Current situation of Neuropsychological Problems of HIV+ persons in Europe:

Role of the European AIDS Clinical Society

6th international symposium on neuropsychiatry & HIV, Barcelona, May 2013

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Chief physician, Center for Viral Diseases @ dept. of infectious diseases, Rigshospitalet
chief, Copenhagen HIV Programme, Panum Instituttet
Denmark

EACS
European AIDS Clinical Society

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European AIDS Clinical Society

The European AIDS Clinical Society (EACS) is a not-for-profit group of European physicians, clinicians and researchers in the field of HIV/ AIDS.

It aims to bring together scientists from all over Europe to help exchange the latest medical and scientific knowledge regarding clinical aspects of HIV/AIDS and its complications.

The main activities of the Society are:

TRAINING & SCHOLARSHIPS
EUROPEAN TREATMENT GUIDELINES
EUROPEAN CONFERENCES

14th EUROPEAN AIDS CONFERENCE
OCTOBER 16–19, 2013
BRUSSELS, BELGIUM

15th International Workshop on
Co-morbidities and Adverse Drug Reactions in HIV
15–17 October 2013, Brussels, Belgium

We are happy to announce that the 15th International Workshop on Co-morbidities & Adverse Drug Reactions in HIV will be affiliated with 2013 EACS

EUROPEAN TREATMENT GUIDELINES

Couv-v6.1-EN

NEW!
Version 6.1 – November 2012

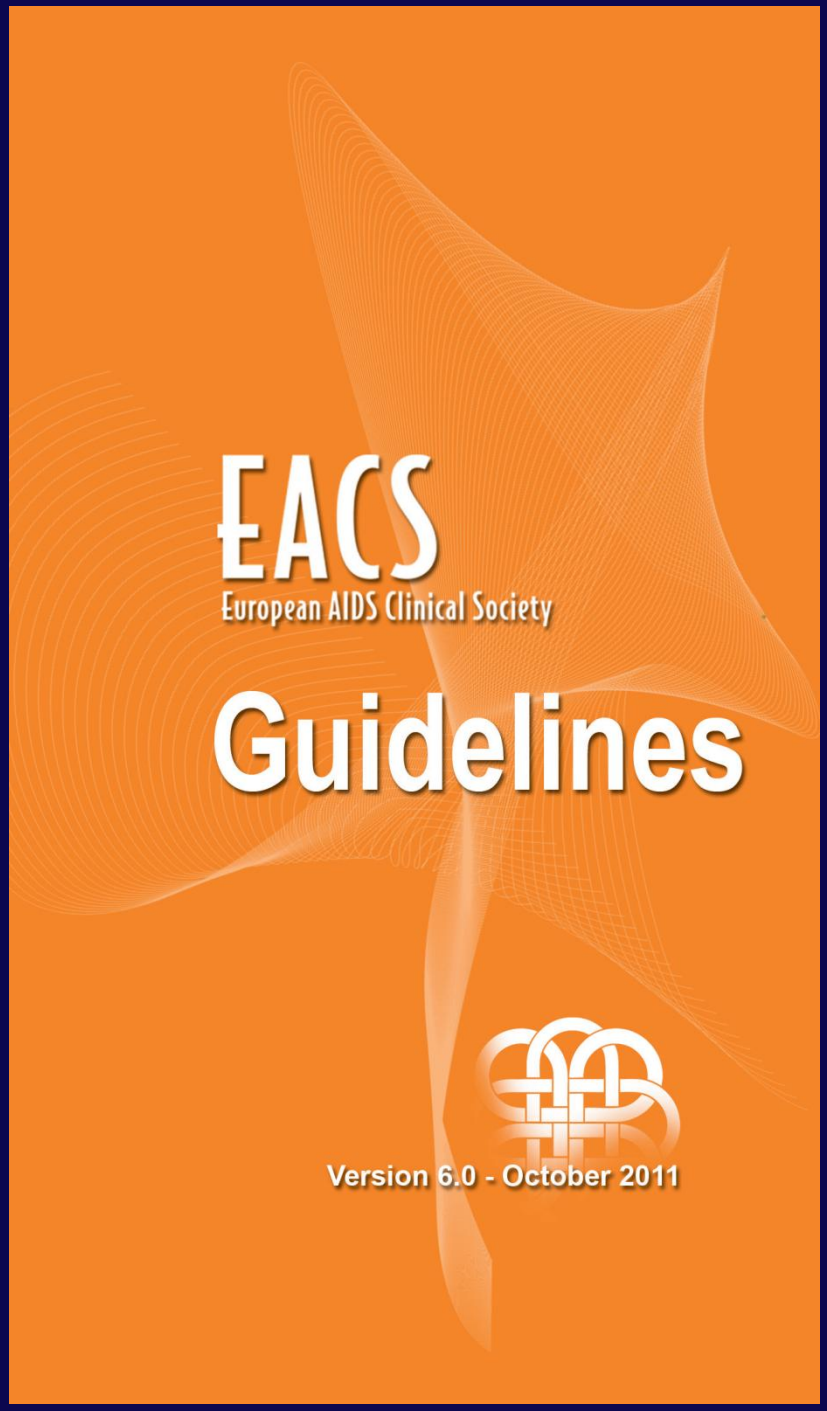
On March 5, 2013, the European Centre for Disease Prevention and Control (ECDC) published its Annual Epidemiological Report 2012 which includes data on HIV, TB and Hepatitis.

It can be found at:

http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=1069

EACS post graduate training

- Advanced course – internate – Montpellier, September – 50-60 younger MD with some/limited experience with clinical handling of HIV+ persons
- Exchange program
  - 1, 4 or 12 month stay at centres of excellence
- (e-learning)



EACS HIV Treatment guidelines :

- Antiretroviral therapy
- Co-morbidity
- Viral hepatitis
- (TB)

Panel Members

HIV Treatment

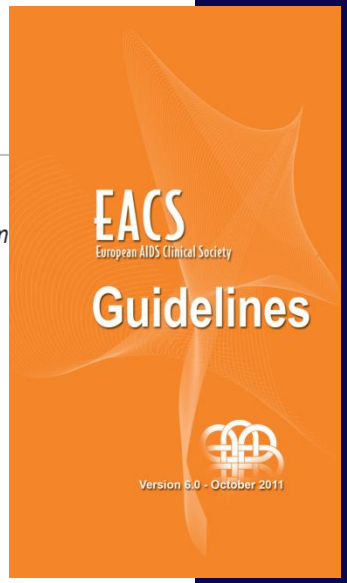
Chair: Nathan Clumeck	Brussels, *Belgium*
Antonella d'Arminio Monforte	Milan, *Italy*
José Arribas	Madrid, *Spain*
Manuel Battegay	Basel, *Switzerland*
Nikos Dedes	Athens, *Greece*
José Gatell	Barcelona, *Spain*
Anna Maria Geretti	London, *United Kingdom*
Christine Katlama	Paris, *France*
Jens D. Lundgren	Copenhagen, *Denmark*
Anton Pozniak	London, *United Kingdom*
François Raffi	Nantes, *France*

Co-morbidities

Chair: Jens D. Lundgren	Copenhagen, *Denmark*
Manuel Battegay	Basel, *Switzerland*
Georg Behrens	Hannover, *Germany*
Mark Bower	London, *United Kingdom*
Paola Cinque	Milan, *Italy*
Simon Collins	London, *United Kingdom*
Juliet Compston	Cambridge, *United Kingdom*
Gilbert Deray	Paris, *France*
Stéphane De Wit	Brussels, *Belgium*
Christoph A. Fux	Bern, *Switzerland*
Giovanni Guaraldi	Modena, *Italy*
Patrick Mallon	Dublin, *Ireland*
Esteban Martinez	Barcelona, *Spain*
Socrates Papapoulos	Leiden, *The Netherlands*
Renaud du Pasquier	Lausanne, *Switzerland*
Neil Poulter	London, *United Kingdom*
Peter Reiss	Amsterdam, *The Netherlands*
Alessandra Vigano	Milan, *Italy*
Ian Williams	London, *United Kingdom*
Alan Winston	London, *United Kingdom*

Coinfections

Chair: Jürgen Rockstroh	Bonn, *Germany*
Sanjay Bhagani	London, *United Kingdom*
Raffaele Bruno	Pavia, *Italy*
Diego García	Alicante, *Spain*
Maxime Journiac	Paris, *France*
Karine Lacombe	Paris, *France*
Stefan Mauss	Dusseldorf, *Germany*
Lars Peters	Copenhagen, *Denmark*
Massimo Puoti	Brescia, *Italy*
Vicente Soriano	Madrid, *Spain*
Cristina Tural	Barcelona, *Spain*



Acknowledgements: the EACS guidelines panels received helpful comments and suggestions from the following: T Brown, D Burger and C Marzolini

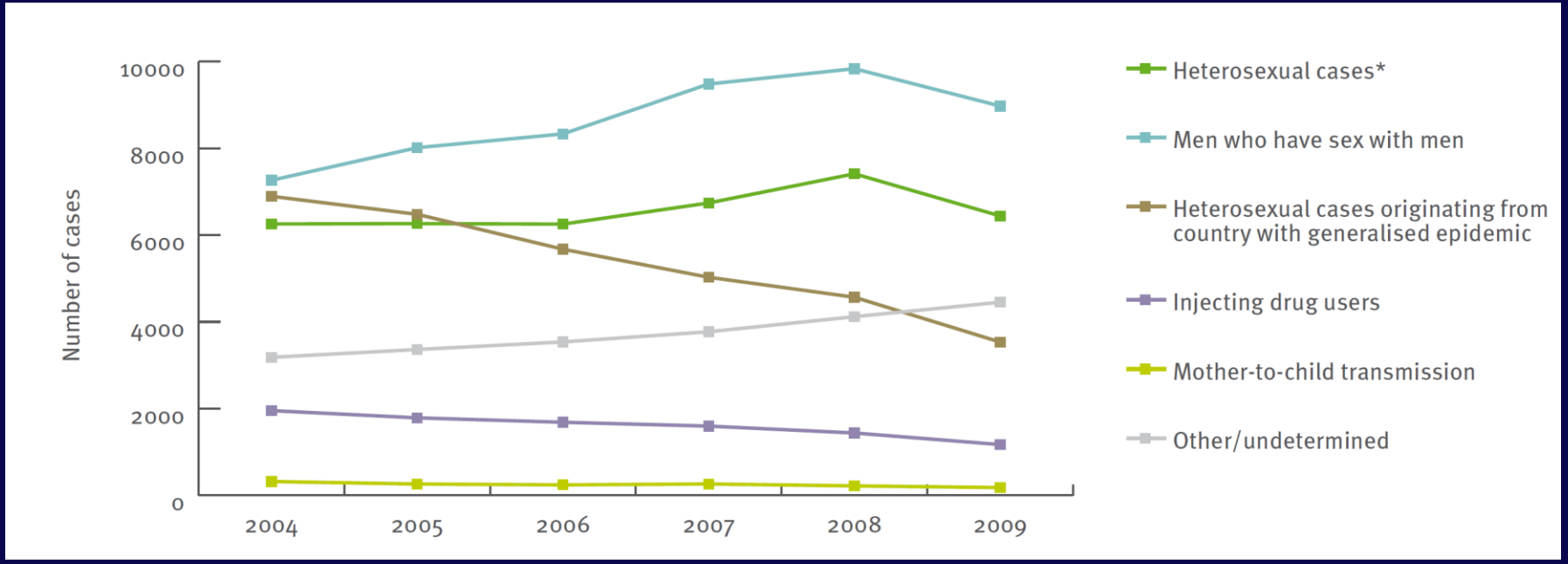
Process:

- Ongoing evaluation
- Paper version biannually
- Online update as needed
- Panel members – co-morbidities
  - HIV expertise
  - Non-HIV disease expertise
- Latest update in 2011 – updated version to be relased in Oct 2013

Purpose of guidelines

- Easy-to-use guidance on day-to-day handling of HIV+ persons in HIV clinics
  - Identify situations where disease-specific expertise is recommended
- Reference of HIV-specific issues
  - differential diagnosis,
  - Treatment of most frequent co-morbidities incl preferred drug regimens and drug-drug interactions etc
- Guidelines are developed by cross-continent panels and widely used
  - translated into 10 languages

Number of new HIV cases diagnosed in EU, EEA/EFTA from 2004-2009



HIV epidemic
In Eastern
Europe/
Central Asia
(= app FSC):
1990
to
2010

Fig. 2.21 Number of people living with HIV, Eastern Europe and Central Asia, 1990–2010

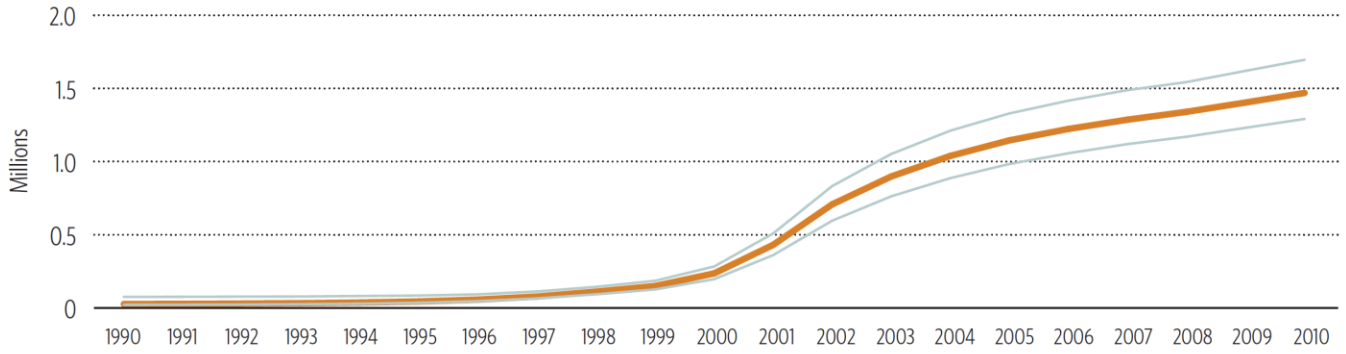


Fig. 2.22 Number of people newly infected with HIV, Eastern Europe and Central Asia, 1990–2010

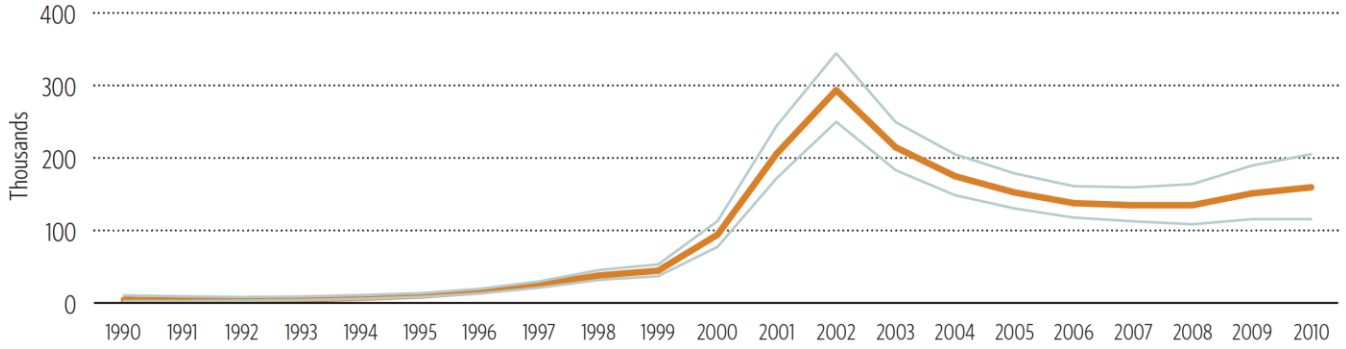
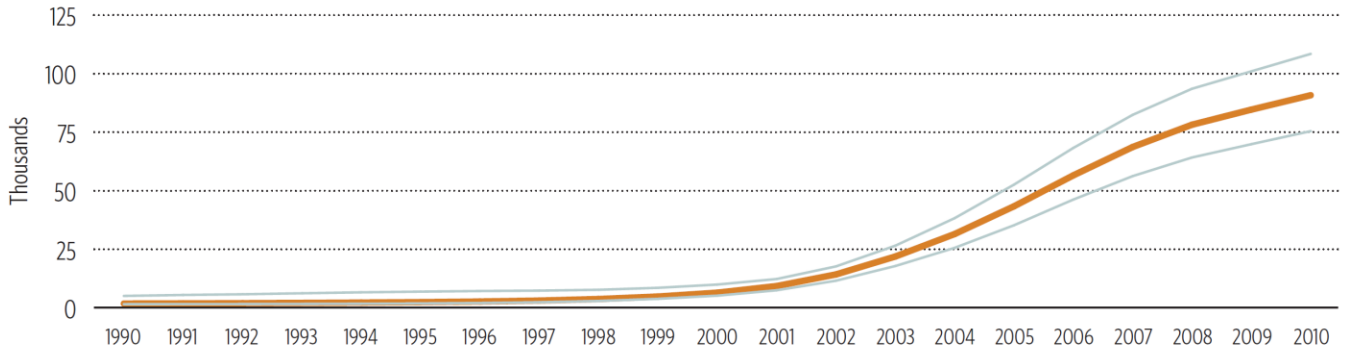
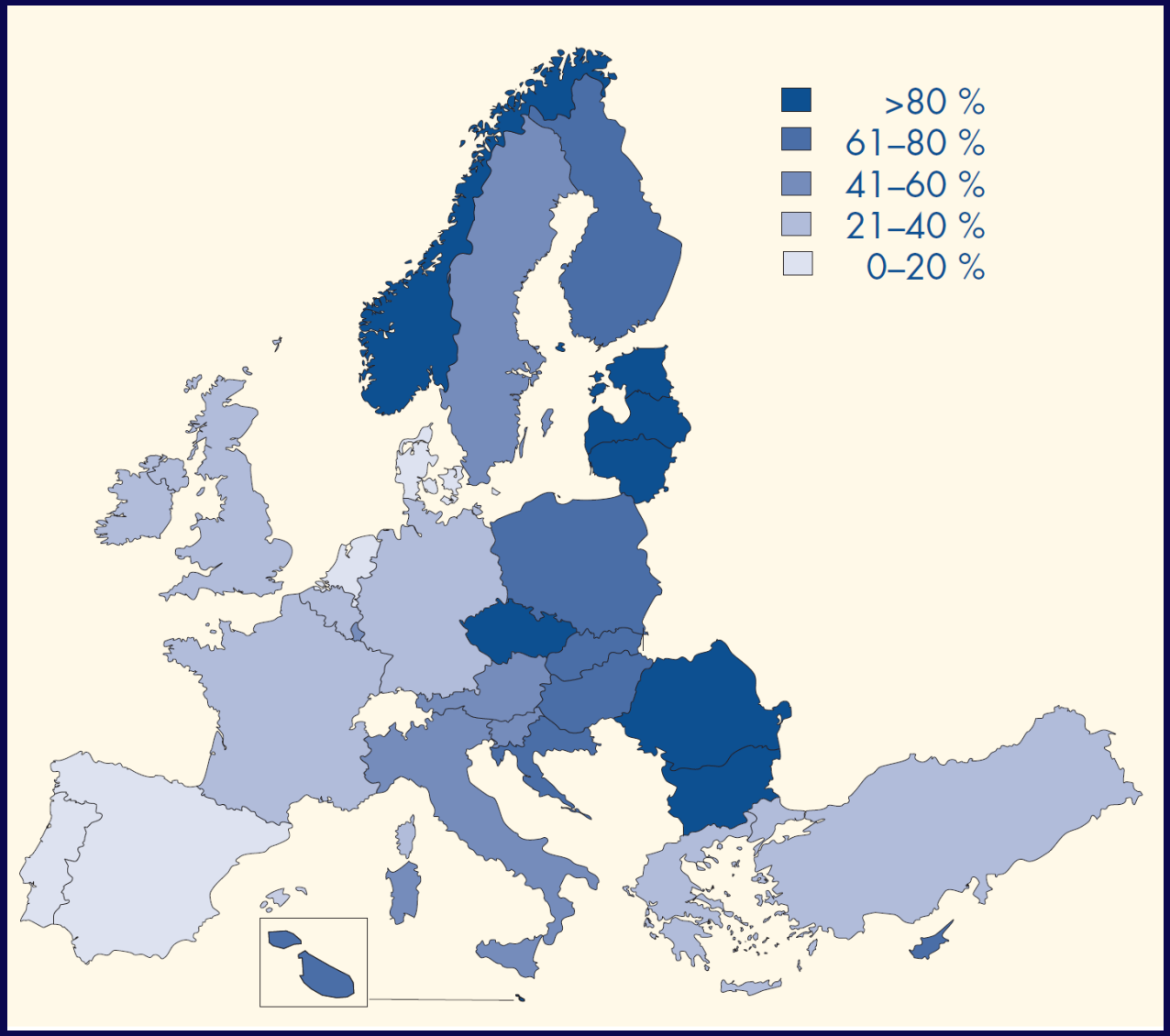


Fig. 2.23 Number of people dying from AIDS-related causes, Eastern Europe and Central Asia, 1990–2010



Injecting as usual mode of administration of heroin among persons entering treatment in 2010



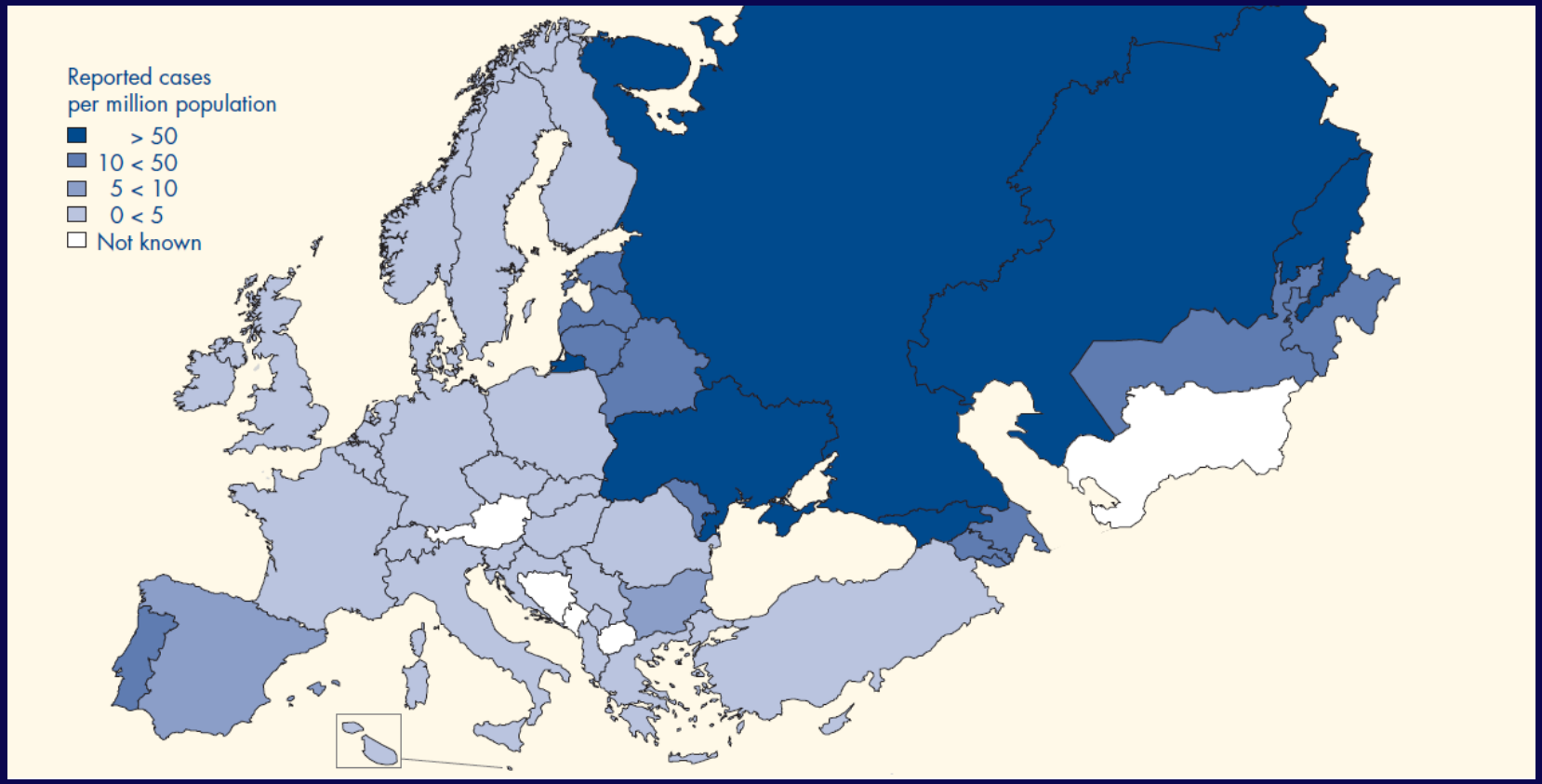
EMCDDA 2012

22×

People who inject drugs have 22 times the rate of HIV infection as the general population in 49 countries with available data.

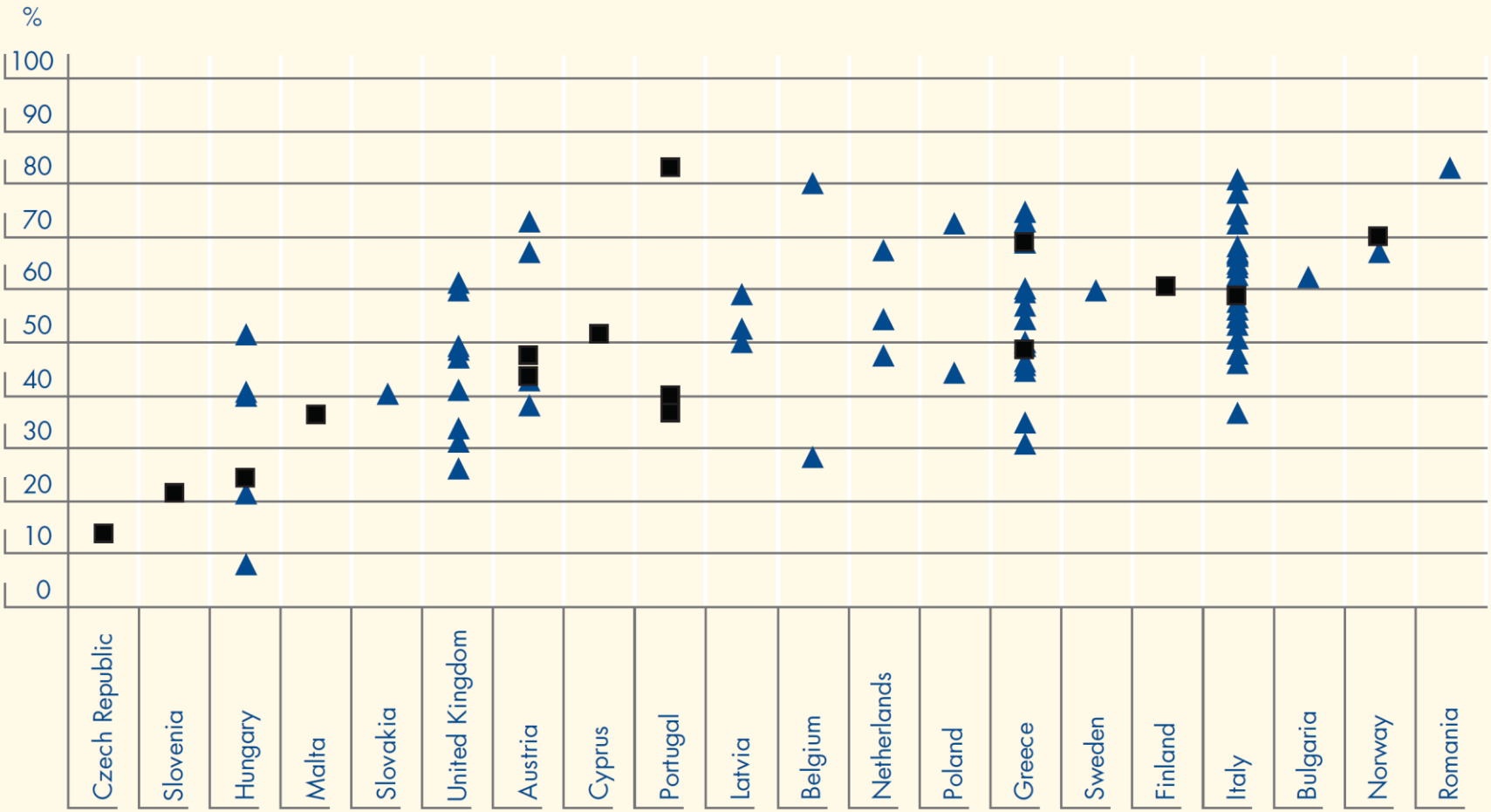
WHO, 2011

Incidence of IDU-related HIV diagnosis in 2010 across Europe



Outbreaks of IDU-related HIV infection in Greece and Romania (2011-2012)

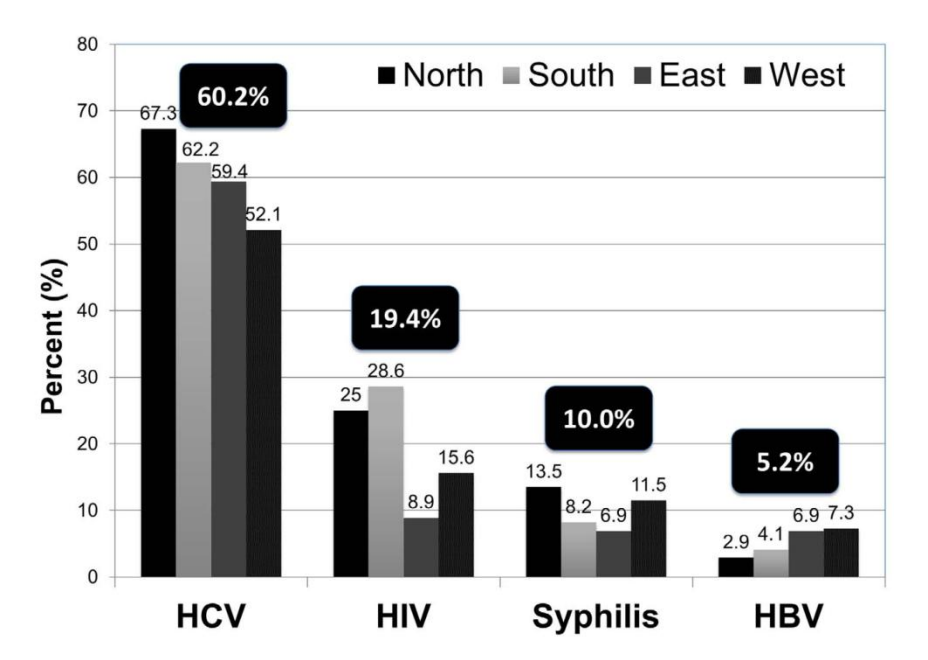
HCV prevalence among IDU's

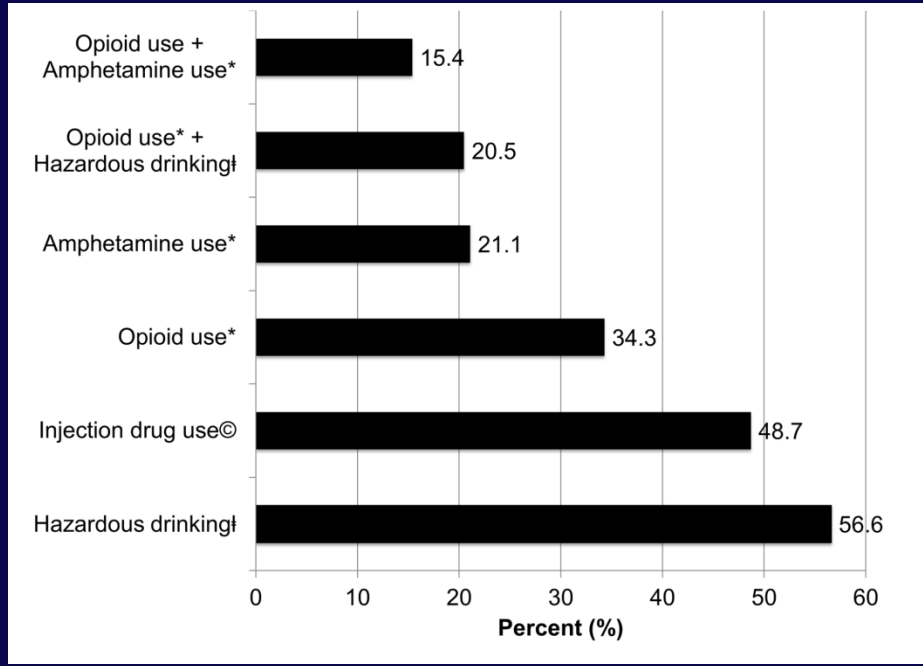


EMCDDA 2012

Burden of Infectious Diseases, Substance Use Disorders, and Mental Illness among Ukrainian Prisoners Transitioning to the Community

Lyuba Azbel[1,2], Jeffrey A. Wickersham[2], Yevgeny Grishaev[1], Sergey Dvoryak[1], Frederick L. Altice[2,3]*

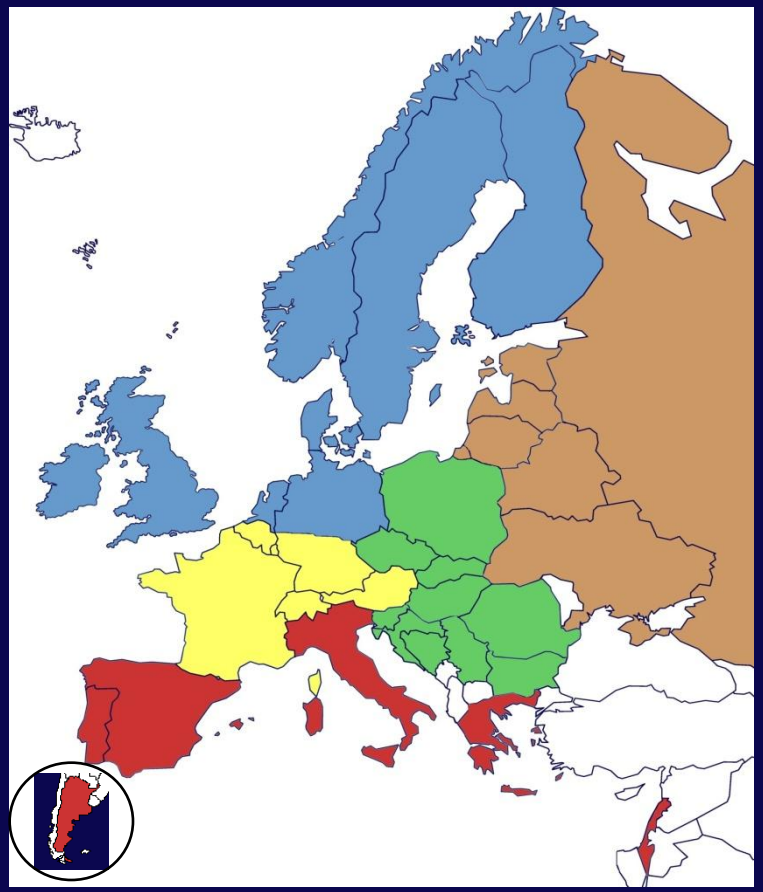




Criminal to ingest illicite drugs

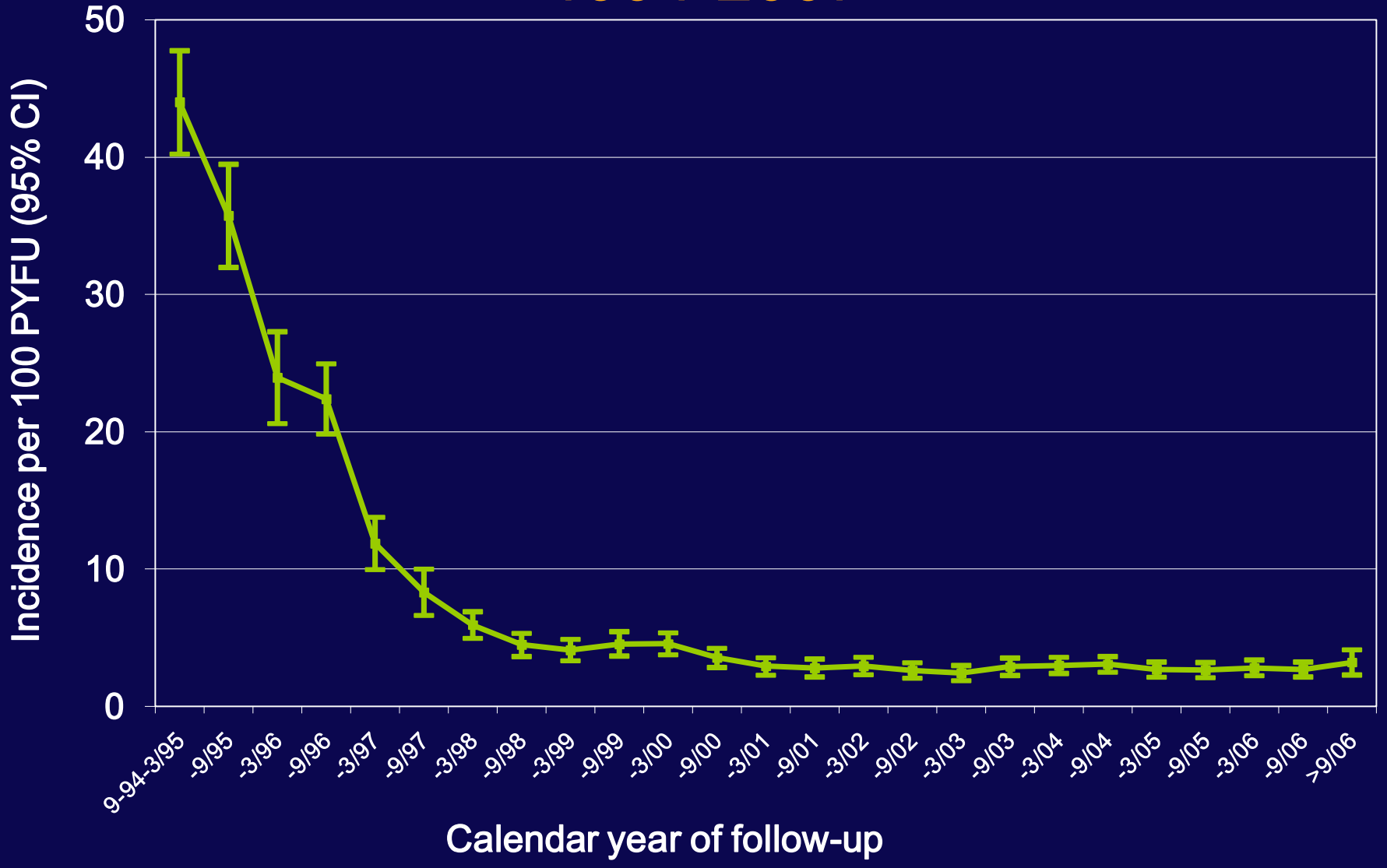
EuroSIDA

EuroSIDA is a large prospective cohort with 16597 patients from 33 European countries, Israel and Argentina. Regularly collecting:



- HIV transmission risk group
- CD4 counts, HIV viral loads
- All treatment start/stop dates
- Clinical AIDS events
- Non-AIDS events (since 2001)
- Deaths and causes of death

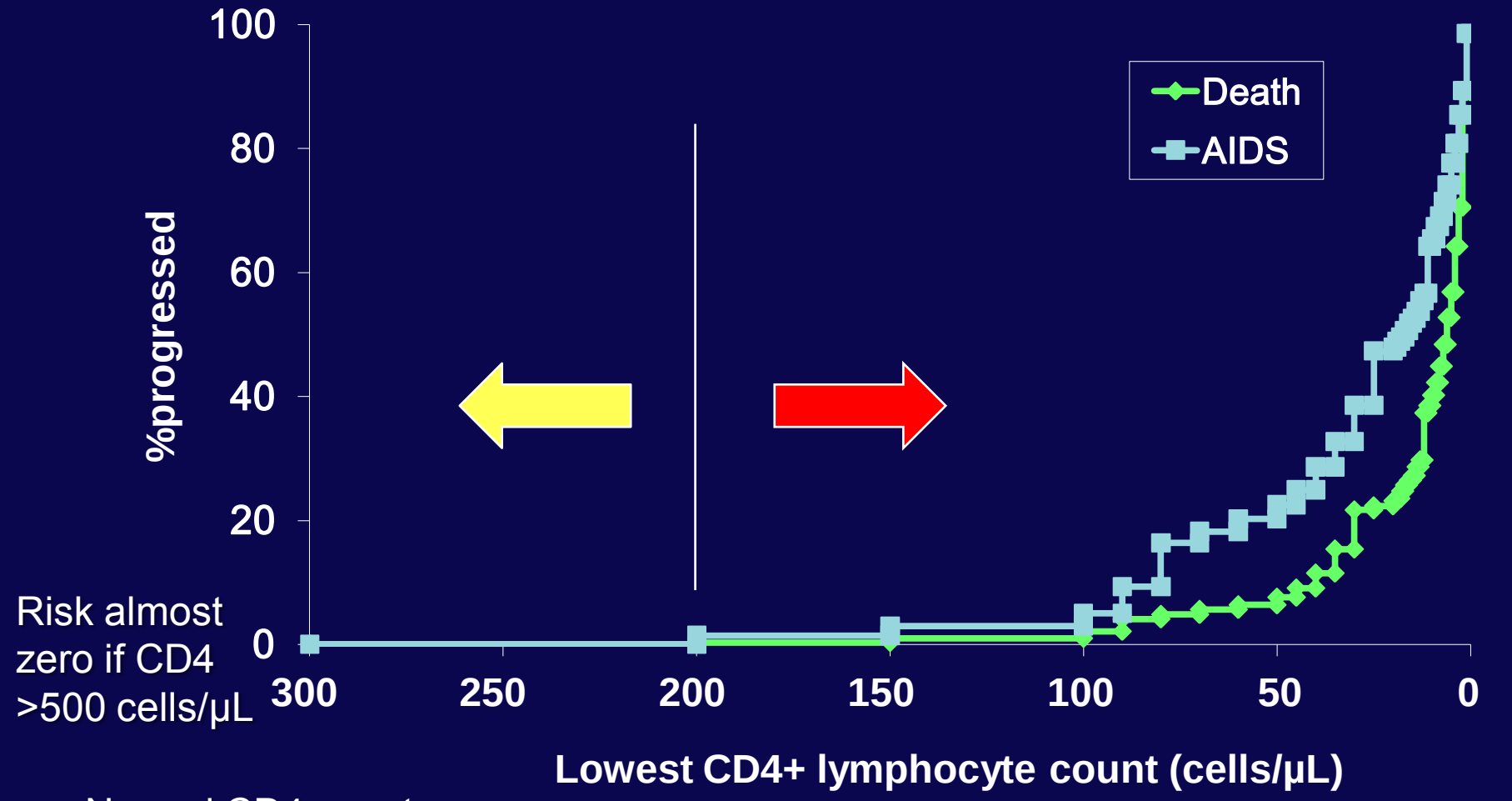
Incidence of AIDS or death in EuroSIDA 1994-2007



COPENHAGEN HIV PROGRAMME

Update of: Mocroft *et al*, Lancet 1998, 2000 & 2003

Risk of disease progression and lowest CD4 count: the cushion and the red zone

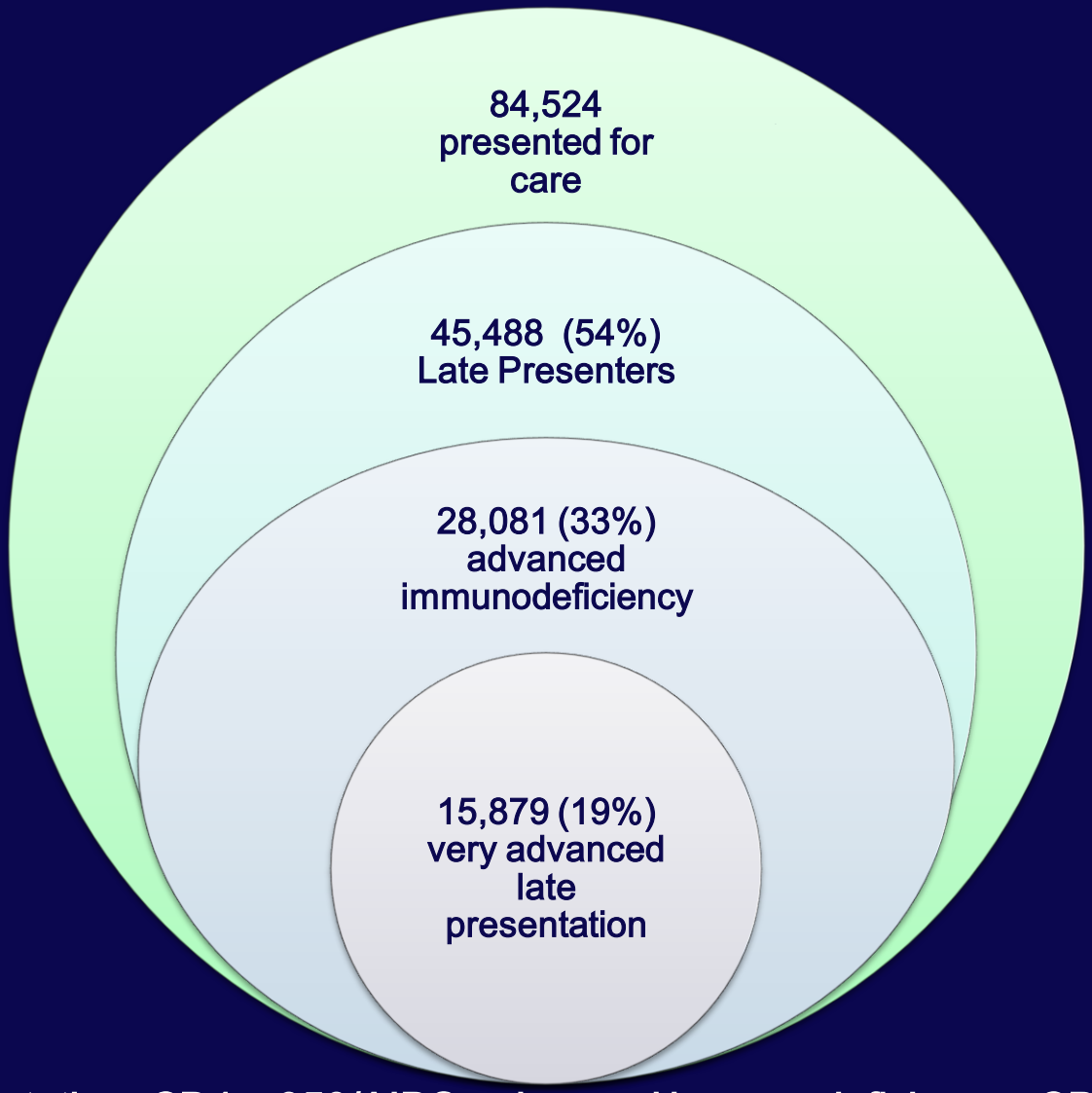


Risk almost zero if CD4 >500 cells/µL

Normal CD4 count : 600-1200 cells/µL

EuroSIDA

Late presenters across Europe



In last decade:
Decrease of
4% (95% CI: 3-5)
/ calendar year

Late presentation=CD4 < 350/AIDS; advanced immunodeficiency : CD4 < 200/AIDS;
very advanced late presentation: CD4 < 50/AIDS

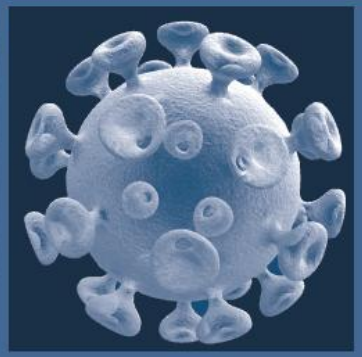
COHERE: Lundgren *et al*, WAC 2012

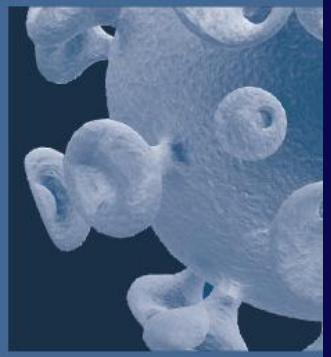
Late presentation deprives benefits from ART and hence impact adversely on health for HIV+ person & allows inadvertent onward transmission

Solution – more effective strategies:

- to test population
- ensure better access to care for those diagnosed

(varies largely by region)





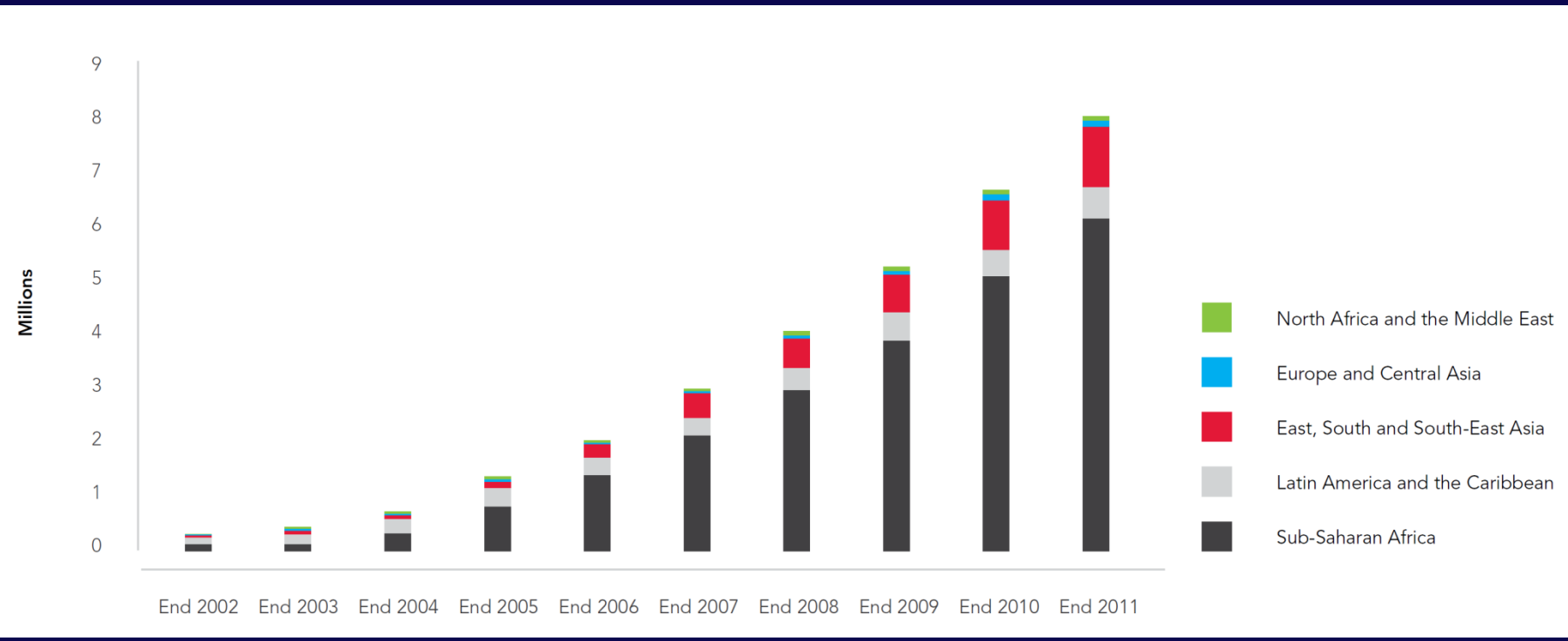
Guidance

on implementation and use of indicator condition-guided HIV testing (2012)

COPENHAGEN HIV PROGRAMME

Can be accessed on HIV In Europe website

Number of persons on ART in ressource-limited settings



UNAIDS, 2012

Recommendations for initiation of ART in HIV-positive persons without prior ART exposure[(i)]

Condition	Current CD4+ lymphocyte count [(ii,iii)]	
	350-500	>500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C

i The consideration to start ART may be individualized regardless of CD4 count and plasma HIV RNA level, especially if a patient is requesting ARV therapy and ready to start, and/or for any other personal reasons. **In serodiscordant couples early initiation of ART as one aspect of the overall strategy to reduce HIV transmission to the seronegative partner should be considered and actively discussed.**

Time should be taken to prepare the patient, in order to optimize compliance and adherence.

Genotypic resistance testing and subtype determination is recommended prior to initiation of ART; ideally at the time of HIV diagnosis, otherwise before initiation of ART. If genotypic testing is not available, it is recommended to include a ritonavir-boosted PI in the first-line regimen.

Before starting treatment, the HIV RNA level and CD4 count should be repeated to obtain a baseline to assess subsequent response.

ii **ART is always recommended in any HIV-positive person with a current CD4 count below 350 cells/μL.**

iii **C**=use of ART should be considered; for patients under these circumstances some experts would recommend starting ART, whereas others would recommend deferral of ART; this clinical equipoise reflects that whereas certain evidence supports starting ART this needs to be balanced against the risk of known or undiscovered adverse drug reactions from use of ART, and hence the risk/benefit ratio for use of ART under these circumstances has not yet been well defined.

D=defer initiation of ART.

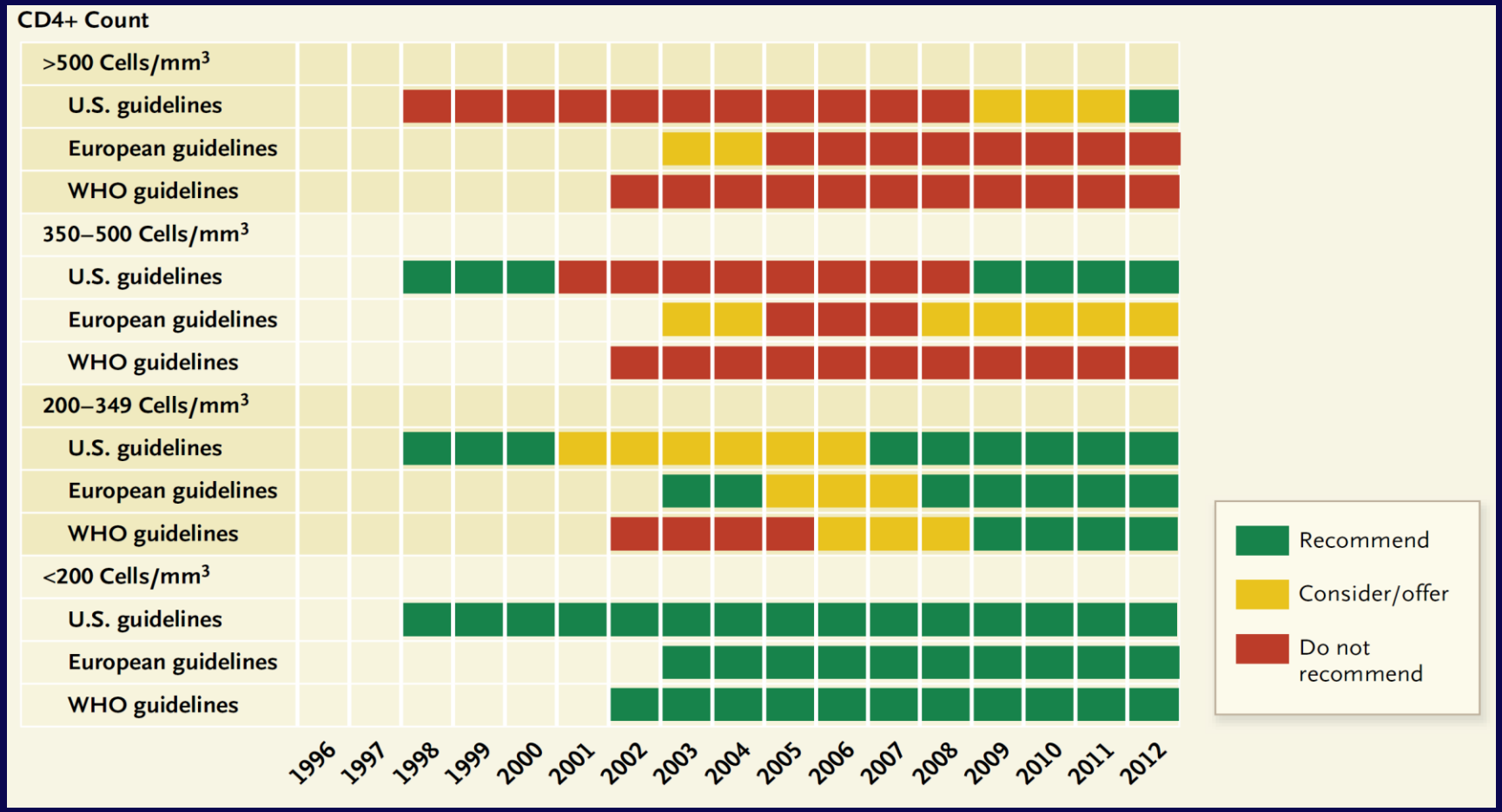
R=use of ART is recommended.

iv Initiation of ART is recommended in those who are HBeAg-positive

v Initiation of ART is recommended to optimize the outcome of HCV treatment

vi HCV treatment to attempt eradication of HCV should be prioritized and ART deferred

Guidelines change but not in syncrony



De Cock & El-Sadr, NEJM 2013

Characteristics at entry and deferral strategies from RCTs comparing deferred vs. immediate initiation of ART in ART-naive HIV+ persons

Study	Sample size	Median baseline CD4 count (cells/ μL)	Deferral Strategy	Median CD4 count at ART initiation in the deferred arm
SMART	249	437	ART deferred until: 1. CD4 declined to < 250 cells/μL 2. CD4 percentage declined to < 15% 3. Symptoms of HIV disease developed	245
CIPRA HT-001	816	281	ART deferred until: 1. CD4 declined to ≤ 200 cells/μL 2. AIDS-defining illness developed	166
HPNT 052	1761	428	ART deferred until: 1. CD4 declined to ≤ 250 cells/μL 2. AIDS-defining illness developed	229

Impact of immediate vs. deferred initiation of ART on mortality and TB: 3 RCTs in ART-naive HIV+ persons

Study	Deaths early ART initiation[a] arm	Deaths deferred ART initiation[b] arm
SMART	0/131	1/118
CIPRA HT-001	6/408	23/408
HPNT 052	10/ 886	13/877
Pooled data from the 3 trials	16/1425	37/1403
HR (early vs deferred) - deaths	57% (95% CI: 86%-23%)	
HR (early vs deferred) - TB	49% (95% CI: 66%-24%)	

[a] Early ART initiation defined as start of ART at CD4> 350 cells/µL

[b] Deferred ART initiation defined as start of ART at CD4 <200 or <250 cells/µL

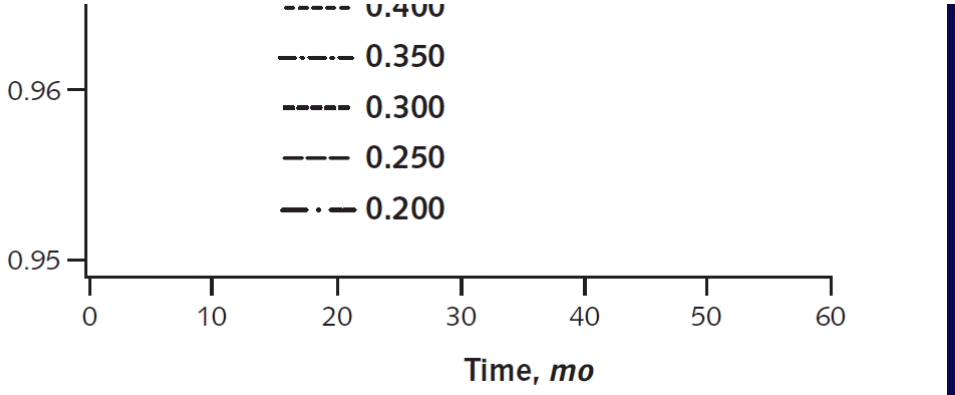
Survival after ART initiated at different CD4 count levels between 200-500: ”causal” modelling

Prop
surv

Implication

Randomized, controlled trials are needed to better define the optimal time of initiation of combined antiretroviral therapy in HIV infection.

—*The Editors*



The HIV-CAUSAL Collaboration, Ann Intern Med 2011

Strategic Timing of Anti-Retroviral Treatment (START) study

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Early ART Group

Initiate ART immediately following randomization

N=2,300

Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=2,300

Primary endpoint: Serious AIDS & serious non-AIDS disease (213)

START Neurology Substudy

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3
N=600 at 36 sites (608 or 101% accrued)

Early ART Group

Initiate ART immediately following randomization

N=300

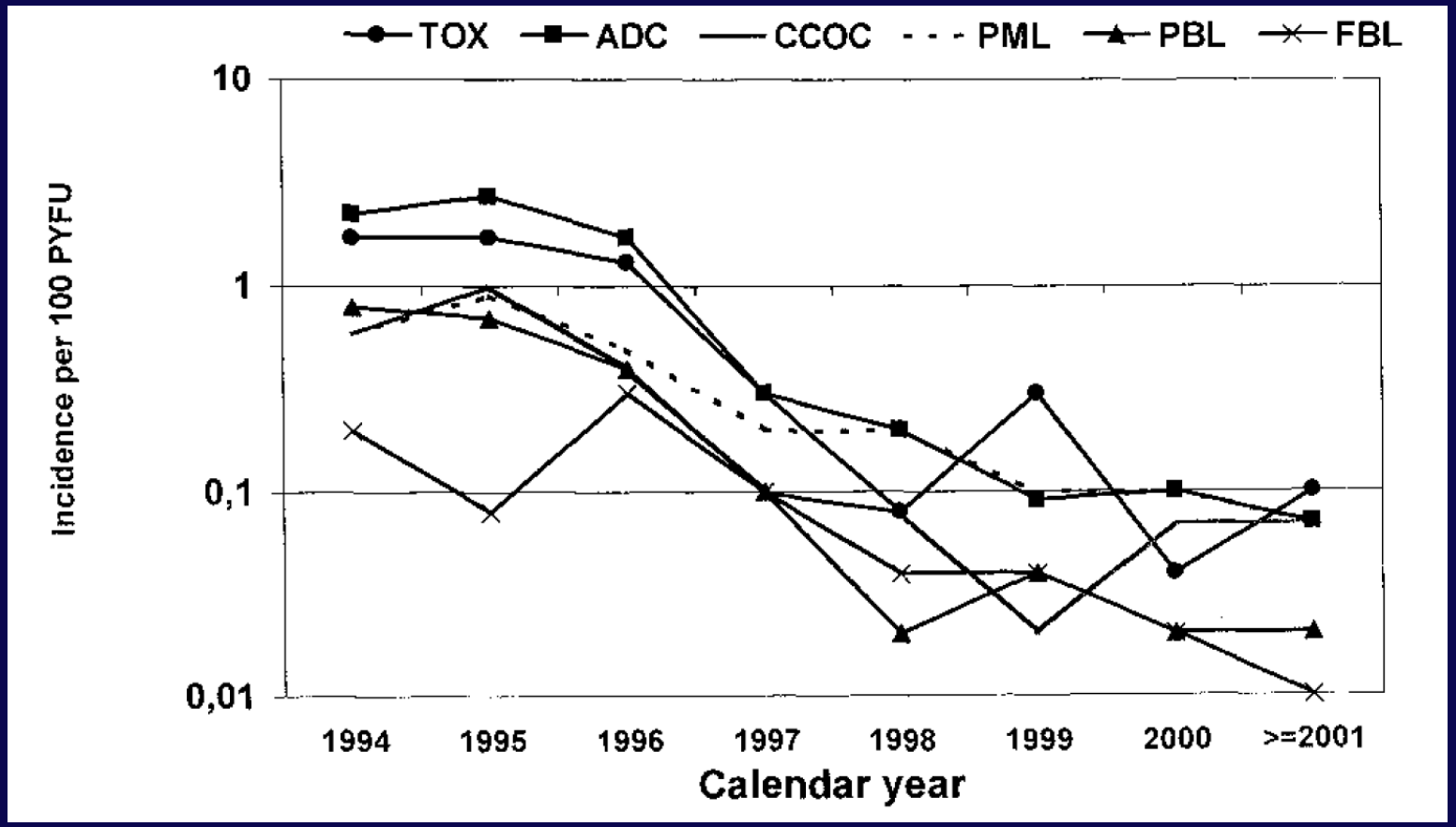
Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=300

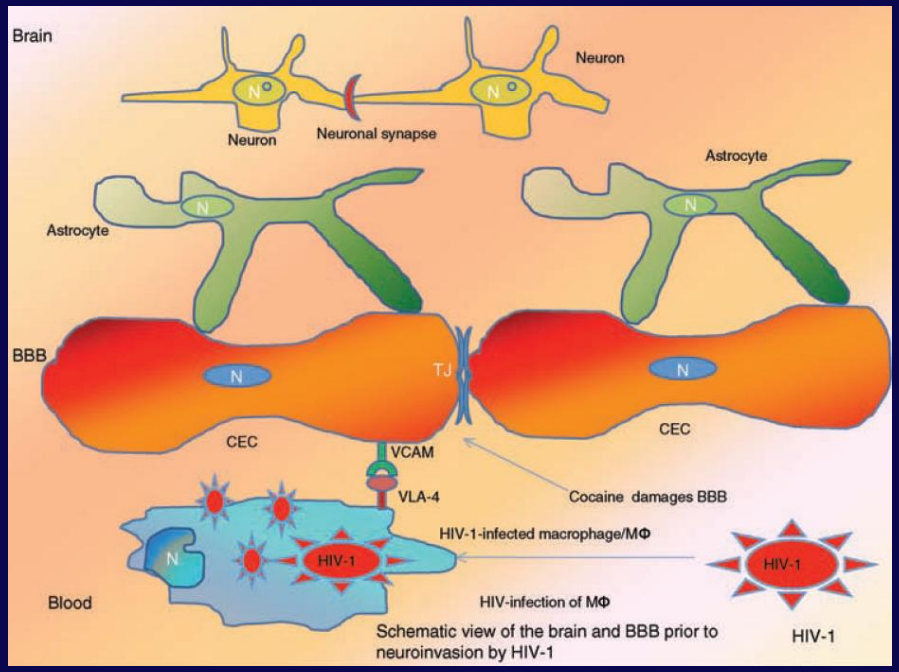
Changing Incidence of Central Nervous System Diseases in the EuroSIDA Cohort

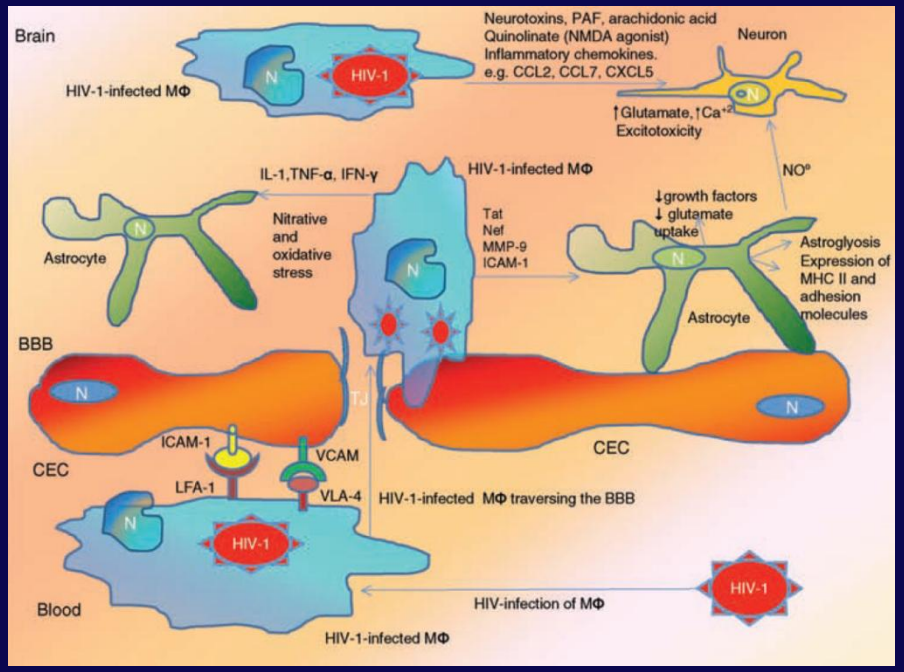
Antonella d'Arminio Monforte, MD,[1] Paola Cinque, MD,[2] Amanda Mocroft, PhD,[3] Frank-Detlev Goebel, MD,[4] Francisco Antunes, MD,[5] Christine Katlama, MD,[6] Ulrik Stenz Justesen, MD,[7] Stefano Vella, MD,[8] Ole Kirk, MD,[9] and Jens Lundgren, MD,[9] for the EuroSIDA Study Group



Monforte et al, Ann Neurology 2004

Blood-brain barrier before (left) and after (right) HIV infection

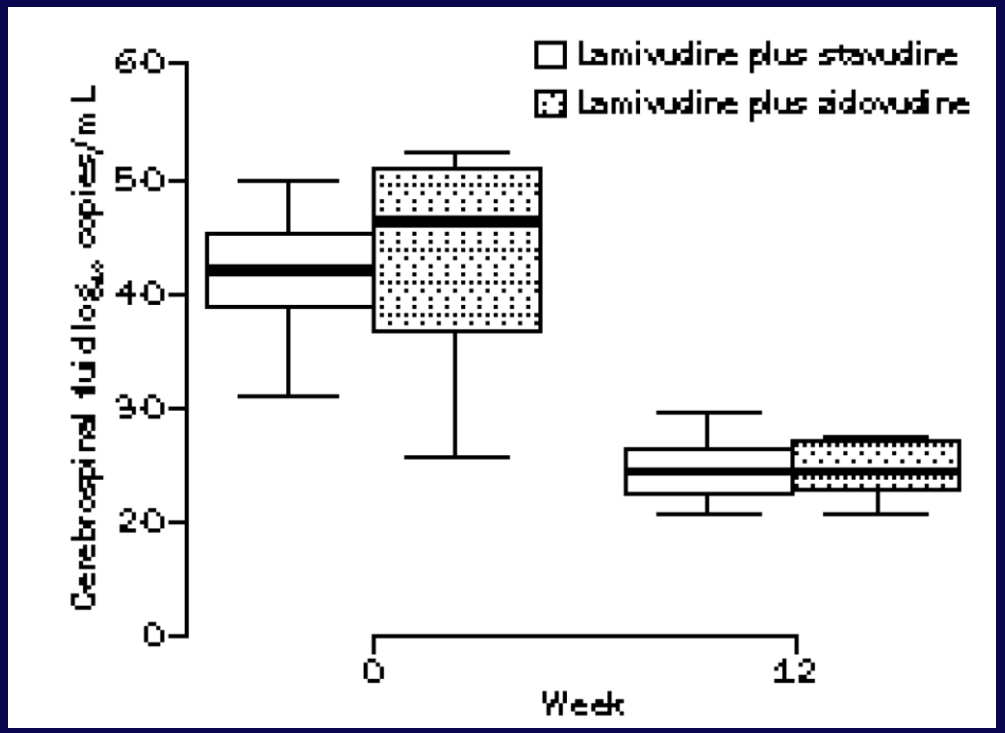


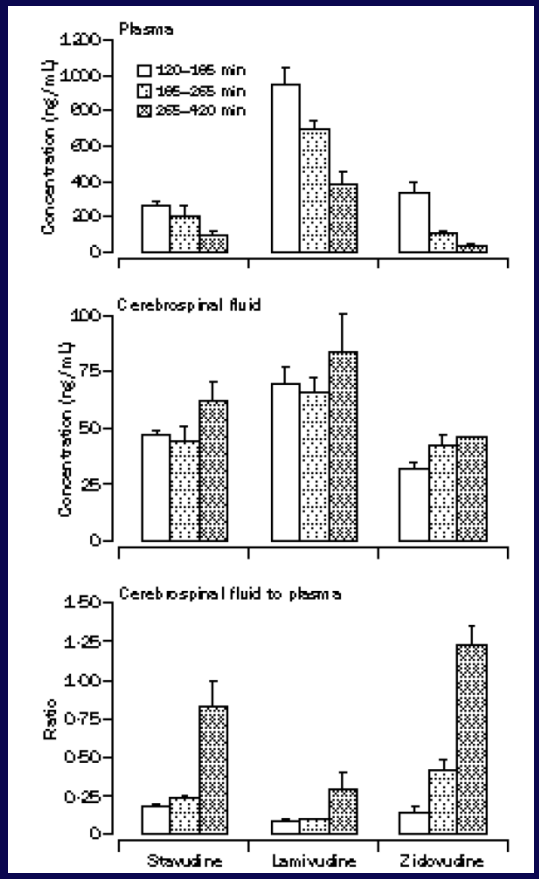


Shapshak et al, AIDS 2011

Cerebrospinal-fluid HIV-1 RNA and drug concentrations after treatment with lamivudine plus zidovudine or stavudine

Norbert A Foudraine, Richard M W Hoetelmans, Joep M A Lange, Frank de Wolf, Birgit H B van Benthem, Jaap J Maas, Ireneus P M Keet, Peter Portegies





Foudraine et al, Lancet 1998

Contemporary challanges in HIV care

- Interval between visit to HIV clinics increases
  - GP more involved in care
  - Requires clear guidance and delegation of responsibility
- Extensive list of screening for comorbidities is recommended
- Polypharmacy, pill burden, and drug-drug interactions
- Prioritisation of care – differentiate between
  - Standard-of-care – supported by solid evidence
  - Experimental considerations not supported by solid state-of-the-art evidence using appropriate research methodology

Drug levels of anti-depressant affected by ARVs:

Need for collaboration between psyciatry and HIV medicine

	antidepressants	ATV/r	DRV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL
SSRI	citalopram	↑[a]	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↔
	escitalopram	↑[a]	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↓39%	↑↓?	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↓	↓49%	↓	↓	↓39%	↓	↓	↔	↔	↔
SNRI	duloxetine	↑↓	↑↓	↑↓	↑↓	↔	↔	↔	↔	↔	↔
	venlafaxine	↑	↑	↑	↑	↓	↓	↓	↔	D	↔
TCA	amitriptyline	↑	↑	↑	↑[b]	↔	↔	↔	↔	↔	↔
	clomipramine	↑	↑	↑	↑[b]	↓	↓	↓	↔	↔	↔
	desipramine	↑	↑	↑5%	↑	↔	↔	↔	↔	↔	↔
	doxepin	↑	↑	↑	↑[b]	↔	↔	↔	↔	↔	↔
	imipramine	↑[a]	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↔
	nortriptyline	↑[a]	↑	↑[a]	↑[ab]	↔	↔	↔	↔	↔	↔
	trimipramine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	mianserine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
Others	bupropion	↓	↓	↓57%	↓	↓55%	↔	↓	↔	↔	↔
	lamotrigine	↓32%	↓	↓50%	↓	↔	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↓	↓E	↓	E	E	↔
	St John's wort	D	D	D	D	D	D	D	D	D	↔
	trazodone	↑	↑	↑	↑[b]	↓	↓	↓	↔	↔	↔

Colors legend:

- no clinically significant interaction expected.
- these drugs should not be coadministered.
- potential interaction which may require a dosage adjustment or close monitoring.
- potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment

Consensus on knowledge of neurological disease in HIV

- Untreated advanced HIV associated with several types of CNS disease incl AIDS dementia
  - Symptomatology incl NCI, depression, anxiety, hallucinations, etc
- ART effectively prevents the emergence of and revert symptomatic CNS disease

Comtemporary CNS-related disease in HIV

- Multiple differential diagnoses
- Increased prevalence – relative to general population
  - Depression *
  - 3rd stage syphilis *
  - Illicit drugs inducing anxiety, NCI, hallucinations, depression etc*
- HIV-specific issues
  - Residual irreversible CNS impairment from resolved opportunistic disease caused by late presentation
  - Adverse drug reactions from ARV's and anti-HCV tx*
  - NCI caused by residual ongoing HIV replication ?

*: solid evidence that specific medical intervention is of benefit

Prevalence of depressive symptoms

2175 HIV+ in routine care: cross sectional study in the UK

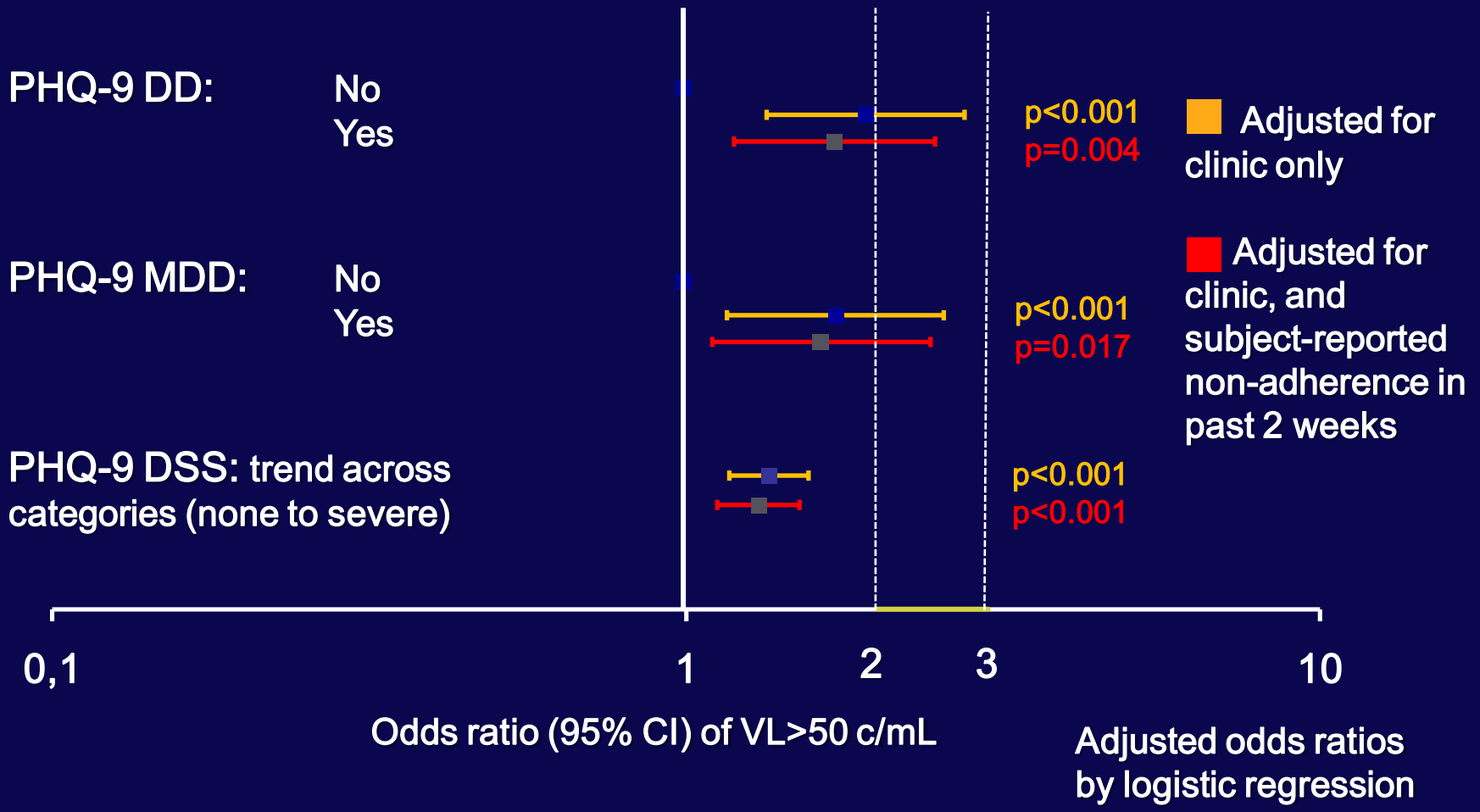
N=2175	n	Prevalence (95% CI)	Prevalence comparison
PHQ-9: DD (Depressive disorder)	579	26.6 % (24.8 %, 28.5 %)	General population (Germany)[1]: 9%
PHQ-9: MDD (Major depressive disorder)	415	19.1 % (17.4 %, 20.7 %)	General population (Germany)[1]: 4% Primary care (Netherlands)[2]: 5%
	n	%	
PHQ-9: DSS (Depression severity score)			General population (England)[3]: PHQ-9 DSS score ≥ 10: 7% Primary care (Netherlands)[2]: PHQ-9 DSS score ≥ 10: 11%
None (0)	411	18.9 %	
Minimal (1-4)	729	33.5 %	
Mild (5-9)	448	20.6 %	
Moderate (10-19)	444	20.4 %	
Severe (≥ 20)	143	6.6 %	
	587	27.0%	

[1]Martin et al. General Hospital Psychiatry 2006; 28: 71
[2]Zuithoff et al. BMC Family Practice 2010; 11: 98
[3]Paranjothy et al. BMC Public Health 2011; 11: 145

Lampe *et al*, BHIVA, 2012

Viral load non-suppression on ART by depressive symptom status

N=1618 participants who started ART ≥ 6 months ago; n=144 with VL>50 c/mL



ASTRA study: Lampre *et al*, BHIVA, 2012

Depressive symptoms and current treatment for depression

PHQ-9 Depressive Disorder status	Current treatment for depression?*	N
PHQ-9 DD (N=579	YES NO	241 338
No PHQ-9 DD (N=1596)	YES NO	200 1396
TOTAL		2175

*Medicine or other therapy for depression

- Total prevalence of depression (treatment or symptoms): 35.8% (779/2175)
- Of all participants with evidence of depression,

  43.4% (338/779) were not receiving any treatment for depression

ASTRA study: Lampre *et al*, BHIVA, 201

Terminology: HIV-associated neurocognitive disorder (HAND)

HAND	HIV Associated Neurocognitive Disease	Umbrella definition comprising ANI, MND and HAD
ANI	Asymptomatic Neurocognitive Impairment	Cognitive impairment (at least 1 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment does not interfere with everyday functioning.
MND	Mild Neurocognitive Disorder	Cognitive impairment (at least 1 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment produces at least mild interference in daily functioning.
HAD	HIV Associated Dementia	Marked cognitive impairment (at least 2 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment produces marked interference with day-to-day functioning.
ADC	AIDS Dementia Complex	Former term of HAD
MCMD	Minor Cognitive Motor Disorder	Former term of ANI and MND combined

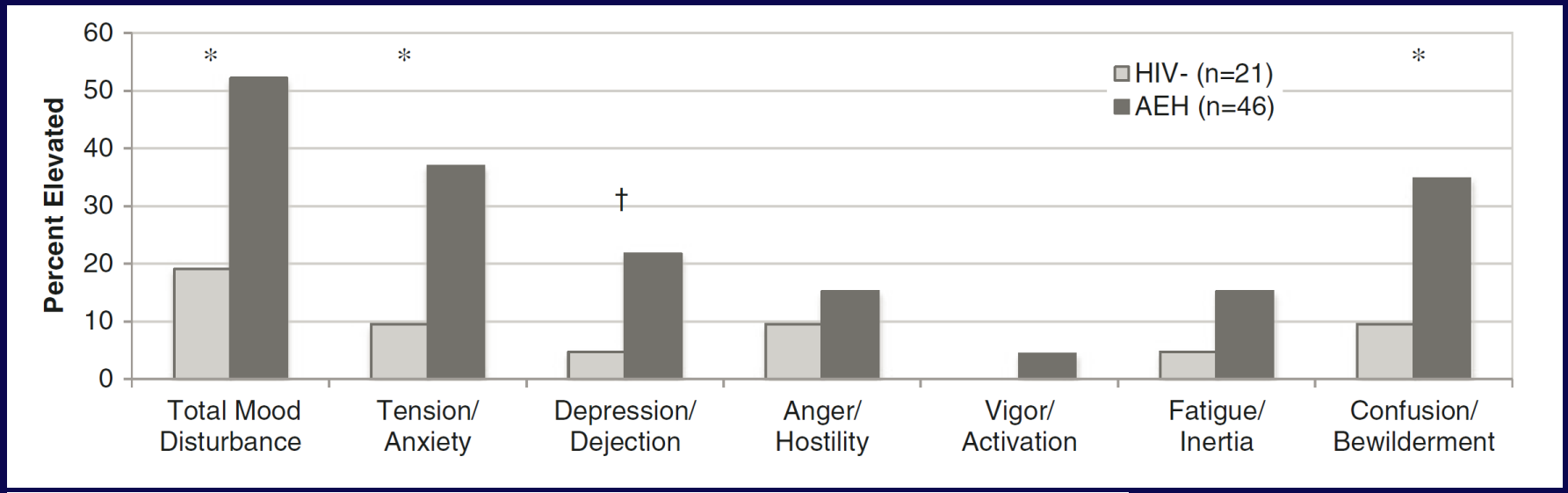
HAND subtype	Neuropsychological profile	Functional impairment
Asymptomatic neurocognitive impairment (ANI)	Acquired impairment in at least two domains (1SD below age–education norms)	None
Mild cognitive impairment (MND)	Acquired impairment in at least two domains (<1SD)	Mild interference in functioning (a) self-report—for example, reduced mental acuity, inefficiency at work and/or (b) observations by knowledge others
HIV-associated dementia (HAD)	Acquired impairment in at least two domains (typically in multiple domains) with at least two domains with severe impairment (<2SD)	Marked interference with daily functioning (work, home life, social activities)

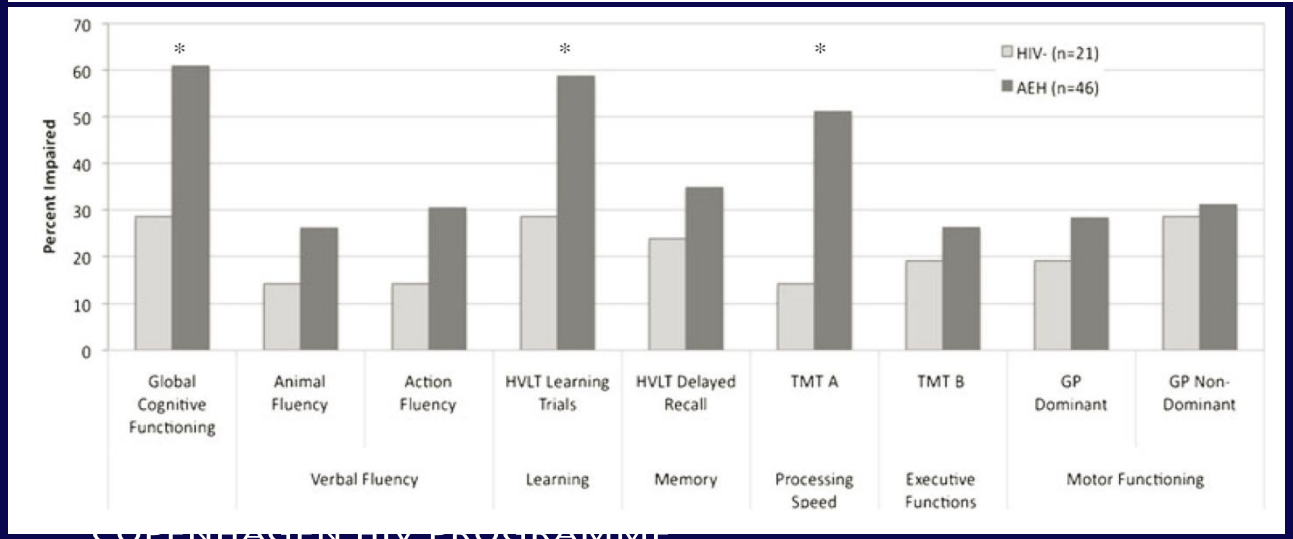
Caveats -

- Cognitive impairment does not meet criteria for delirium.
- There is no evidence of another pre-existing cause of dementia (central nervous system (CNS) infection, neoplasm, cerebrovascular disease, pre-existing neurological disease or severe substance abuse compatible with a CNS disorder.
- The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstract/executive; memory (learning, recall); speed of information processing; sensory-perceptual motor skills.

Manji et al JNNP, 2013

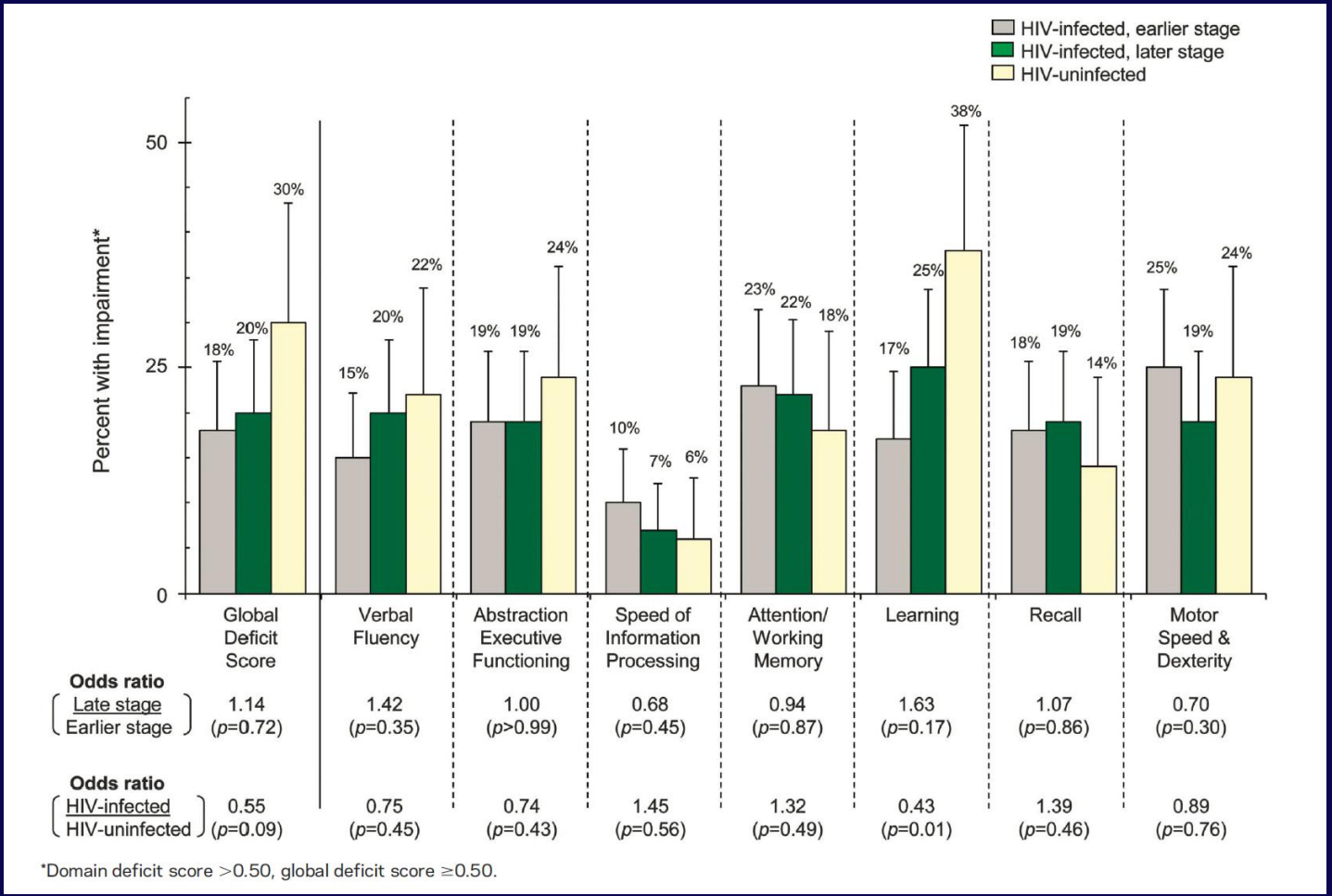
Selfreported neuropsychiatric distress among HIV- vs acute/early HIV+ (CSS)





TMARC study:
Weber et al
J Neurovirol 2013

Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons



N=200 (HIV+) and 50 (HIV-)
Cross sectional study

COPENHAGEN HIV PROGRAMME

Crum-Cianflone *et al*, Neurology 2013

Acceptance of being HIV+, stigma, THE scare

- HIV+ status not well accepted in society
  - stigmatization
- Risk of transmission to HIV neg partner
- Illicit drug use
- Research hypothesis articulated as facts creates scary scenarios
  - ”accelerated aging”
  - Long-term adverse outcomes from ARV’s
  - HAND

Factors associated with symptomatic neurocognitive disorders in HIV+

Characteristic ($n = 369$)	Separate multivariable models: Initial model Odds ratio	Initial model P	Final model Odds ratio	Final model [95% CI]	Complete multivariable model: Initial model Odds ratio	Initial model P	Final model Odds ratio	Final model [95% CI]
HIV-infection-related variables								
AIDS stage								
No AIDS stage	1	0.013	1		1	0.032	1	
AIDS stage (except for neuroAIDS)	1.41		1.37	[0.79;2.37]	1.34		1.53	[0.86;2.75]
NeuroAIDS	5.15		4.72	[1.62;13.8]	4.46		4.87	[1.59;14.9]
On efavirenz treatment (yes vs. no)	0.70	0.28	0.68	[0.35;1.30]	0.76	0.46		
Transmission group								
i.v. drug use	1.32	0.37	1.36	[0.72;2.56]	1.18	0.66		
Homosexuals (except for i.v. drug use)	0.79		0.80	[0.49; 1.28]	0.86			
Heterosexual/others	1		1		1			
History of zidovudine treatment (yes vs. no)	1.63	0.12	1.63	[0.94;2.80]	1.13	0.69		
CD4 nadir (cells/μl)*								
>350	1	0.56						
[200;350[	0.64							
<200	0.73							
Active hepatitis C co-infection (yes vs. no)	1.03	0.94						
Time since HIV diagnosis (years)		0.47						
<7	1							
[7;12]	0.78							
[12;17]	1.33							
>17	0.99							
Non HIV-infection-related variables								
Education level								
High school	1	0.001	1		1	0.008	1	
Technical school	2.21		2.21	[1.34;3.65]	1.99		2.16	[1.31;3.55]
No diploma	3.18		3.18	[1.34;7.54]	2.94		3.39	[1.48 ;7.80]
History of cardiovascular event (yes vs. no)	2.35	0.201	2.35	[0.63;8.75]	2.02	0.32		
Hypercholesterolemia (yes vs. no)	1.37	0.23	1.37	[0.82;2.29]	1.35	0.28		
Hypertriglyceridemia (yes vs. no)	1.45	0.15	1.45	[0.87;2.43]	1.32	0.30		
Dysthymia disorder (yes vs. no)	1.64	0.15	1.64	[0.83 ;3.22]	1.70	0.13		
Generalized anxiety (yes vs. no)	2.33	0.006	2.33	[1.28;4.26]	2.47	0.004	2.93	[1.67;5.14]
Depressive symptoms (yes vs. no)	2.13	0.01	2.13	[1.20;3.81]	1.89	0.036	2.11	[1.23;3.63]
Alcohol dependence (yes vs. no)	2.01	0.11	2.01	[0.84;4.81]	2.17	0.08		
Any history of neurological disease except for neuroAIDS – stroke, brain trauma, neurologic disease-(yes vs. no)	2.16	0.008	2.16	[1.22;3.81]	2.12	0.011	2.05	[1.18;3.58]

N=400 cross sectional study

ANRS CO3 Aquitaine Cohort: Bonnet et al, AIDS 2013

CNS Targeted HAART: A randomised trial for HIV associated neurocognitive disorders (HAND)

- Eligibility:
  - HAND – Impaired on NP testing
  - Stable (>8 weeks) on HAART or no HAART
  - Planned change to ART
    - VF, AEs or HAND despite ART
  - Exclude major comorbidity or substance use

Ellis R et al. CROI 2013 (20)

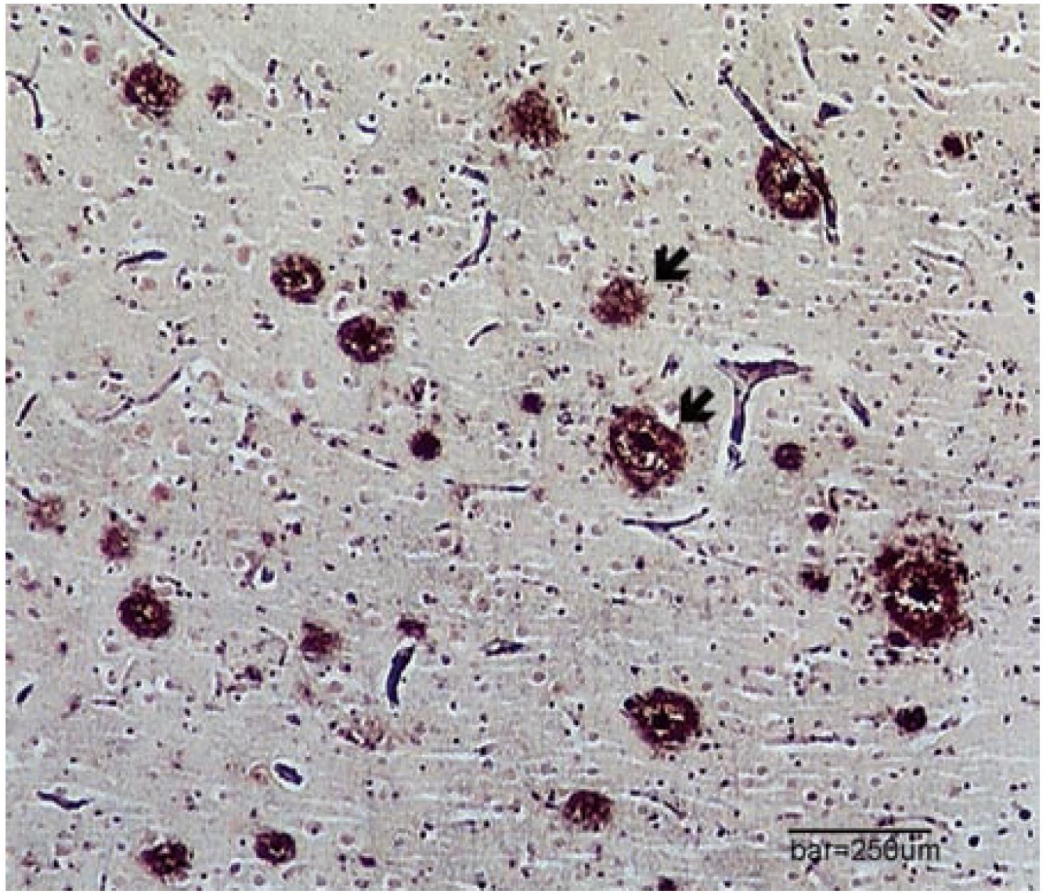
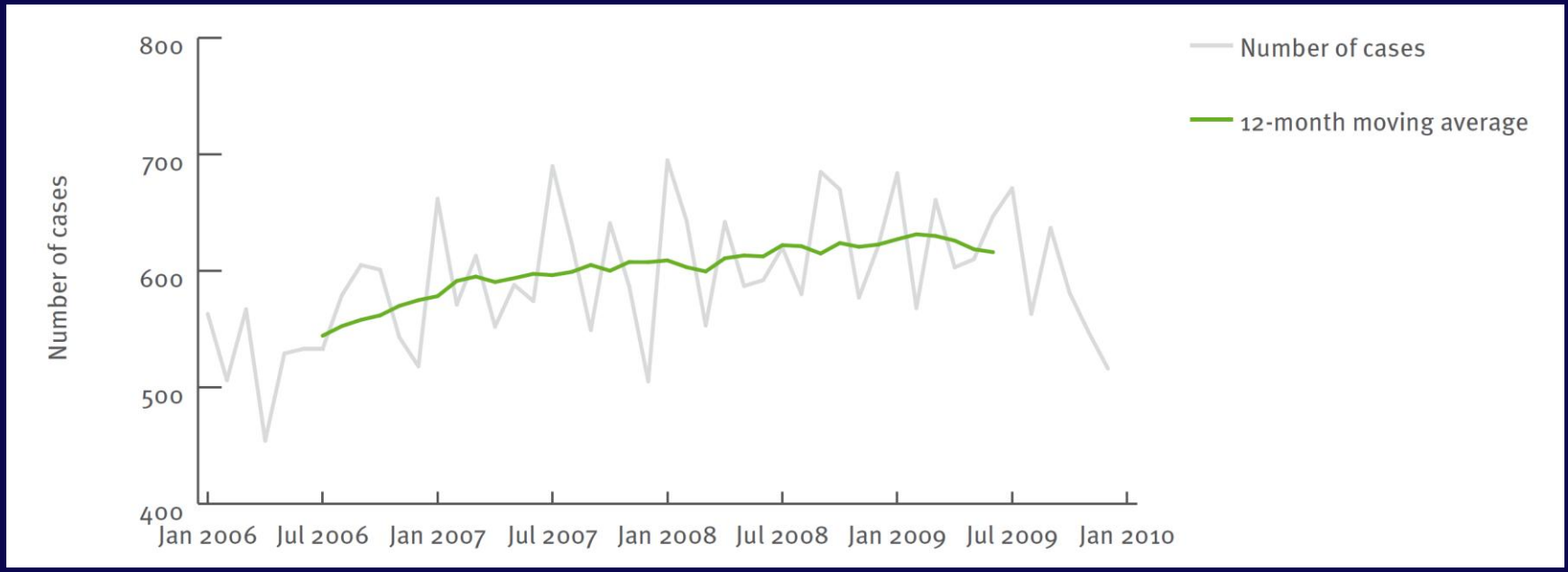


Fig. 1. Amyloid-containing plaques (arrows) in the frontal cortex of a demented 69-year-old HIV-1-positive woman. Clinically, HIV-associated neurocognitive disorder was only one factor contributing to her dementia. At death, her brain contained numerous amyloid plaques and tau-neurofibrillary tangles (not shown), typical of AD (modified Bielschowsky silver stain, bar equals 250 μm). AD, Alzheimer's disease.

Number of syphilis cases diagnosed pr month in EU, EEA/EFTA countries: 2006-2010



ECDC, 2012

TB and HIV

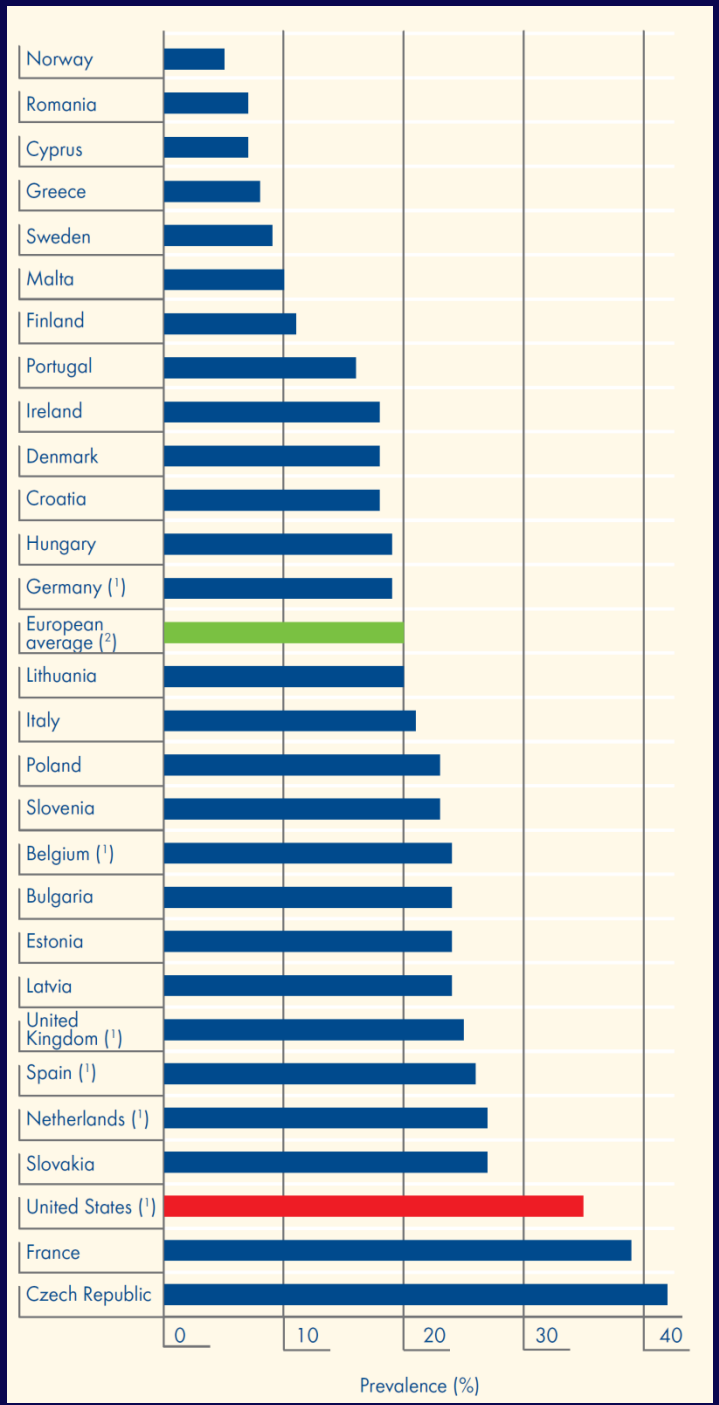
	Estimated number of people acquiring TB who are living with HIV (thousands)			Number of people with TB with known HIV status (thousands)	% of people with notified TB tested for HIV	% of tested people with TB who are living with HIV	% of people identified as living with HIV and TB starting antiretroviral therapy	Number of people living with HIV screened for TB
	Best estimate	Low estimate	High estimate					
Caribbean	6.2	5.4	7.2	14 248	71	20	31	2 341
East Asia	13	9.2	18	227 528	21	2.1	36	179 946
Eastern Europe and Central Asia	20	17	22.4	169 870	60	6.8	42	8 245
Latin America	29	26	32	101 272	50	17	70	312
Middle East and North Africa	7.3	6.4	8.3	26 636	19	4.8	57	974
North America	1	0.9	1.2	9 056	76	8.3	NA	NA
Oceania	2.2	1.4	3.2	6 432	33	8.7	67	2 182
South and South-East Asia	164	140	190	882 810	30	7.1	58	448 468
Sub-Saharan Africa	874	800	951	1 005 082	69	46	46	2 798 326
Western and Central Europe	2.7	2.4	2.9	25.436	30	3.5	81	928
TOTAL	1 100	1 000	1 200	2 468 370	40	23	48	3 441 722

Total global incidence in 2011: 8.7 mill

Use of opioid substitution therapy (OST) among IDU

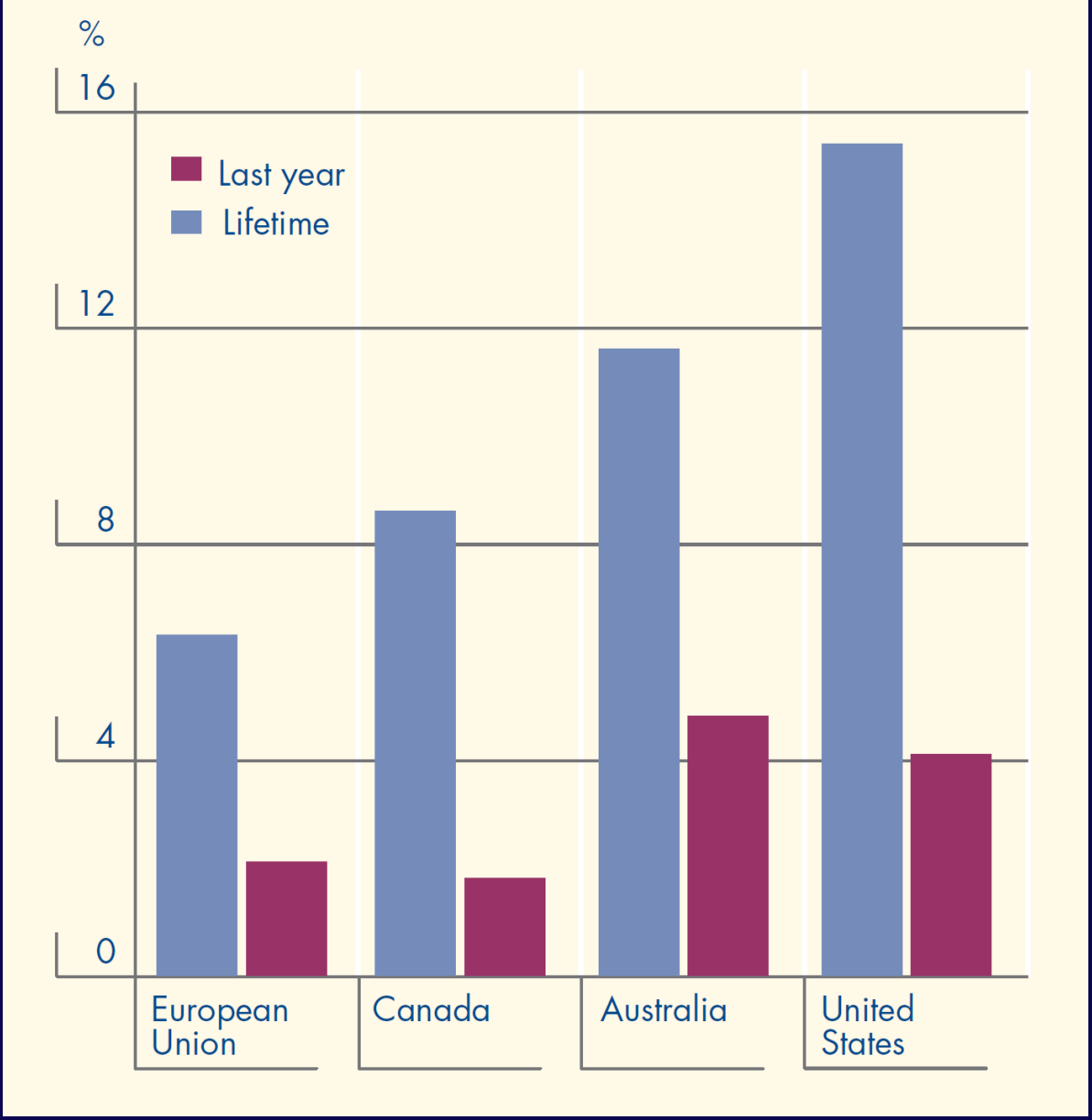
Region	Number of OST recipients per 100 IDUs (range)
Europe	
West/Central	61 (48–79)
East/South–East	1 (<1–1)
Africa	
North	1 (<1–1)
Sub–Saharan	1 (<1–<1)
Americas	
North	13 (9–19)
Carribean	5 (4–7)
Asia	
East/South–East	3 (3–5)
South	19 (15–25)
Central	<1 (<1–<1)
Near and Middle East	1 (<1–1)
Global	8 (6–12)

Prevalence of cannabis use by 15 year old across Europe and in US



EMCDDA 2012

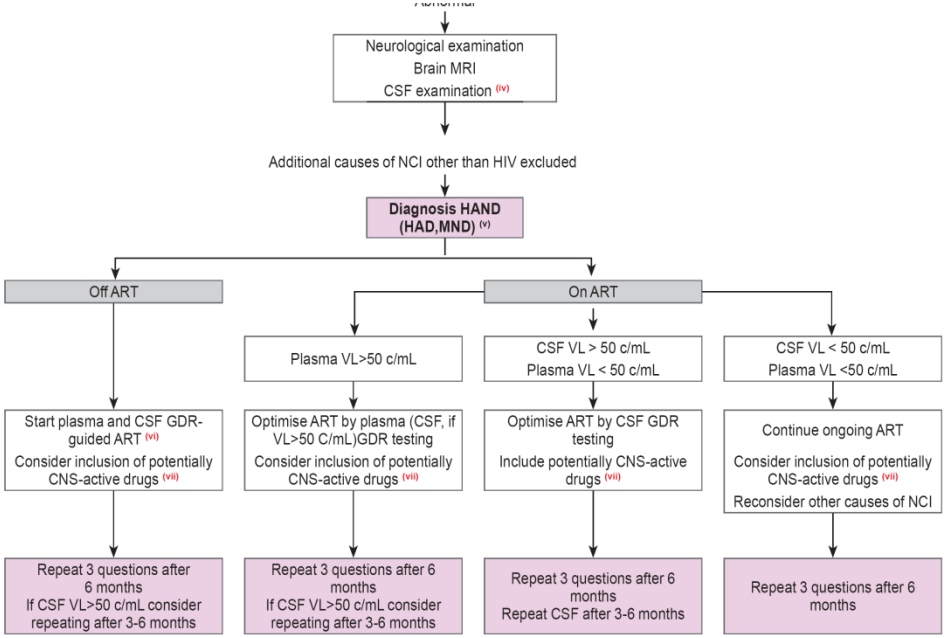
Cocaine use in 15-34 year old: life-long and in last year



Neurocognitive impairment: diagnosis and management

- Neurocogr
  - ✓ IADL (Ins

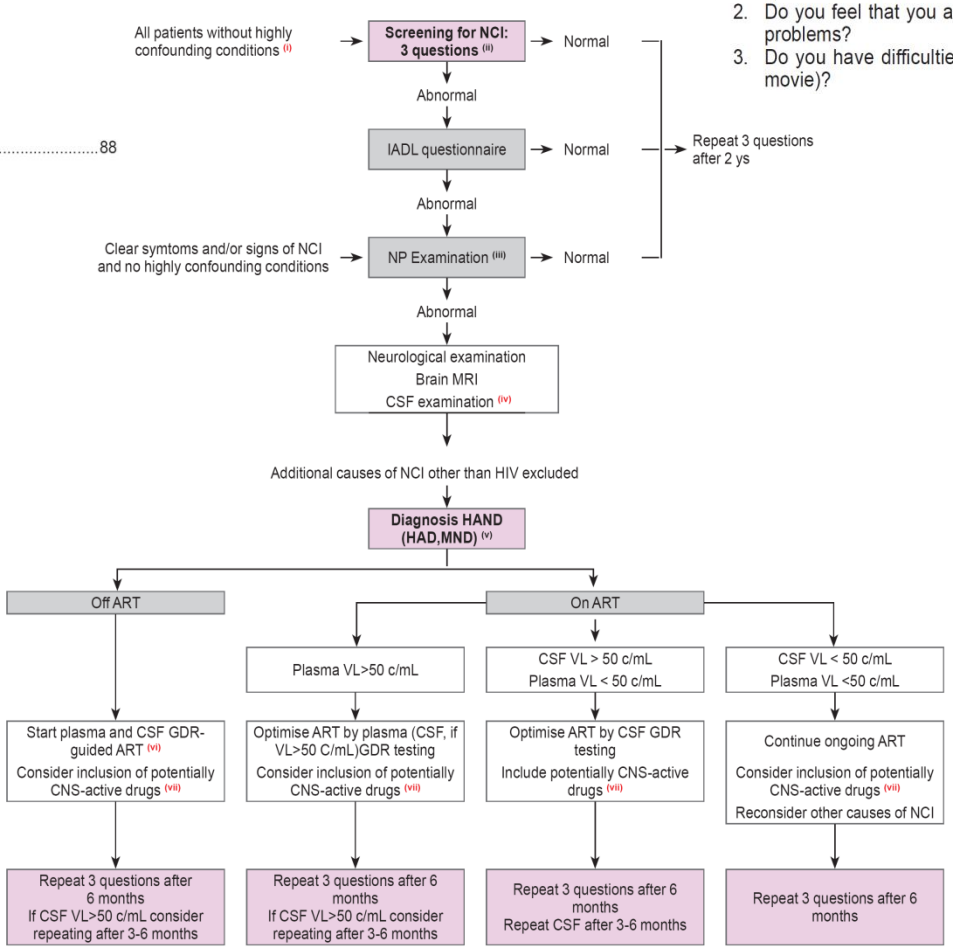
1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?



Neurocognitive impairment: diagnosis and management

- Neurocognitive impairment: diagnosis and management 88
  - ✓ IADL (Instrumental Activities of Daily Living) scale (online only)

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)



1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

Summary

- ART prevent and revert recognised HIV-induced morbidity and mortality incl from CNS
- Several conditions associated with NCI – potentially modifiable – reasonable evidence
- Available evidence insufficient to make strong recommendations on whether optimisation of ART improves NCI in persons with residual intracerebral HIV replication
- More and better designed research on neurological complications in HIV urgently required

Acknowledgements

- ASTRA: Fiona Lampre, Alison Rodger, Andrew Phillips et al, UCL, UK
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- START protocol – in particular neurology substudy team: Edwina Wright, Birgit Grund, Mollie Roediger, Bruce Brew, Lucette Cysique, Richard Price, Kevin Robertson