20.3 (4.9)	Fluoxetine 36 mg	7	Yes	33%	0.95	0.05	21%	Intent to treat
Rabkin (1999)	120	39.0	67	98	295 (287) 51	DSM-IV	19.3 (4.8)	Fluoxetine 37 mg	8	No	59%	0.30	NS	27%	Completers
Targ (1994)	20	33.0	84	100	389 (178) 0	≥ 16 on HDS & clinical judgment?	20.3 (4.6)	Fluoxetine 20 mg	12	Yes	68%	-0.04	NS	10%	Completers

<sup>a</sup>Parallel control trial.DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HDS, Hamilton Depression Scale; SD, standard deviation.

# Patient Information on Efavirenz

- Generally, CNS symptoms will first occur at the beginning of therapy and will subside after the first few weeks
- Psychiatrc symptoms are rare; they tend to occur more frequently if for patients with a psychiatric disease in their history
- Taking them before going to bed and on an empty stomach can help improve tolerance and reduce CNS side effects
- Patients suffering from initial CNS side effects (e.g. dizziness, difficulties concentrating and/or drowsiness), should avoid engaging in any potentially dangerous activities such as driving a car or operating machinery at the beginning of treatment

# Natürlicher Verlauf der HIV-Infektion und zeitliche Korrelation primärer und sekundärer Neuromanifestation



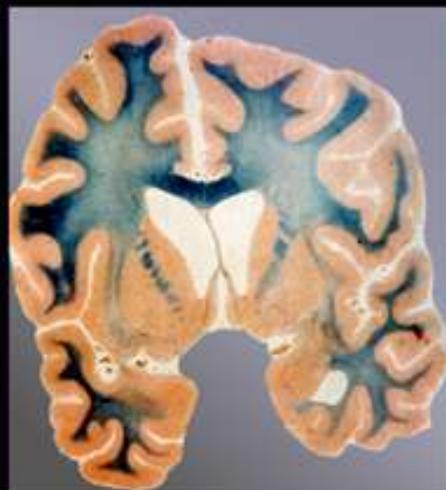
# Etiopathogenesis of HIV-Associated DEMENTIA

A:Distinct HIV-ass. bilateral leucoencephalopathy  
(frontal section, Kluver-Barrera stain)

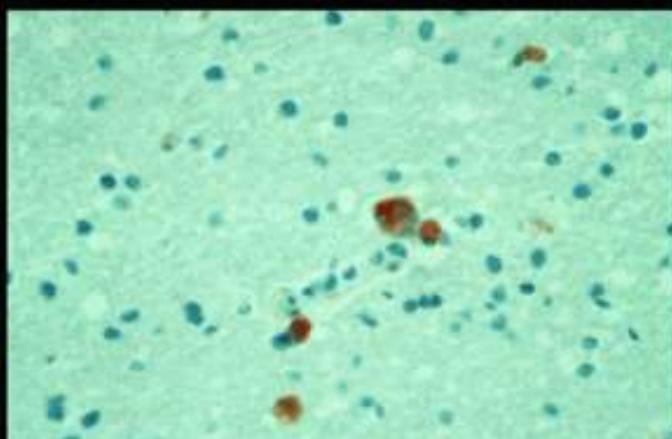
B:Detection of HI-virus by *in situ*-hybridization in the brain  
(HE,128x125).

C:Multi-core giant cell (HE 128x125 stain)

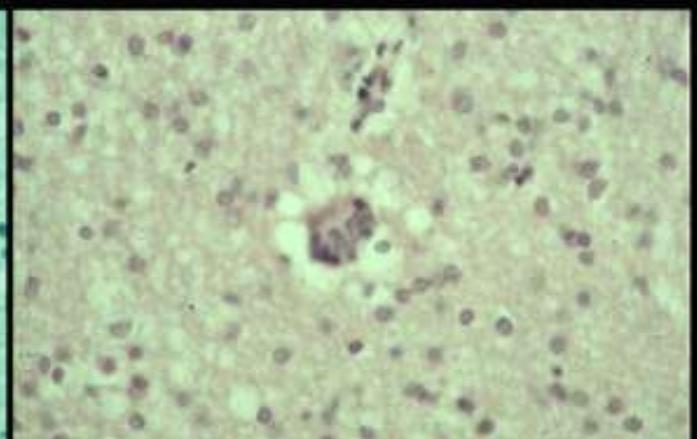
A



B



C



# Symptome und Befunde bei HIV-assozierter neurokog. Störung (n=299)

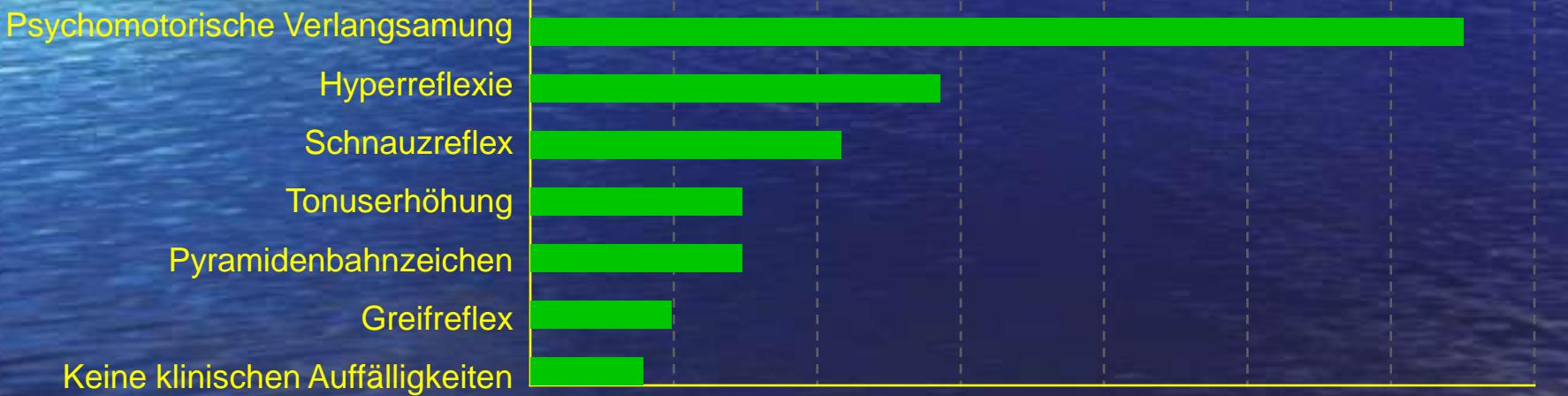
al. 1997

Brew et

## Symptome



## Klinische Befunde

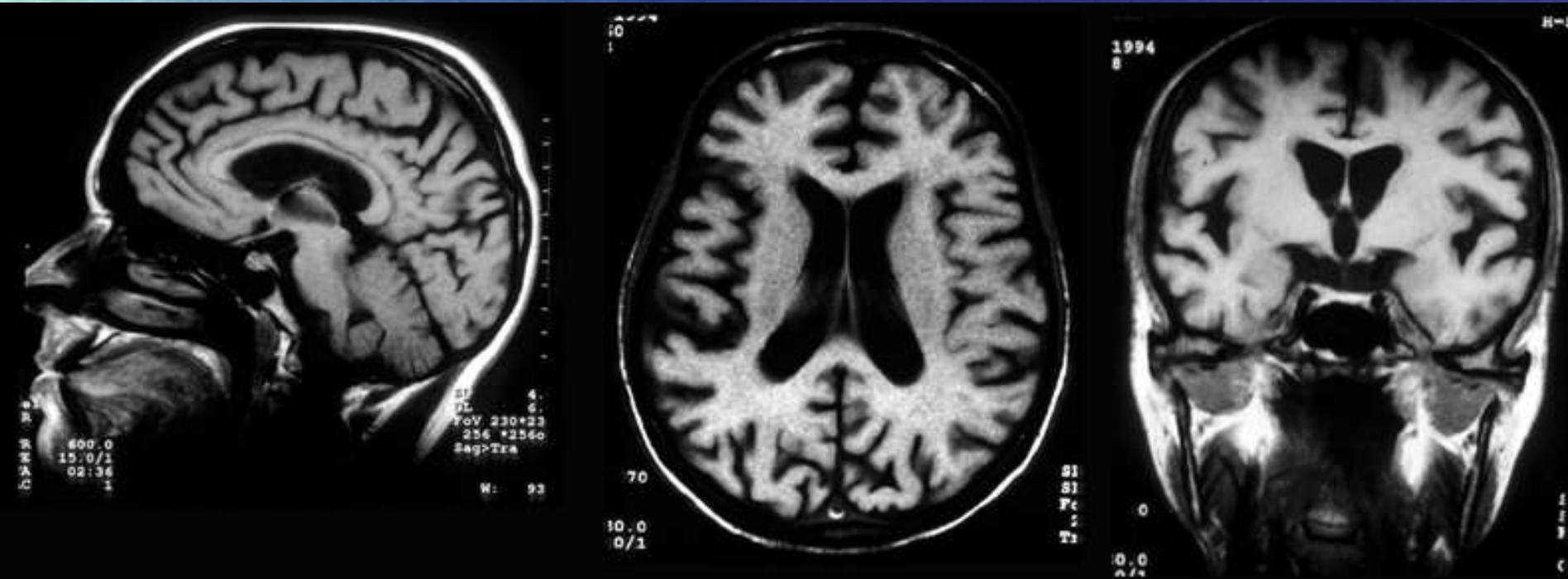


%



# Kernspintomographie des Schädelns 14 Jahre nach Aquisition der HIV-Infektion.

Zu diesem Zeitpunkt besteht eine schwere HIV-assoziierte Demenz mit ausgeprägter Atrophie und Erweiterung der inneren und äußeren Liquorräume.



# Ätiopathogenese der HIV-assoziierten DEMENZ

A:Ausgeprägte HIV-ass. Leukoenzephalopathie beiderseits  
(Frontalschnitt, Färbung nach Clüver-Barrera)

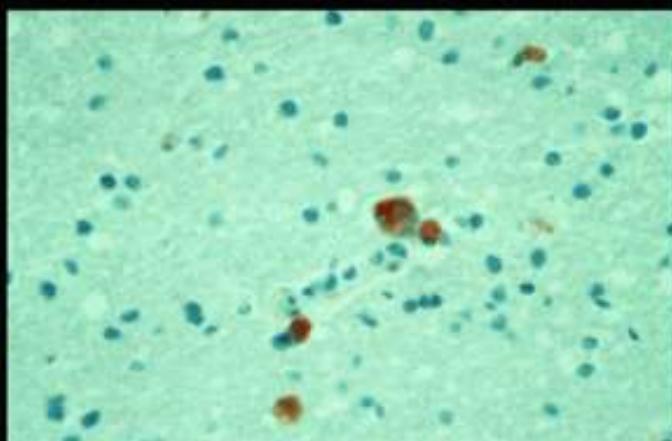
B:Nachweis des HI-Virus durch in situ-Hybridisierung im Gehirn  
(HE,128x125).

C:Mehrkernige Riesenzelle (Färbung HE 128x125)

A



B



C



# Depression - Epidemiologie

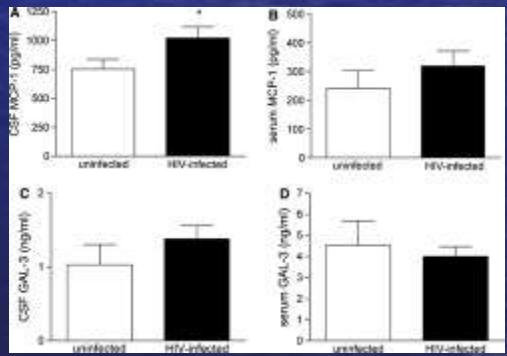
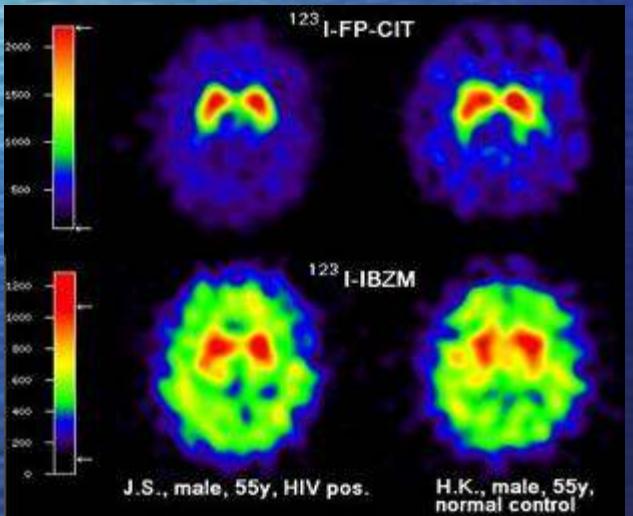
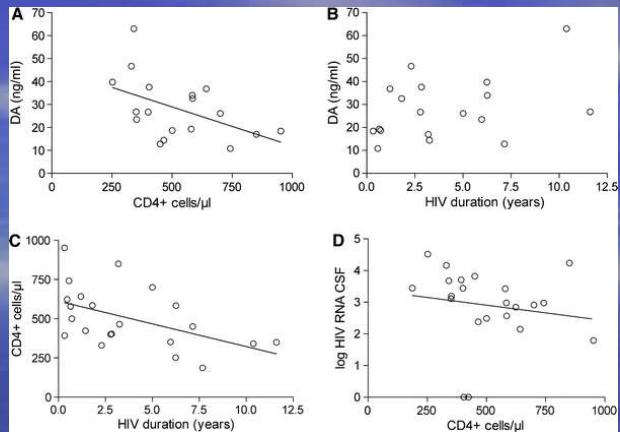
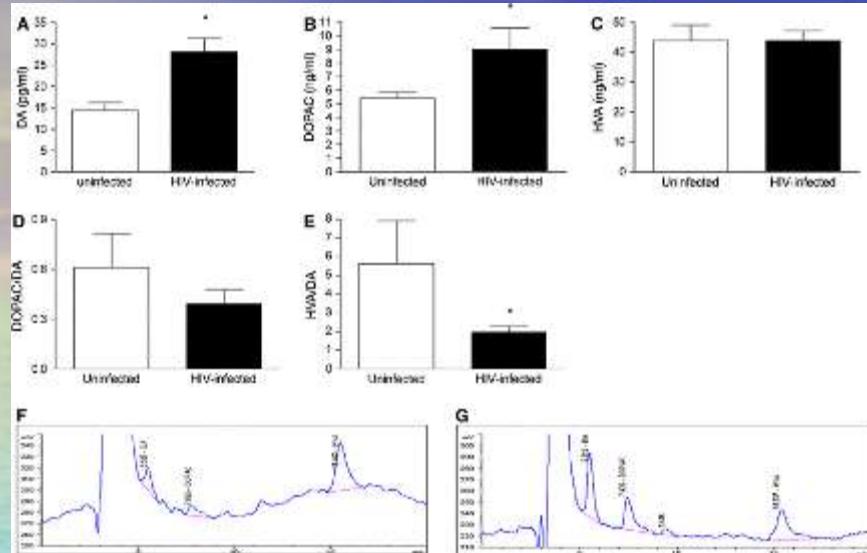
- Erstauftreten meistens zwischen 35 und 40
- 60 > J. erkranken nur noch etwa 10 %
- Die Lebenszeitprävalenz beträgt für Männer 12 %, für Frauen 20 %.
- Das Lebenszeitrisiko liegt bei etwa 17 %.
- Nur 50 % der Depressionen werden richtig erkannt, nur 10 % ausreichend behandelt.

# HIV und Depression

## Epidemiologie

- 85 % der AIDS-Behandler in den USA geben an, dass ihre Patienten unter Depressionen leiden (telephone alert 2002)
- Depression nach Mitteilung der HIV-Infektion:
  - 50 % durchleben depressive Episode
  - 5 % haben kurzfristige suizidale Ideen
  - 2 % unternehmen einen Suizidversuch
- Die Inzidenz suizidaler Krisen ist bei HIV-Infizierten > als bei Patienten mit Malignomen
- Inzidenz und Schwere depressiver Episoden:
  - leicht: 25 %
  - schwer: 14 %





# Prävalenz psychischer Erkrankungen bei HIV-Infizierten

(n = 1744)

- Psychische Erkrankungen
  - Depressive Episode 57 %
  - Angststörung 34 %
  - Psychose 9 %
  - Persönlichkeitsstörung 10 %
- Substanzmissbrauch
  - Alkohol 29 %
  - Cocain 18 %
  - Amphetamin 17 %
  - Opiate 12 %



# HIV / AIDS und depressive Episode

## Versorgung in der Praxis

- 50 % korrekt diagnostiziert
- 10-15 % falsch positive Diagnosen
- Nur 10 % adäquat behandelt
- 83 % der Patienten mit depressiven Episoden stellen primär körperliche Beschwerden in den Vordergrund
  - 58 % verschiedene Körperbeschwerden
  - 25 % Schmerzen
  - 7 % Niedergeschlagenheit
  - 4 % Angst



# Depressive Episode

## Typischen Symptome einer depressiven Episode:

- Interessenverlust
- Freudlosigkeit
- Verminderung des Antriebs
- „Gefühl der Gefühllosigkeit“
- Konzentrationsprobleme
- Schuldgefühle
- Vermindertes Selbstvertrauen
- Pessimistische Sicht der Zukunft
- Selbstmordgedanken
- Sozialer Rückzug
- Verminderter Appetit, Schlafstörungen
- Reizbarkeit und Ängste



# HIV und depressive Episode

Fragen zur depressiven  
Episode:

Fühlen Sie sich...? / Können  
Sie noch...? Müssen Sie...?  
Haben Sie ...?

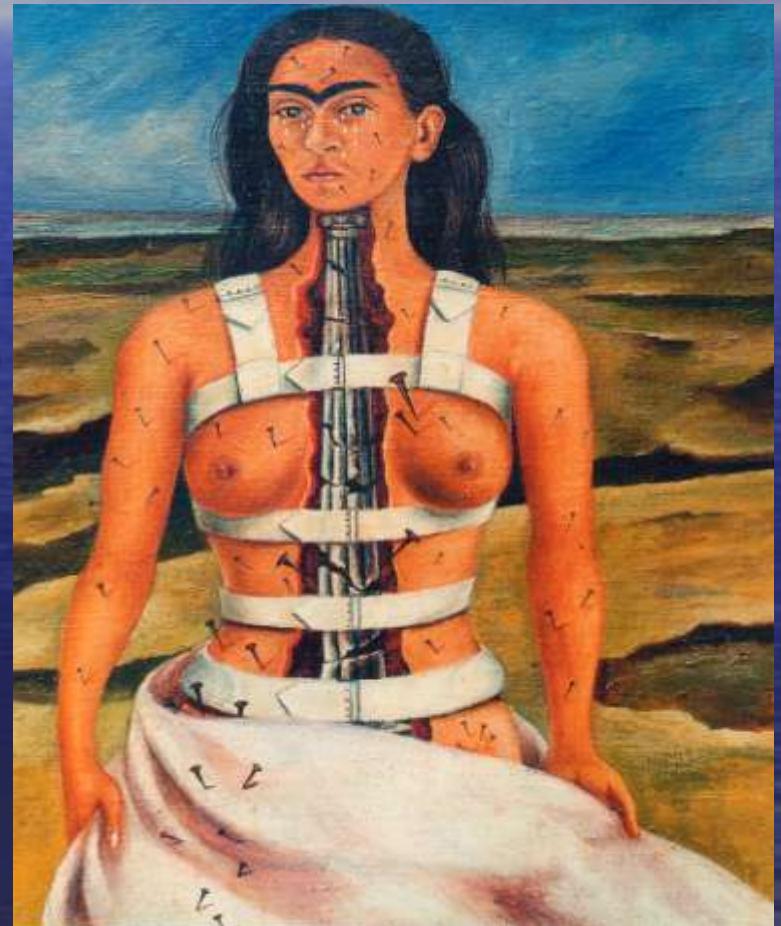
- Traurig?
- Noch freuen?
- Grübeln?
- Selbstvertrauen?
- Selbstvorwürfe
- Schuldgefühle?
- Antrieb?
- Suizid?
- Lebenssinn?
- Schlafstörung?
- Konzentrationsstörung?
- Häufiges Aufwachen?
- Pessimistische Zukunfts-  
perspektiven?



# HIV und depressive Episode

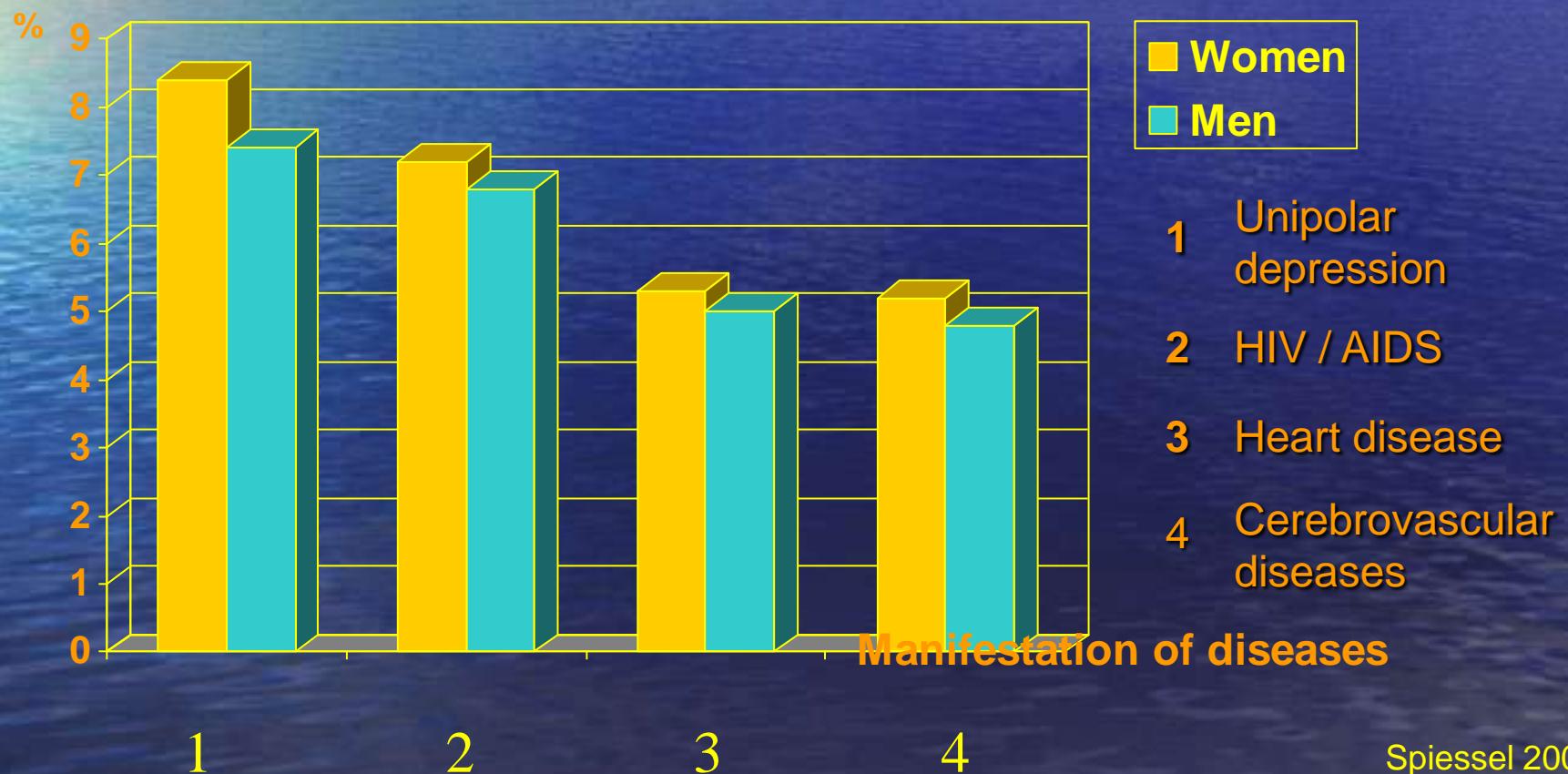
## Häufige unspezifische Symptome

- Verminderte körperliche Leistungsfähigkeit
- Diffuse, schlecht lokalisierbare Schmerzen im Abdomen, Thorax, Kopf
- Verdauungsbeschwerden
- Diffuse Muskel- und Gelenkbeschwerden
- Schlafstörungen
- Schwindel



# HIV / AIDS and Depressive Episodes

Most common causes for loosing healthy years of one's life



# HIV und Depression

## Differentialdiagnose der depressiven Episode

- **Reaktiv:** Nach gravierendem Lebensereignis
- **Endogen:** Wiederholtes Auftreten von langen, schweren depressiven Phasen
- **Neurotisch:** Wiederholtes Auftreten in Konfliktsituationen
- **Organisch:** z.B. HIV-assoziierte neurokognitive Störung, Schlaganfall, M. Alzheimer



# HIV und depressive Episode

## Differentialdiagnosen

- HIV-assoziierte neurokognitive Störung: (asymptomatisch, mild, dementiell) (wichtigste DD überhaupt): Ausschlussdiagnostik durch NMR, Liquor, Neurophysiologie, Neuropsychologie siehe auch [www.dnaa.de](http://www.dnaa.de)
- Depressive Episode bei Abusus durch Drogen, Alkohol, Tranquillizer, Medikamente
- Depressive Episode bei Mangelzuständen, z.B. B-12-Avitaminose
- Depressive Episode als Medikamentennebenwirkung von HAART, z.B. bei Amprenavir, Delavirdin, Efavirenz, Saquinavir, Stavudin, Zidovudin

# Mögliche organische Ursachen einer depressiven Episode

- **Schilddrüsenerkrankungen:** Über-/Unterfunktion
- **Neurologische Erkrankungen:** HIV-assozierte neurokognitive Störung, M.Alzheimer, M.Parkinson, Schlaganfall, Hirntumore
- **Schwere körperliche Erkrankungen:** Herzinfarkt, schweres Asthma, Lebererkrankungen
- **Infektionen:** Lungenentzündung, Borreliose
- **Tumorerkrankungen**
- **Drogen und Alkohol:** Cannabis, Opiate, Aufputschmittel
- **Medikamente:** Antibiotika, Herz-Kreislauf, orale Kontrazeptiva, Kortison

# **HIV-Infektion, Hepatitis, Interferon alpha und depressive Episode**

- HIV-Infektion und chronische Hepatitis C n=113
- 45 entwickelten eine depressive Episode
- 31 entwickelten eine depressive Episode in den ersten 3 Monaten nach Therapiebeginn, 20 wurden mit Citalopram behandelt
- Frühe Diagnose und Behandlung der depressiven Episode verbessert die Adhärenz zur Therapie wesentlich und steigert die Lebensqualität beträchtlich

# Allgemeine Überlegungen bezüglich EFV-Therapie und damit verbundenen Nebenwirkungen

- Routinemäßiges Screening auf depressive Episoden
- Kontinuierliche Patientenaufklärung und Unterstützung
- Enges Follow-Up der Patienten
- Sicherstellen, dass Patienten Unterstützung erhalten
- Patienten Telefonnummer nennen, die im Fall von Problemen angerufen werden kann
- Patienten für Follow-Up an Tag 1 oder 2 anrufen / erste Woche
- Therapie nicht vor dem Wochenende oder Urlaub beginnen, da bei Schwierigkeiten dann nur eine verzögerte oder gar keine Kontaktaufnahme möglich ist

# HIV und Depression Gründe schlechter Adhärenz

## Warum Patienten mit HIV-Infektion Medikamente nicht einnehmen:

- Einfach vergessen 66 %
- Beschäftigt mit anderen Dingen 53 %
- Vor Dosiseinnahme eingeschlafen 46 %
- Regelmäßige Einnahme schwer 40 %
- Möchte Nebenwirkungen vermeiden 24 %
- Sich depressiv fühlen 18 %
- Muss zu viele Medikamente einnehmen 14 %
- Andere sollen nichts von der Einnahme wissen 14 %

# **Wann ist der Einsatz eines Antidepressivums notwendig?**

- Wenn der Neurologe/ PsychiaterArzt eine depressive Episode eindeutig diagnostiziert,
- Wirkt gezielt auf die gestörte Neurotransmission
- Früher Beginn führt zur leichteren und schnelleren Remission
- Je früher die Behandlung startet, desto schneller weicht die Depression und der Betroffene steht wieder voll im Leben.

# Im Zweifel für die Therapie

- Eine Depression wurde vormals aus Angst vor Nebenwirkungen eher nicht behandelt
- Depression oft als sozialer Makel empfunden
- Heutige Empfehlung: „Im Zweifelsfall eine Behandlung riskieren!“
- Viele Patienten, die oft über Monate erheblichen Leidensdruck erleben mussten, fühlen sich unter der Therapie wesentlich gebessert
- Können nach langer Zeit wieder am täglichen Leben teilnehmen und sind beruflich reintegriert.

# Antidepressiva und Interaktionen mit HAART

## SSRI

<u>Substanz</u>	<u>1A2</u>	<u>2C9/10</u>	<u>2C19</u>	<u>2D6</u>	<u>3A3/4</u>
Citalopram (Cipramil)	•	•	•	++	•
Escitalopram (Cipralex)	•	•	•	++	•
Fluoxetin (Fluctin)	•	++	++	+++	+
Fluvoxamin (Feverin)	+++	+++	+++	•	++
Sertralin (Zoloft)	•	•	•	+	•

# Prevalence of Neuromanifestations during HIV-infection

<b>Primary neuromanifestations</b>	<b>Prevalence (%)</b>
Acute HIV-meningoencephalitis	< 1
HIV-associated neurocognitive disorder	5 - 30
Distal, symmetric polyneuropathy	35 - 88
Myopathy	2 - 4
Vacuolar myopathy	5 - 15
Headache	10 - 55
<b>Secondary neuromanifestations</b>	<b>Prevalence (%)</b>
Progressive multifocal leucencephalopathy	2 - 4
Cerebral toxoplasmosis	10 - 20
Primary CNS lymphoma	2 - 3
Cerebral metastasation of systemic lymphoma	1 - 2
Stroke	1 - 2

# MRI of the Brain 14 Years following Aquisition of HIV Infection

At this time, the patient is affected by severe HIV-associated dementia accompanied by distinct atrophy and expansion of the intra- and extracerebral CSF spaces.

