Medical Education Workshops on HIV/AIDS

GreenShoots
FOUNDATION

Introduction to HIV

Jürgen Rockstroh, Department of Medicine I,
University Hospital Bonn, Bonn, Germany

GreenShoots
FOUNDATION

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

June 5, 1981 / Vol. 30 / No. 21

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexua treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different h in Los Angeles, California. Two of the patients died. All 5 patients had lab confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneun oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum compleme CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's deteriorated despite courses of treatment with trimethoprim-sulfamethoxa pentamidine, and acyclovir. He died May 3, and postmortem examinati pneumonia, but no evidence of neoplasia.

developed *P. carinii* pn

The New England
Journal of Medicine

Volume 305 DECEMBER 10, 1981 Number 24

SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS

FREDERICK P. SIEGAL, M.D., CARLOS LOPEZ, PH.D., GLENN S. HAMMER, M.D., ARTHUR E. BROWN, M.D., STEPHEN J. KORNFELD, M.D., JONATHAN GOLD, M.D., JOSEPH HASSETT, M.D., SHALOM Z. HIRSCHMAN, M.D., CHARLOTTE CUNNINGHAM-RUNDLES, M.D., PH.D., BERNARD R. ADELSBERG, M.D., DAVID M. PARHAM, M.D., MARTA SIEGAL, M.A., SUSANNA CUNNINGHAM-RUNDLES, PH.D., AND DONALD ARMSTRONG, M.D.

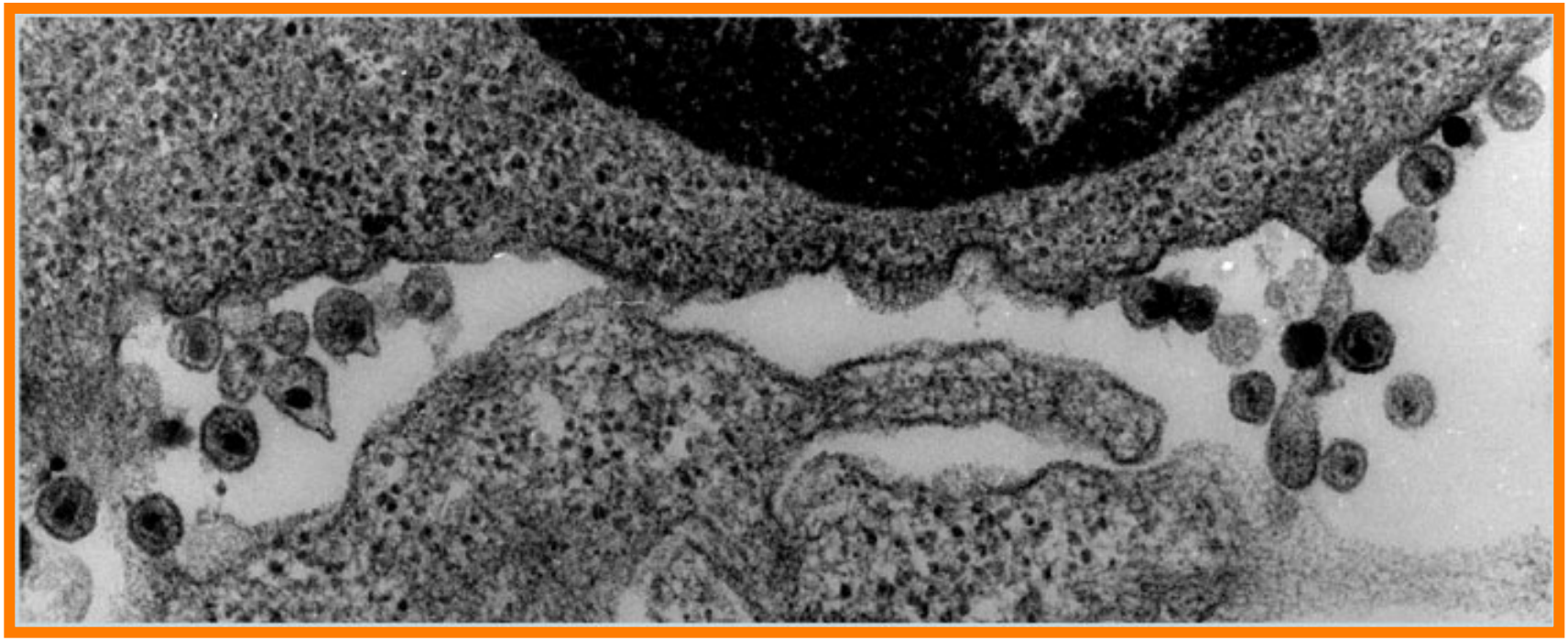
Abstract Four homosexual men presented with gradually enlarging perianal ulcers, from which herpes simplex virus was cultured. Each patient had a prolonged course characterized by weight loss, fever, and evidence of infection by other opportunistic mi-

ty, as evidenced by skin anergy, lymphopenia, and poor or absent responses to plant lectins and antigens in vitro. Natural-killer-cell activity directed against target cells infected with herpes simplex virus was depressed in all patients. The absence of a histo-

C.I.M.

I have it!

- Friday, 4 February 1983, 5:45 pm at Pasteur Institute



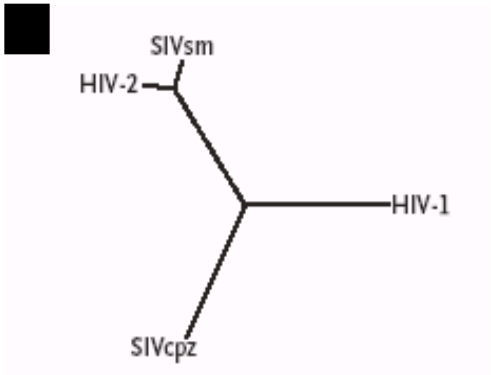
Françoise Barré-Sinoussi. Science 1983

The Origin of HIV-1

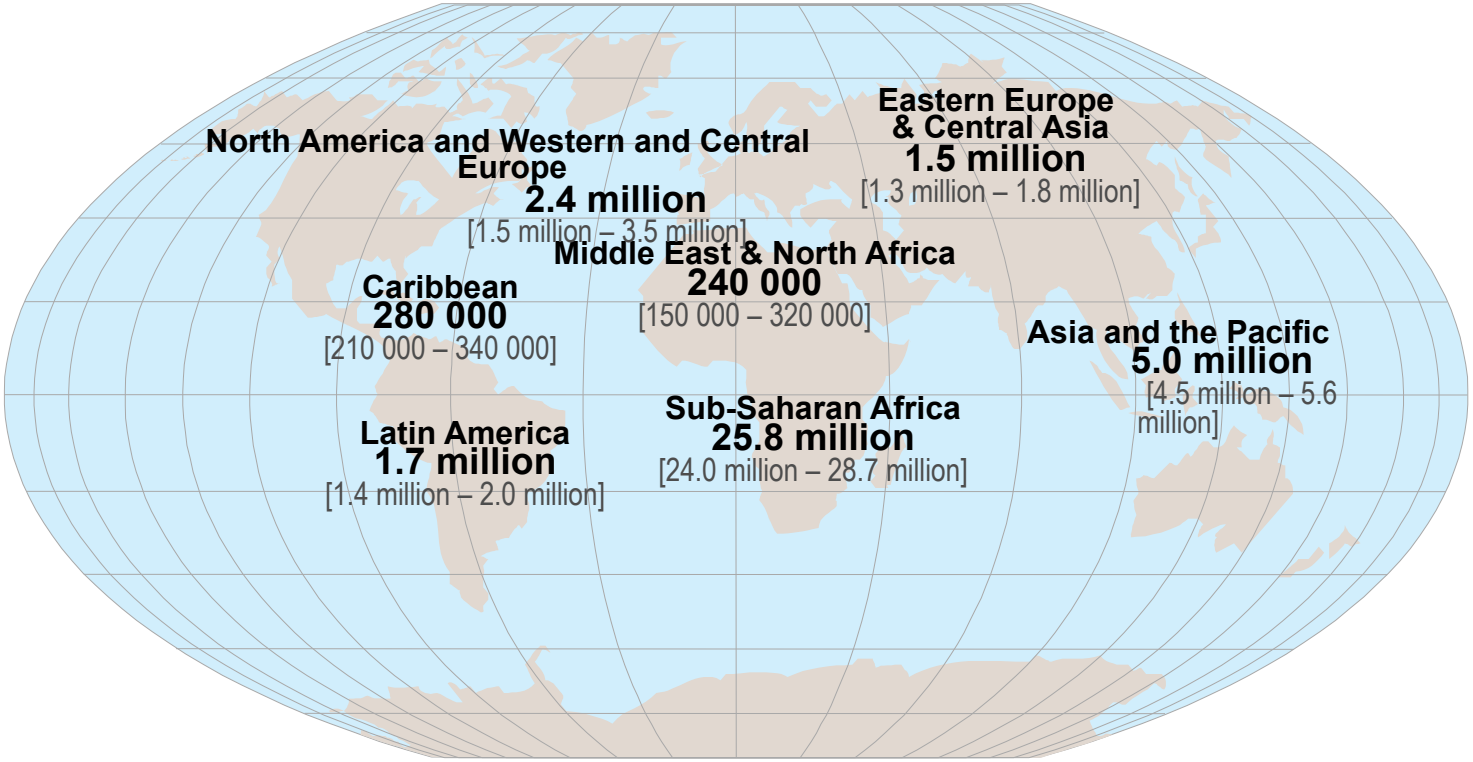
letters to nature

Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

Feng Gao*, Elizabeth Bailes†, David L. Robertson‡, Yalu Chen*, Cynthia M. Rodenburg*, Scott F. Michael*§, Larry B. Cummins‖, Larry O. Arthur¶, Martine Peeters#, George M. Shaw*☆, Paul M. Sharp† & Beatrice H. Hahn*



Adults and children estimated to be living with HIV 2014



Total: 36.9 million [34.3 million – 41.4 million]

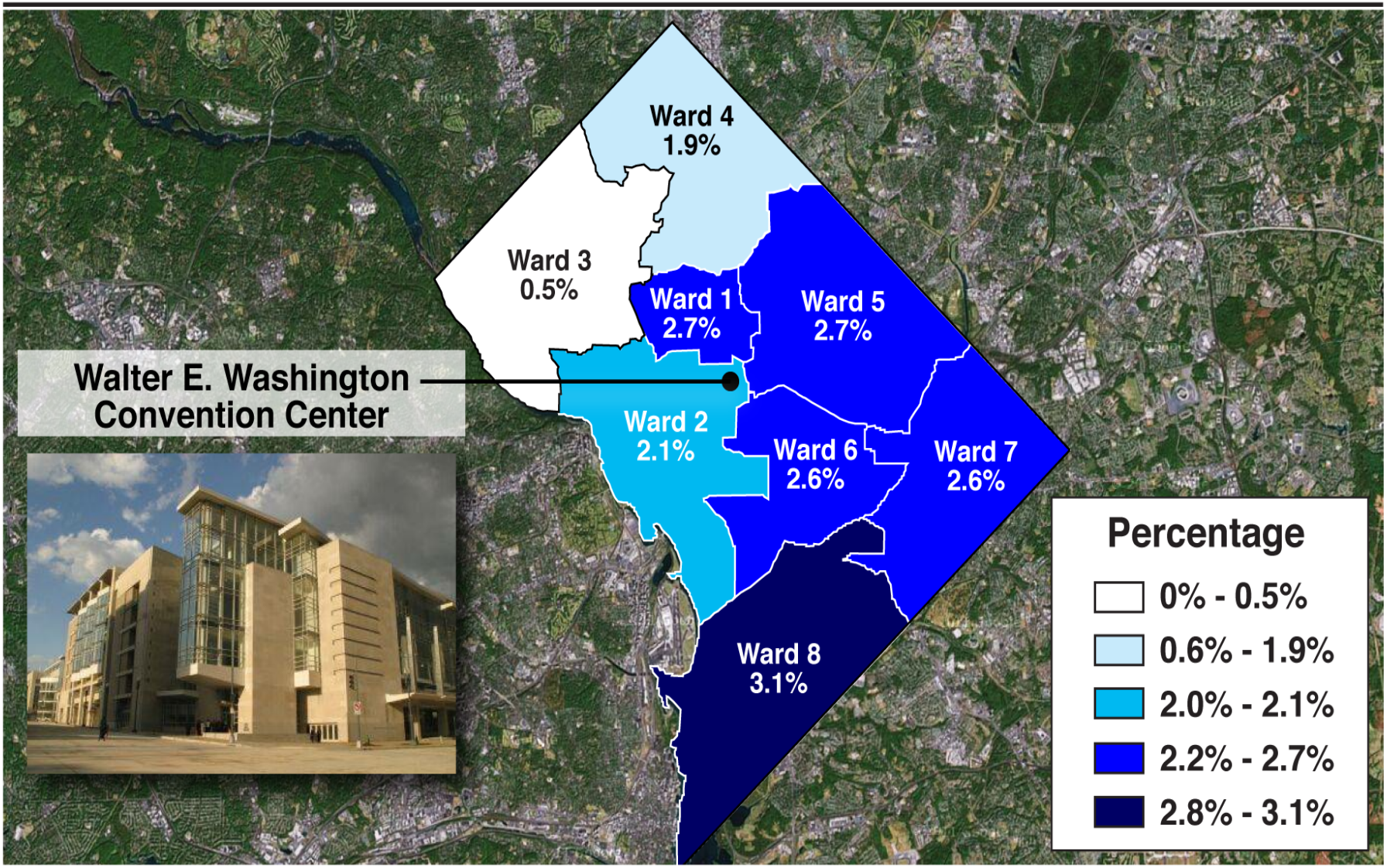
UNAIDS report 2014

Moving towards end of AIDS: main results and new ambitious targets..

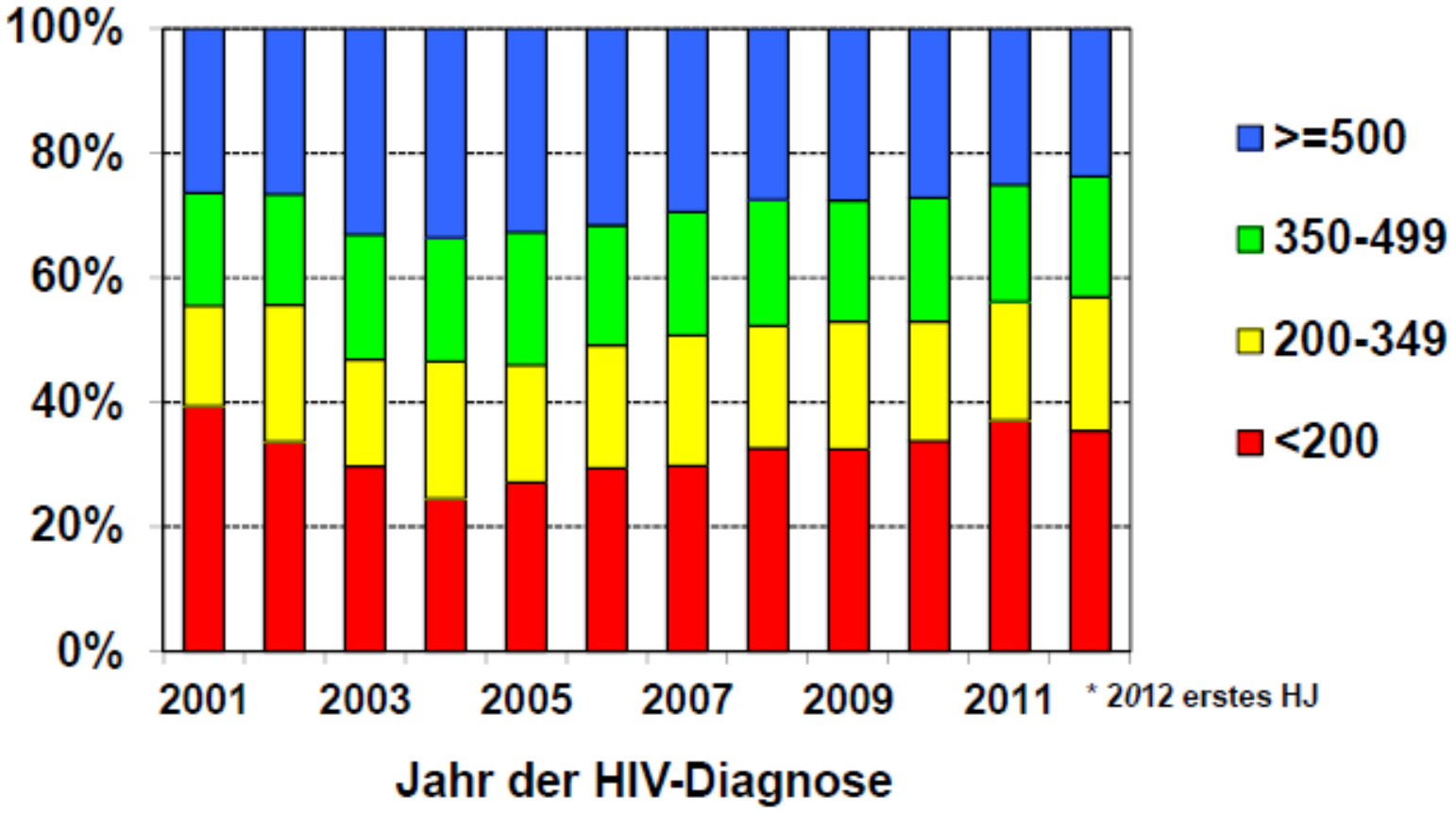
Key parameters	2005	2015	2020	2030
New HIV infections	3 million	2 million [↓ 35%]	500,000	200,000
AIDS-associated deaths	2.4 million	1.2 million [↓ 50%]	500,000	400,000
PLHIV accessing ART	1.5 million	15 million [↑ 10x]	30 million	ALL
Investments for global HIV response (US$)	7 billion	20 billion [↑ 3x]	32 billion	29 billion

WHO & UNAIDS reports , 2014 & 2015

Washington, D.C.: Proportion of Adults/ Adolescents Living with HIV/AIDS by Ward, 2010



CD4 at HIV diagnosis in Germany



ROBERT KOCH INSTITUT

Definition Late Presenters

CD4 <350 CD4 T cells/µl

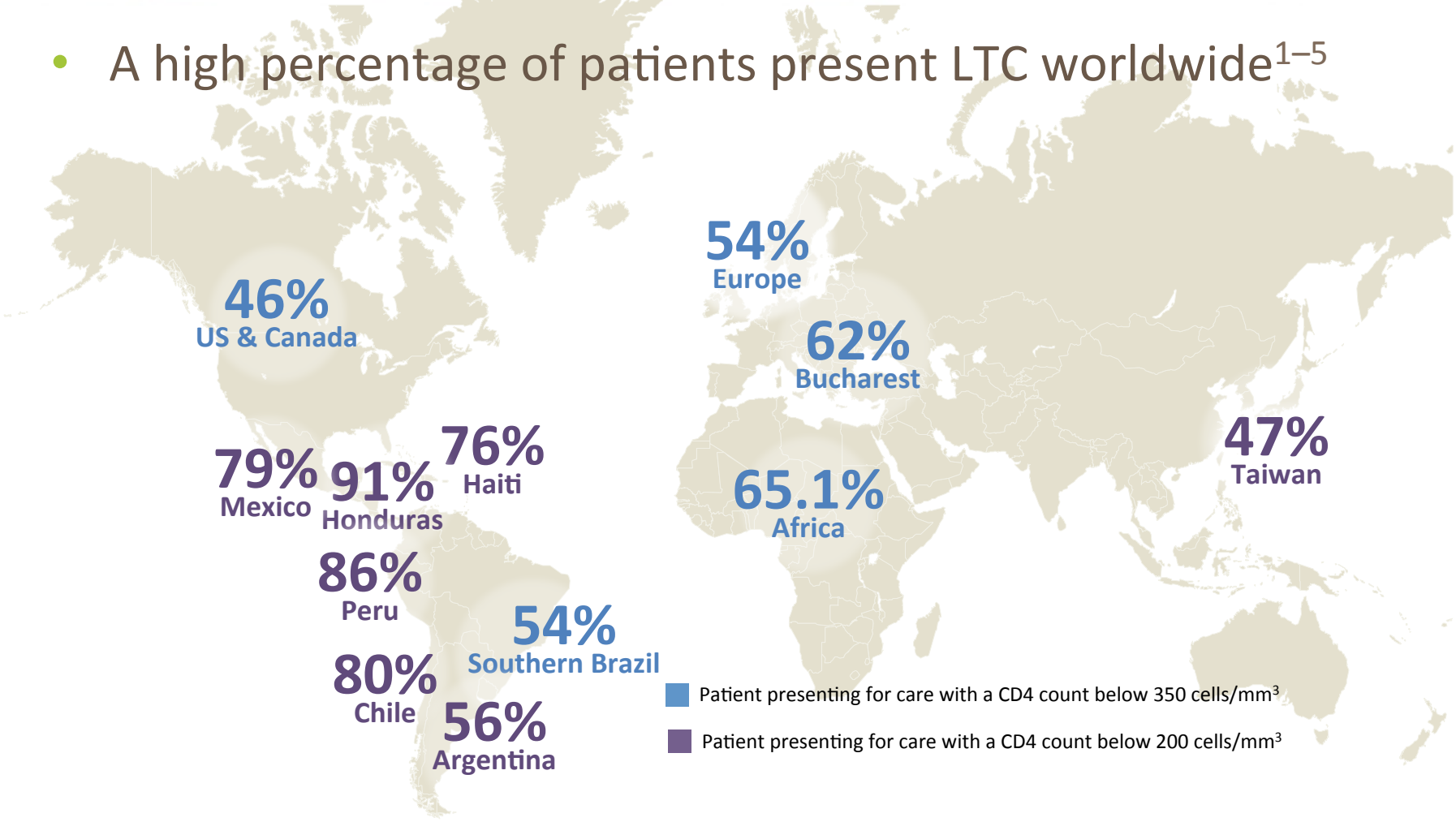
and / or

AIDS-defining illness at HIV diagnosis

Johnson et al. Antiviral Therapy 2010 15 Suppl. 1:3-8.

Epidemiology: worldwide

- A high percentage of patients present LTC worldwide[1–5]



1. Mocroft A, *et al. PLoS Med* 2013;10(9):e1001510
2. Crabtree-Ramirez B, *et al. PLoS One.* 2011;6(5):e20272
3. Lo YC, *et al. J Formos Med Assoc.* 2011;110(5):306–315
4. Jipa RE, *et al. J Int AIDS Soc.* 2014;17(suppl 3):19691
5. Althoff KE, *et al. Clin Infect Dis.* 2010: 50(11):1512–20

HIV Transmission

The main transmission routes of HIV are:

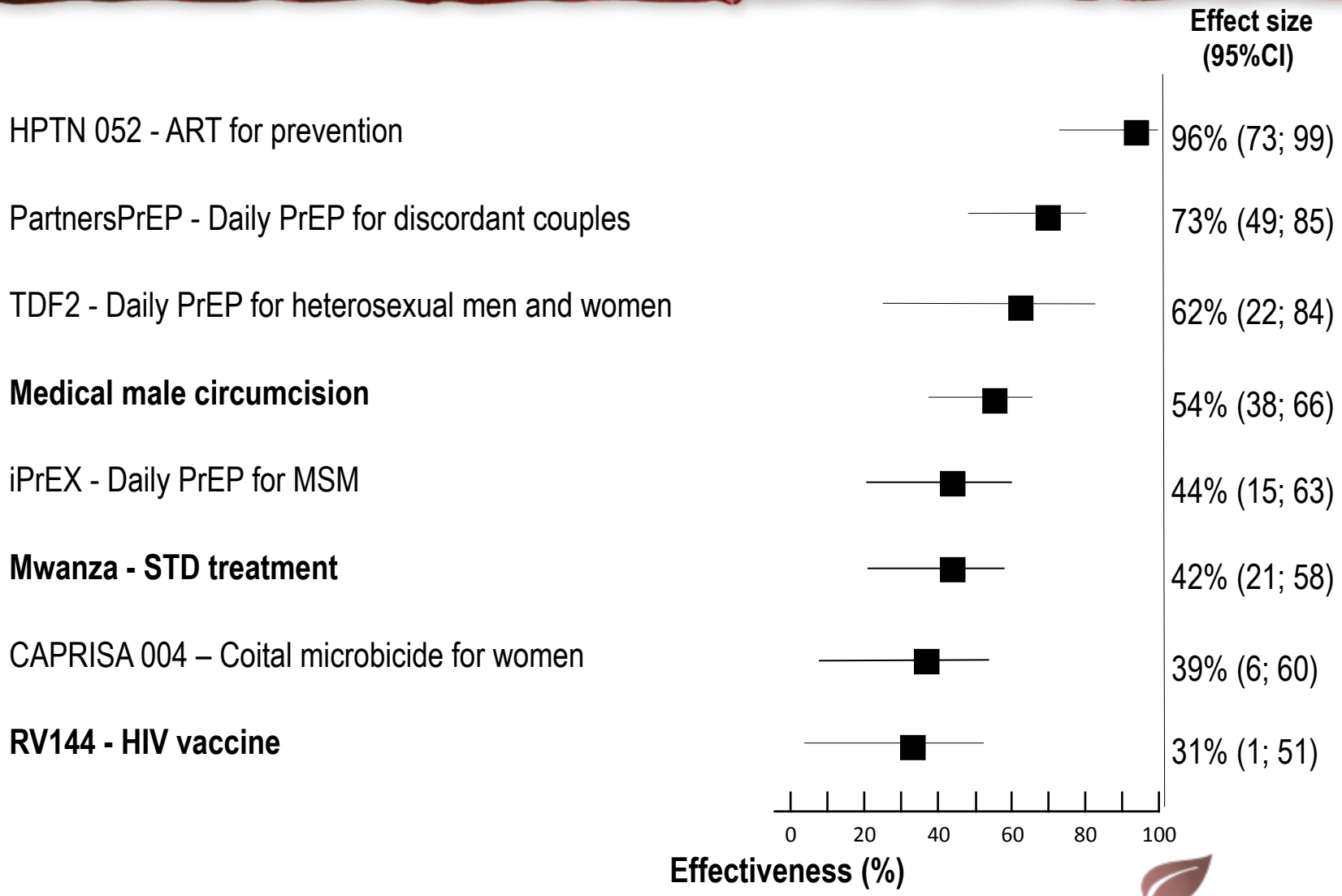
- 1. unsafe sex with an HIV-infected partner
- 2. sharing injection paraphernalia with an HIV-infected partner
- 3. vertical transmission of HIV from the HIV-infected mother to the newborn (be-fore or at birth; or later, due to breastfeeding)

All other transmission routes, for the most part case reports, are notably rare. Among these are transmissions due to transfusion of blood or blood products in countries where blood donations are not routinely screened for HIV.

HIV - Transmission

Exposition	Transmission risk (%)
Percutanous needle stick	0,3
Receptive vaginal intercourse	0,05 – 0,15
Insertive vaginal intercourse	0,03 – 0,09
Receptive anal intercourse	0,8 – 3,2
insertiver anal intrcourse	0,02 – 0,19
Oral sex	ca. 0,03
vertical	15 – 40

Clinical trial evidence for preventing sexual HIV transmission – July 2011



Source: Adapted from Abdool Karim SS & Abdool Karim Q. Lancet 2011

Hepatitis A (ELISA):
Anti-HAV: _____ Anti-HAV-IgM: _____

Hepatitis B (ELISA):
HBs-Ag: _____ HBe-Ag: _____
Anti-HBs: _____ Anti-HBe: _____
Anti-HBc: _____ **Hepatitis Delta** (ELISA):
Anti-HBc-IgM: _____ Anti-HDV: _____

Cytomegalie (KBR): _____ **Hepatitis C** (ELISA):
CMV-IgM (IF/ELISA): _____ Anti-HCV: NEGATIV
CMV-IgG (IF/ELISA): _____ **Inf. Mononucleose:**

HIV 1 - Antikörper: _____ Heterophile Antik.: _____
ELISA: POSITIV (Paul-Bunnell-Test)
Immunfl.: POSITIV EBV-IgM (Immunfl.): _____
Immunoblot: POSITIV EBV-IgG (Immunfl.): _____

Beurteilung:

1 Akute Hepatitis A: ausgeschlossen - nachgewiesen - möglich

2 Hepatitis A-Anamnese: Infektion durchgemacht* - nicht durchgemacht

3 Akute Hepatitis B: 1. Phase - 2. Phase - unwahrscheinlich - ausgeschlossen

4 Persistierende Hepatitis B-Inf.: unwahrscheinlich - Ergebnisse sprechen für - hohe / geringe - Infektiosität, für / gegen Aktivität

5 Hepatitis B-Anamnese: Infektion durchgemacht* - nicht durchgemacht - protektive Antikörper vorhanden* - beabsichtigte oder unbeabsichtigte Immunisierung?

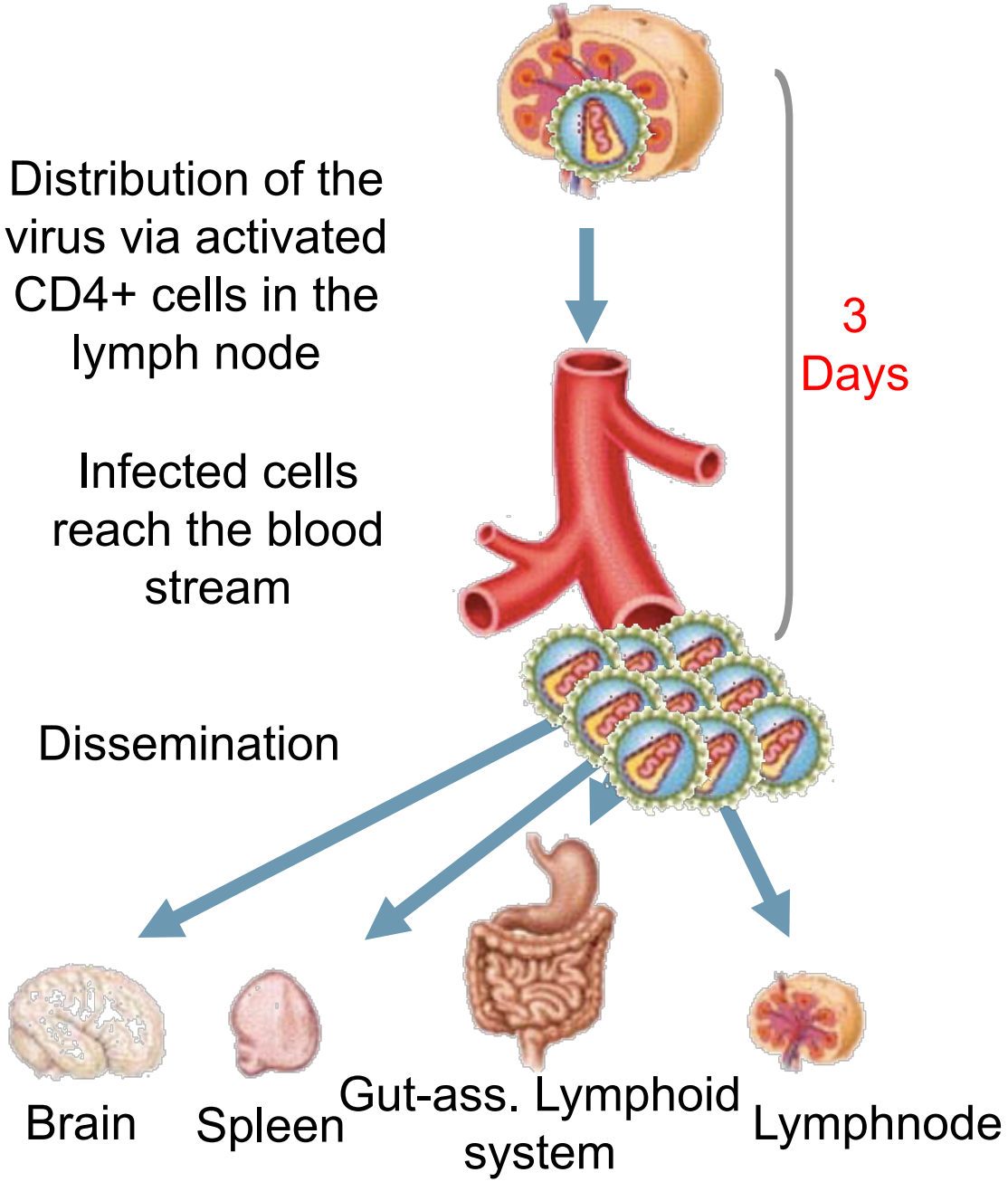
6 Cytomegalie: Aktive CMV-Inf.: anzunehmen - nicht anzunehmen -
infektion

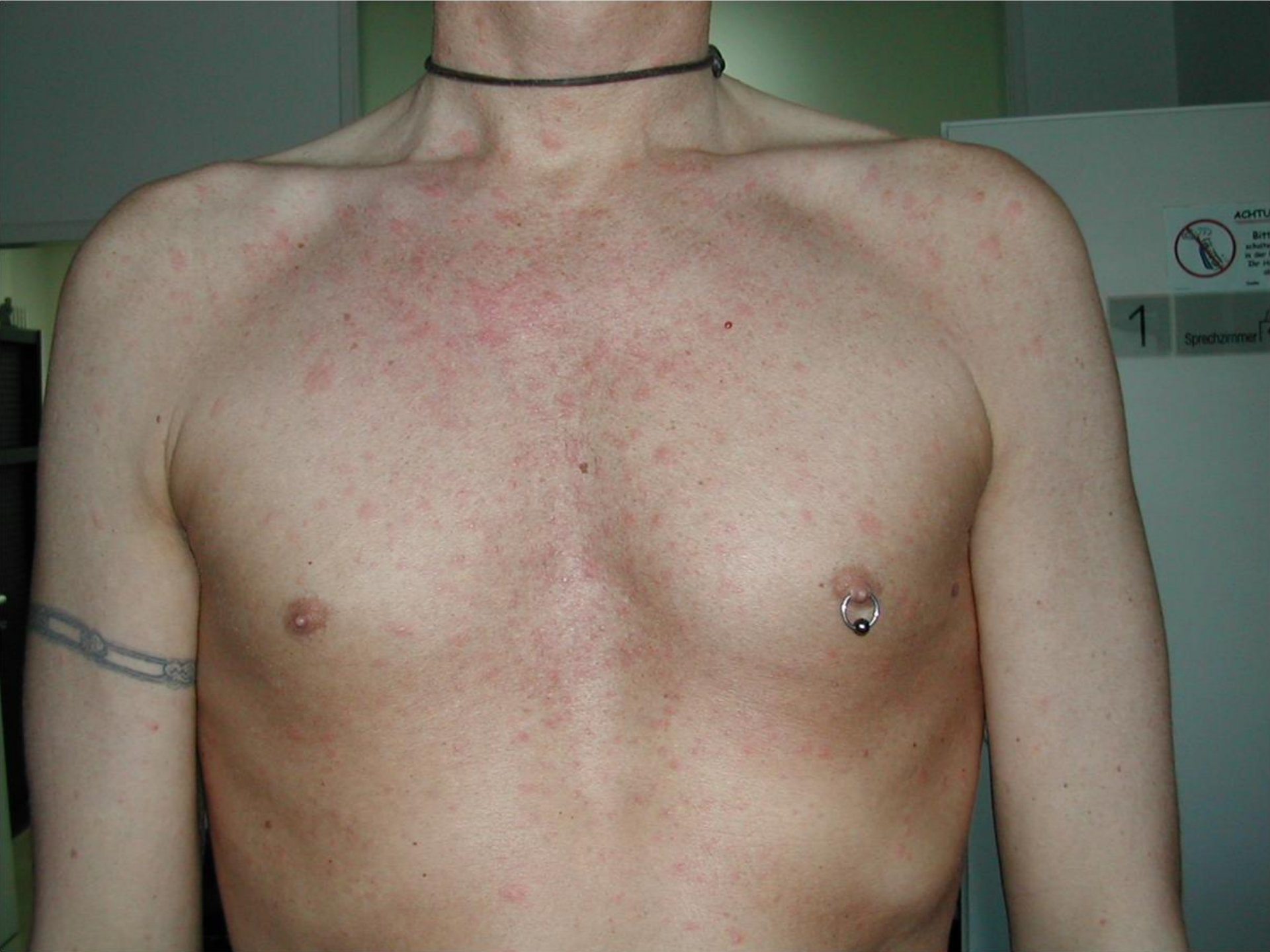
Um Verwechslungsmöglichkeiten ganz sicher auszuschließen, empfiehlt es sich ein Kontrollserum unter Angabe dieser Befundnummer einzusenden.

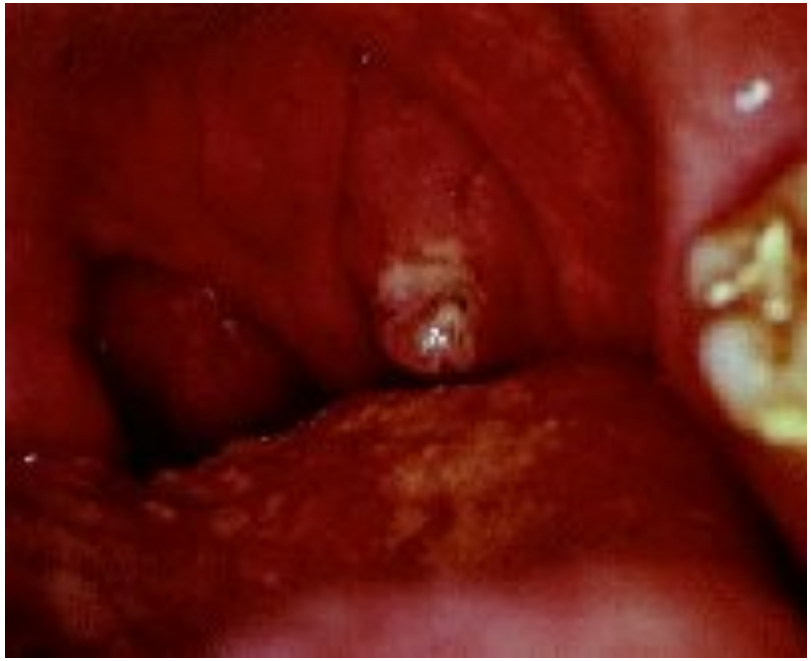
(Bei der Einsendung bitte Datum der letzten Impfung angeben!)

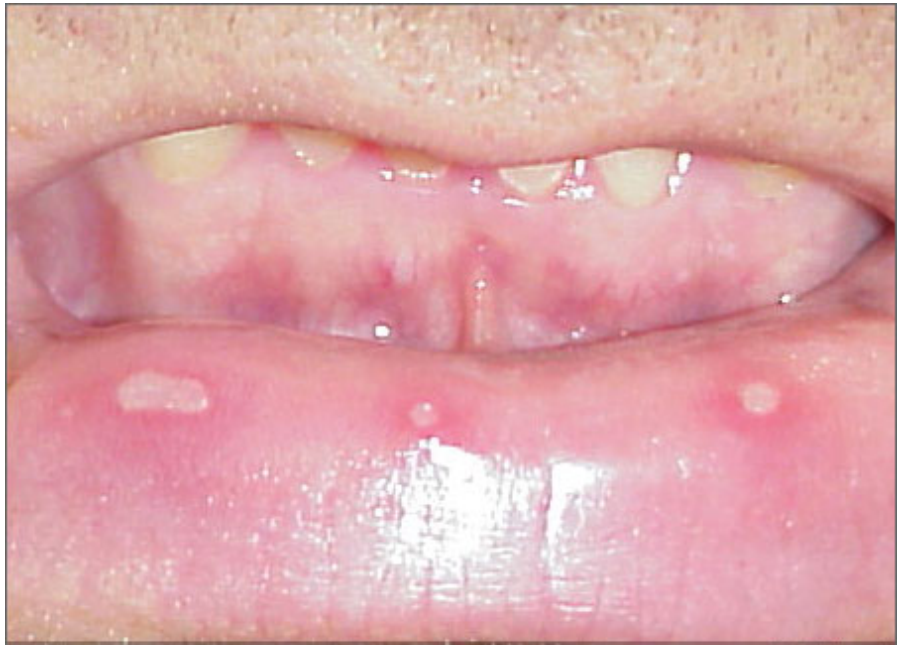
Serologisch kein Anhalt für eine chronsich Hepatitis C Virus-infektion, eine akute Infektion wird durch diesen Befund aber nicht ausgeschlossen.

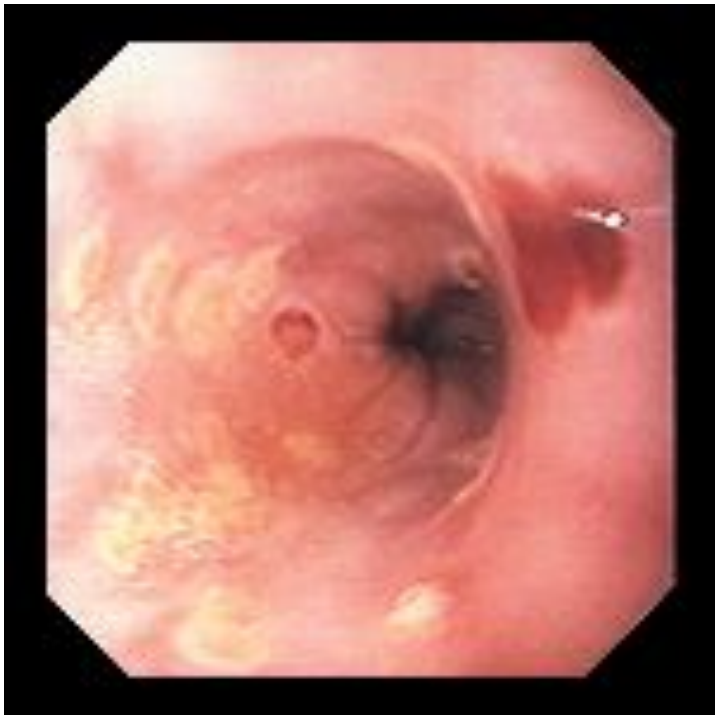
* Fremdblut-Einfluß kann zu falscher Beurteilung führen.

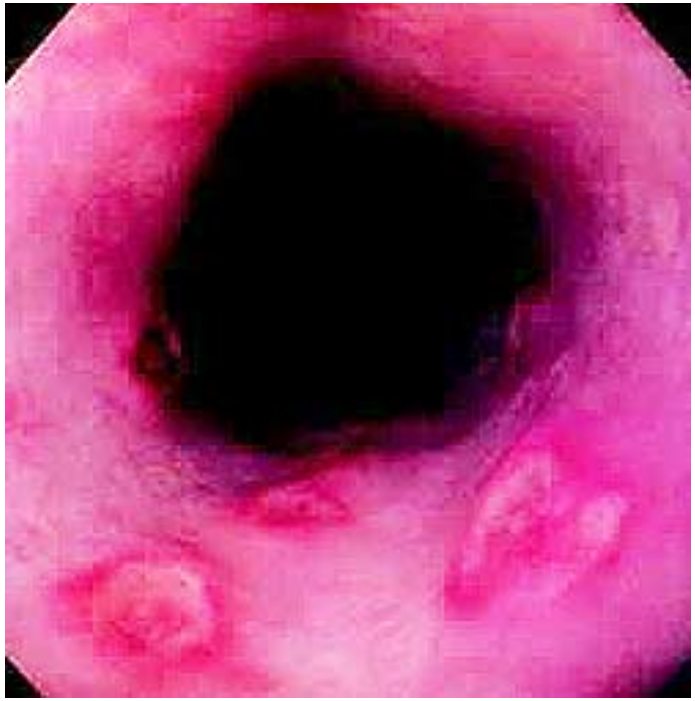

Distribution of the virus via activated CD4+ cells in the lymph node
Infected cells reach the blood stream
Dissemination
3 Days
Brain
Spleen
Gut-ass. Lymphoid system
Lymphnode


1
Sprechzimmer





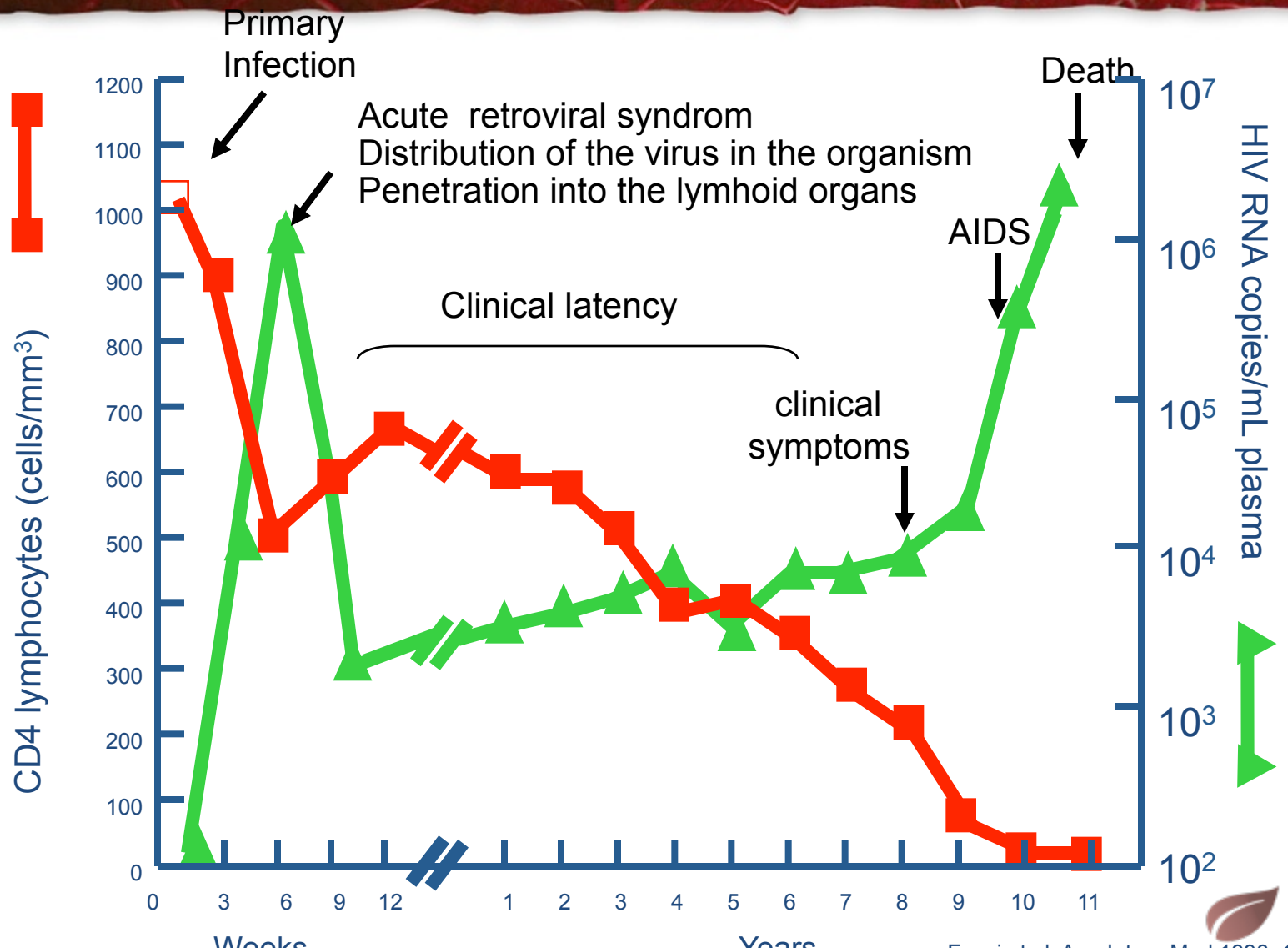




Acute HIV-Infection

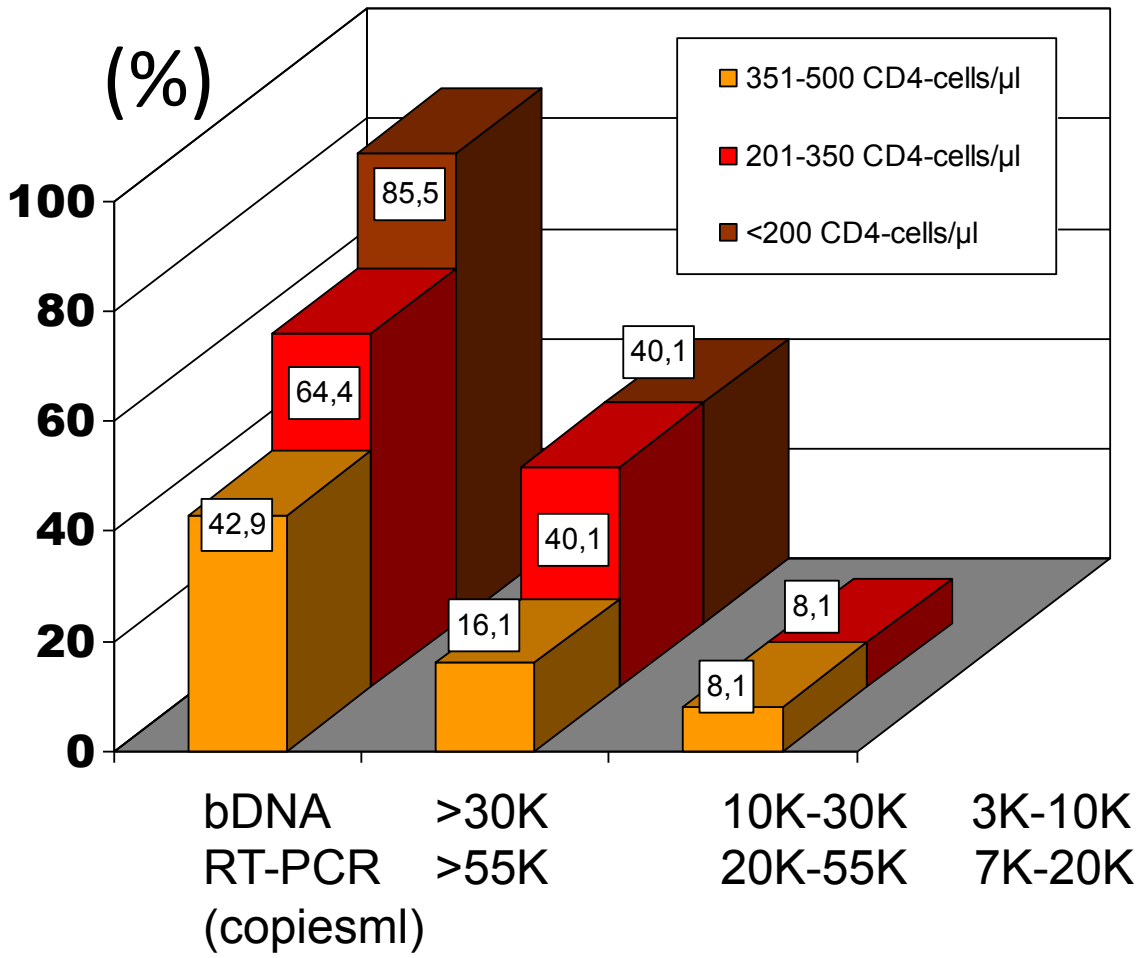
- 40-90% symptomatic
- Incubation time: several days up to few weeks
- Clinical presentation: Fever, maculopapulous rash, oral ulcerations, lymphadenopathy, arthralgia, pharyngitis, fatigue
- Therapy: combination antiretroviral therapy (cART)

HIV – natural course



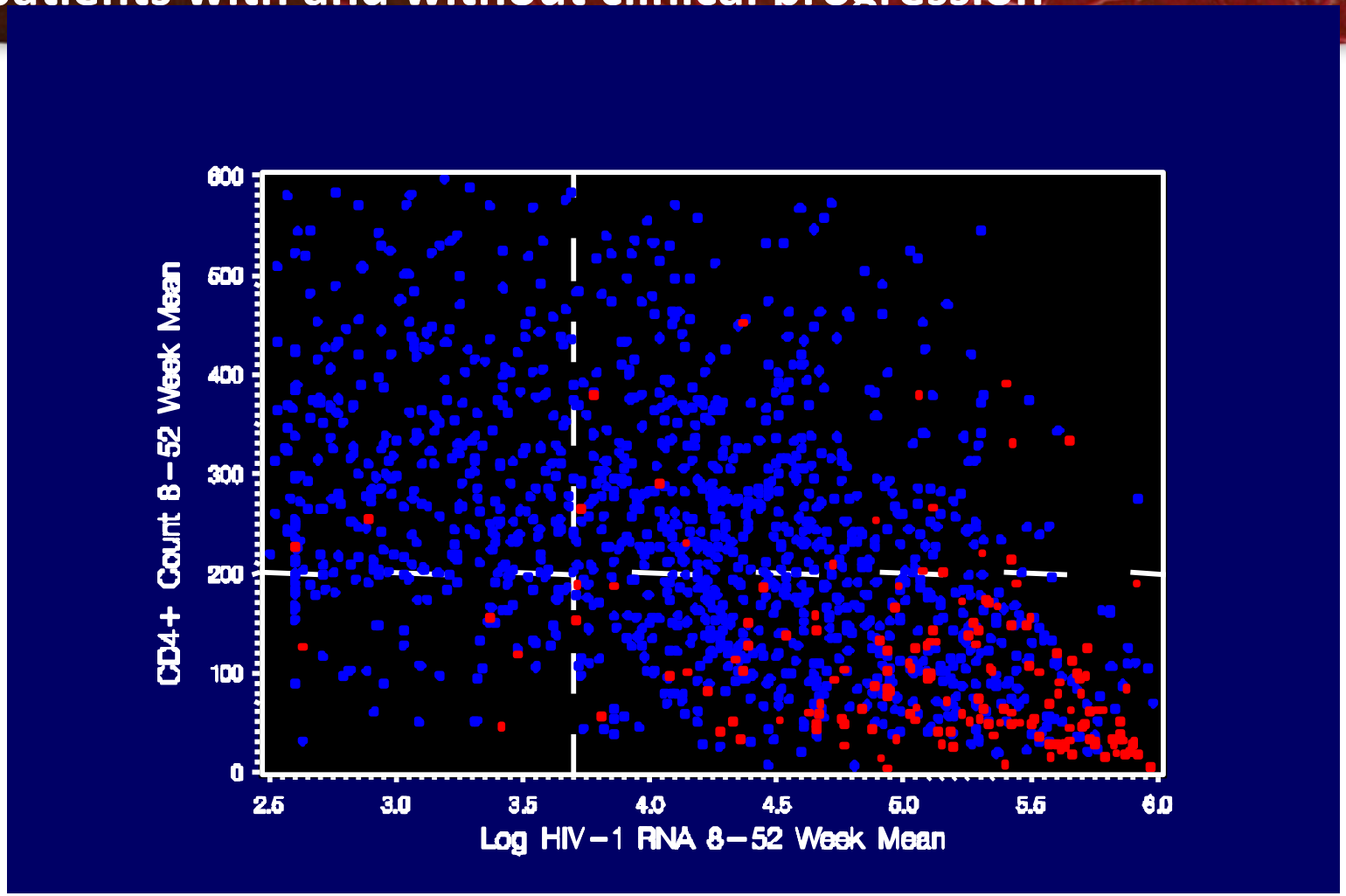
Fauci et al. Ann Intern Med 1996; 124: 654 - 663

Probability to develop AIDS 3 years after becoming HIV-infected

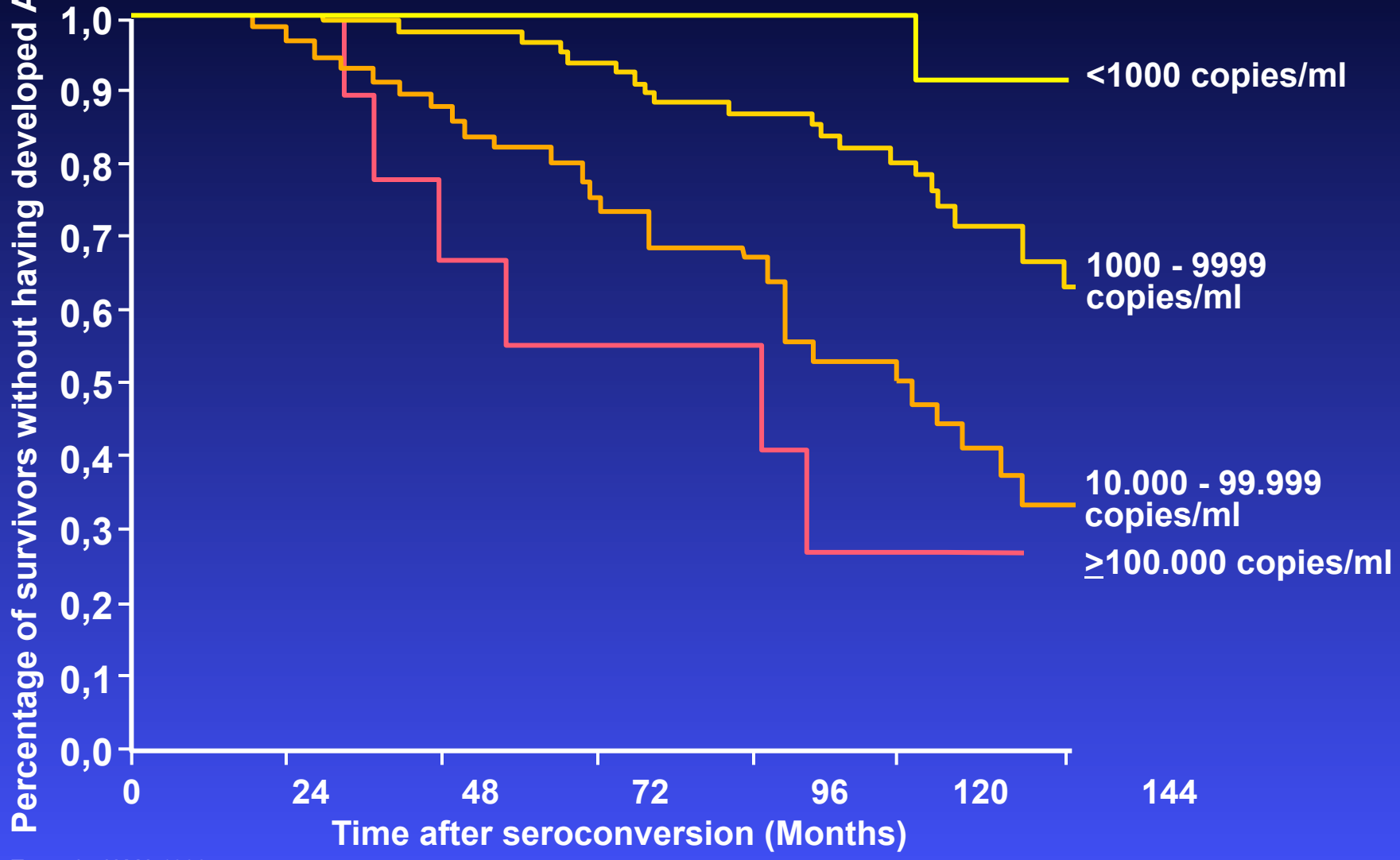


Adaptad from: Mellors JW et al. Ann Intern Med 1997; 126 (12):946-54

CD4 cell count and HIV RNA level – Comparision between patients with and without clinical progression



Impact of HIV-RNA on survival

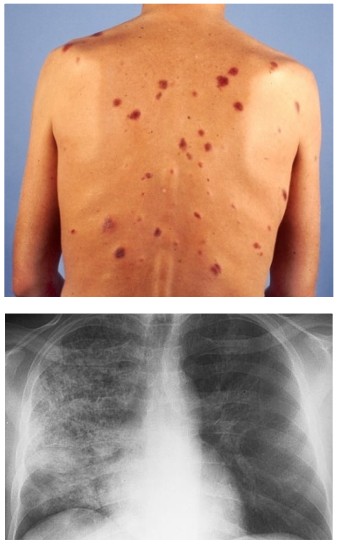


Brian Tr. et al., JAMA 1996

CDC classification

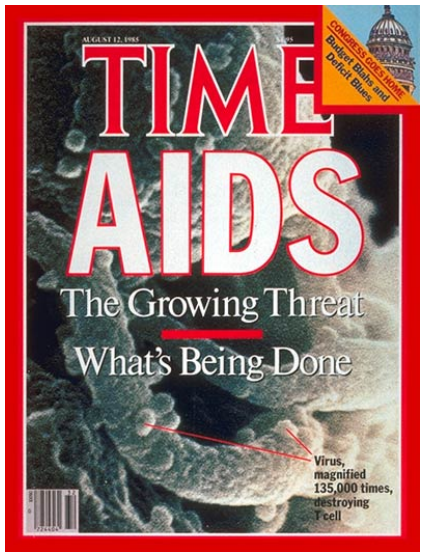
category A	category C (AIDS defining)
acute HIV – infection **persistent lymphadenopathy syndrome** **asymptomatic HIV – infection**	**pneumocystis carinii pneumonia** **cerebral toxoplasmosis** **esophageal/ bronchopulmonary candidiasis** **CMV – retinitis, generalised CMV – Infection** **kaposi – sarcoma** **tuberculosis** **MAI – infection** **recurrent salmonella sepsis** **chronic intestinal cryptosporidiosis** **extrapulmonal cryptococcosis** **malignant lymphoma** **invasive cervix carcinoma** **HIV – encephalopathy** **PML** **Wasting – Syndrome**
category B	
oral thrush **chronic vulvovaginal candidiasis** **oral hairy leucplakia** **cervical dysplasia, Ca in situ** **herpes zooster (several dermatoms, relapses)** **idiopathic thrombocytopenic purpura** **persistent fever of unknown origin > 38,5°** **persistent diarrhe without pathogen**	

Stadium 1	Stadium 2	Stadium 3
CD4 > 500/µl	CD4 > 200 – 500/µl	CD4 < 200/µl

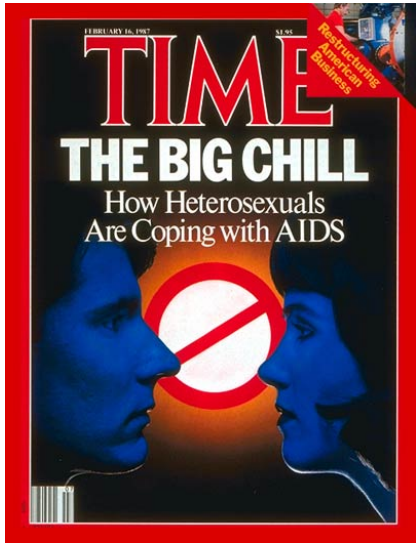


1981

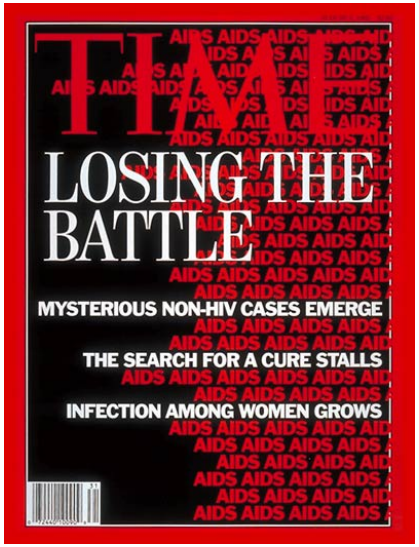
July 1983



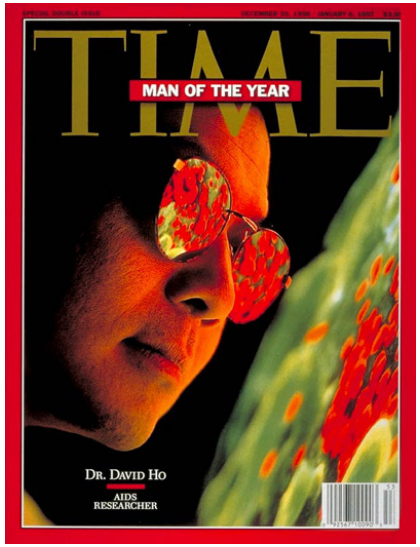
August 1985



February 1987

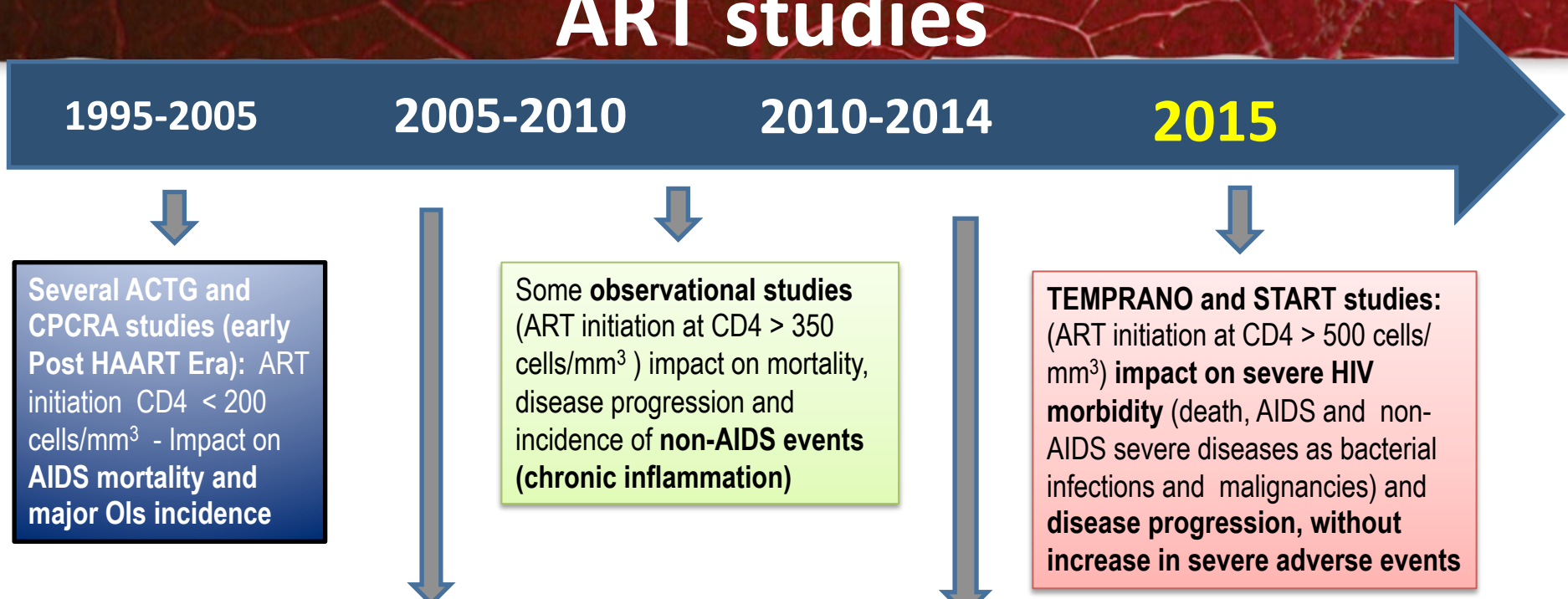


August 1992



December 1996

Overview of major "when to start" ART studies



M Vitoria, 2015,

START Study: DESIGN

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

Immediate ART Group	Deferred ART Group
Initiated ART immediately Following randomization	Defer ART until the CD4+ count declines to <350 cells/mm^3
N=2,326	**N=2,359**

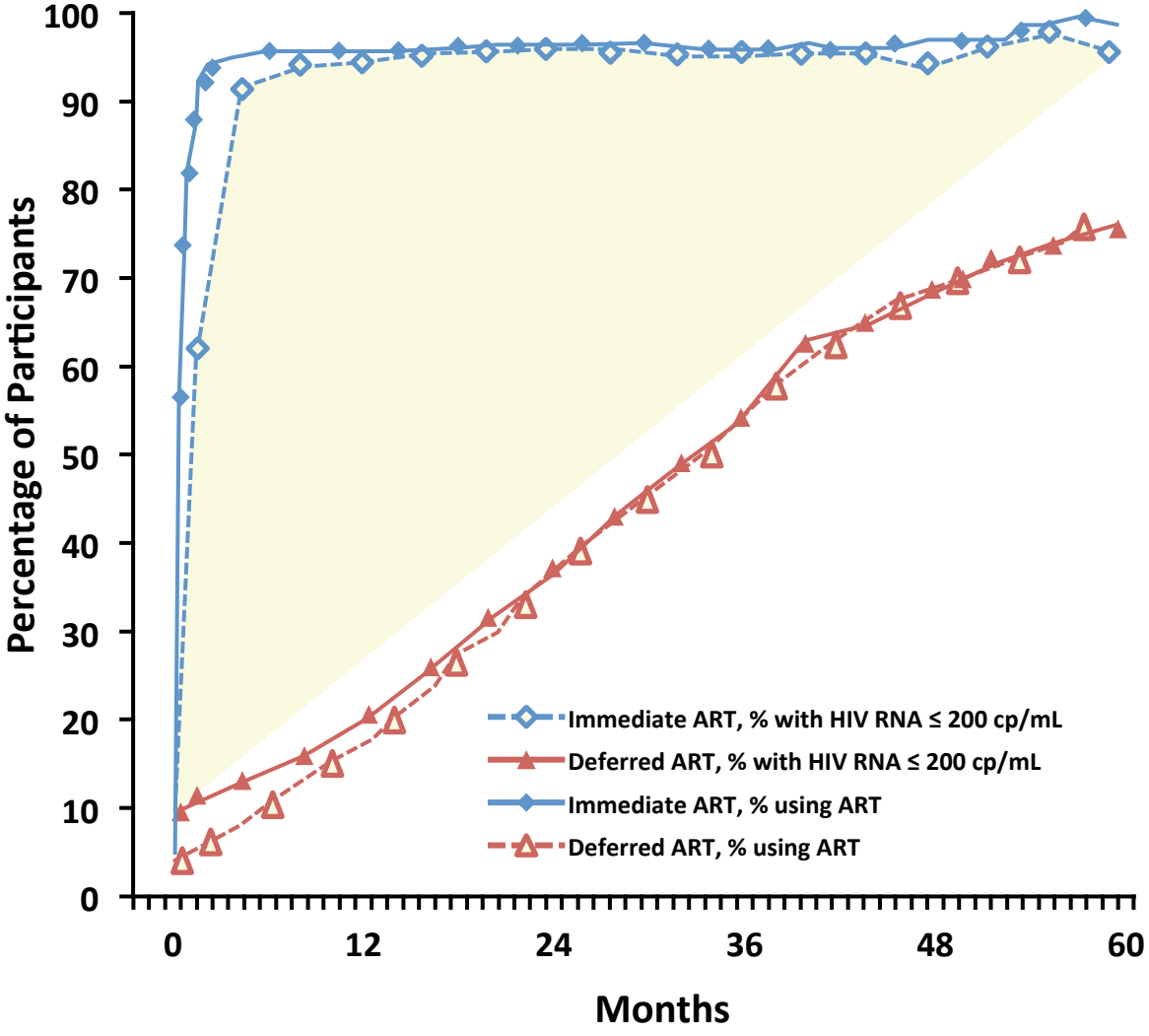
Primary Composite Endpoint, Target =213

- Serious AIDS or death from AIDS
- Serious Non-AIDS Events and death not attributable to AIDS
  - CVD, ESRD, decompensated live disease, & non-AIDS defining cancers

DSMB Stopped Study on May 27, 2015

Lundgren J, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. MOSY0301.

START Study: Proportion on ART



	% of Follow-up on ART
Immediate	94
Deferred	28

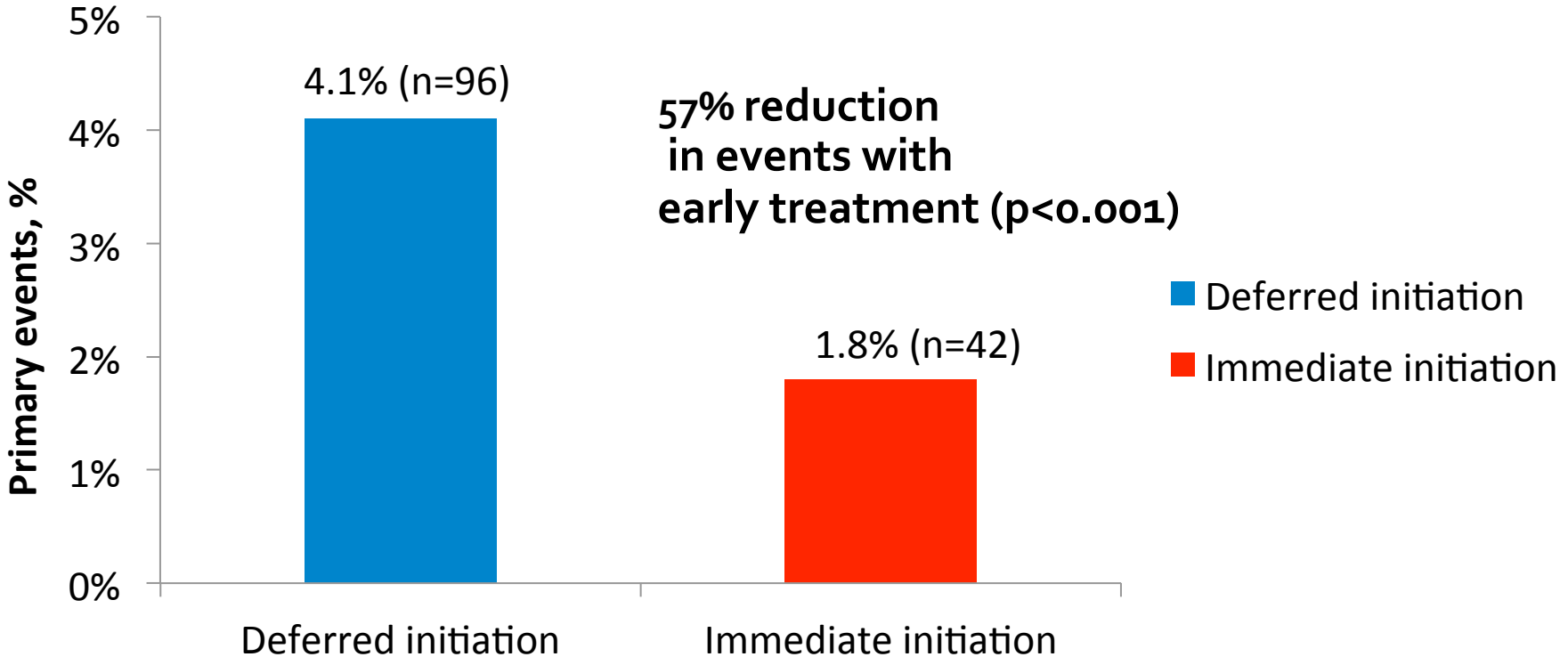
Deferred Arm:
Median time to ART
3 years (IQR 1.6-4.8)
(projected 4 years)

Lundgren J, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. MOSY0301.

START study

Primary composite endpoint

Hazard of developing AIDS, serious non-AIDS events, or death

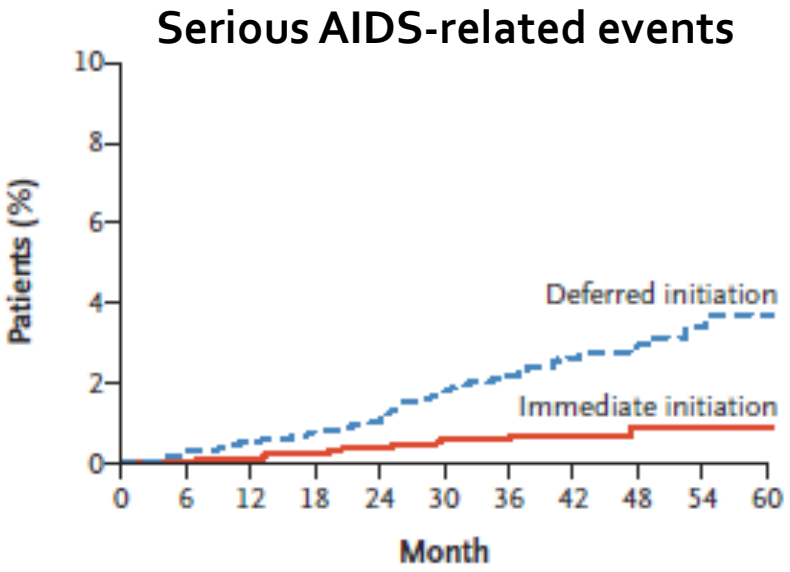


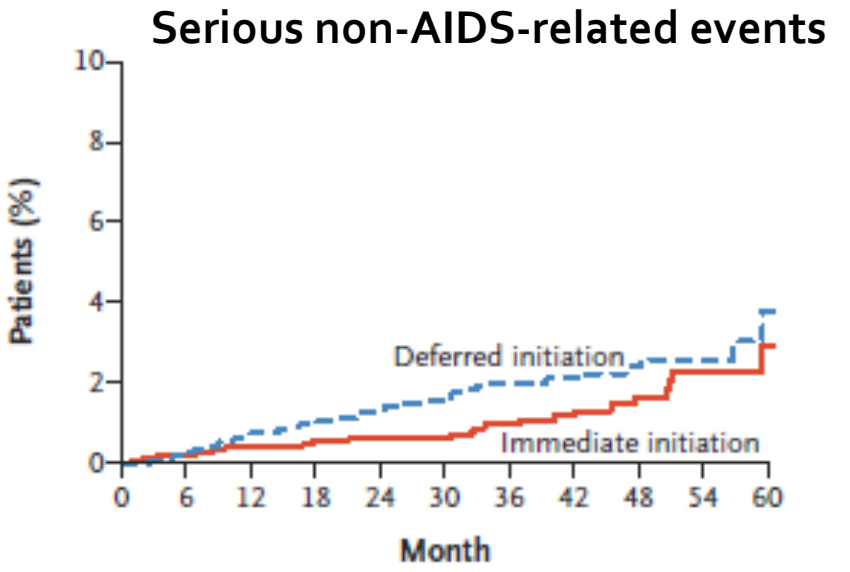
"Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count."

Lundgren JD et al. IAS 2015. Vancouver, CAN. Oral # MOSY03
INSIGHT START Study Group. NEJM 2015 Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

START study
Primary composite endpoint

- The estimated hazard ratio was 0.28 (95% CI, 0.15 to 0.50; P<0.001) for a serious AIDS-related event, 0.61 (95% CI, 0.38 to 0.97; P=0.04) for a serious non–AIDS-related event





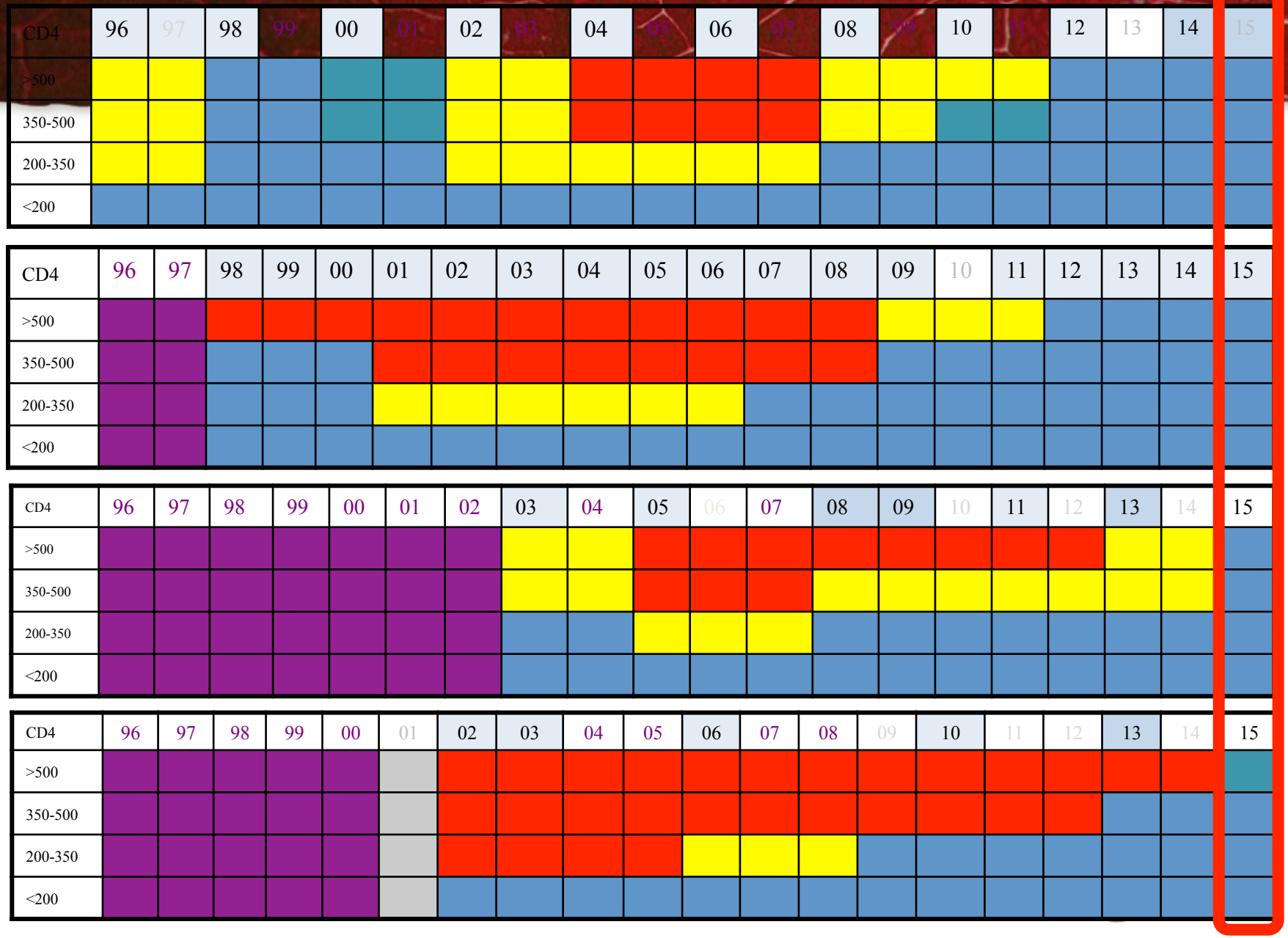
- Risk of AIDS was not zero among patients receiving antiretroviral therapy, even among those who had full viral suppression while receiving antiretroviral drugs
- Damage to the immune system may occur early in the course of HIV infection, supporting the need for better markers of impaired immune function and research on treatments to use along with antiretroviral therapy to reduce disease among HIV-positive patients
- START results showed a significant benefit in the immediate initiation of antiretroviral therapy in patients with HIV infection regardless of CD4+ count

INSIGHT START Study Group. NEJM 2015 Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

When to Start
Major Guidelines for ART Initiation in 2015

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm^3	CD4+ Cell Count 200-350/mm^3	CD4+ Cell Count 350-500/mm^3	CD4+ Cell Count > 500 cells/mm^3
Spanish 2015	Yes	Yes	Yes	Yes[1]	Yes[2]
European AIDS Clinical Society (Nov/2014)	Yes	Yes	Yes	Yes	Yes
Draft British HIV Association (2015)	Yes	Yes	Yes	Yes	Yes

Temporal Evolution of CD4 Criteria to Initiate ART in Asymptomatic HIV+ Adults (1996-2015) (IAS, DHHS, EACS and WHO ART Guidelines)



Topic	2002	2003	2006	2010	2013	2015*
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Regardless CD4 for TB and HBV	CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC - CD4 ≤ 350 as priority	**Towards treatment initiation at any CD4 cell count**
Earlier initiation						
1st Line ART	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDF preferred - d4T dose reduction	6 options & FDCs - AZT or TDF preferred - d4T phase out	1 preferred option & FDCs - TDF and EFV preferred across all pops	**Continue with FDC approach and phased introduction of new options (DTG, EFV_{400})**
Simpler treatment						
2nd Line ART	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	Boosted PIs - Heat stable FDC: ATV/r, LPV/r	**Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)**
Less toxic, more robust regimens						
3rd Line ART	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV	**Encourage HIV DR to guide**
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)	**Support for scale up of VL using all technologies**
Better and simpler monitoring						

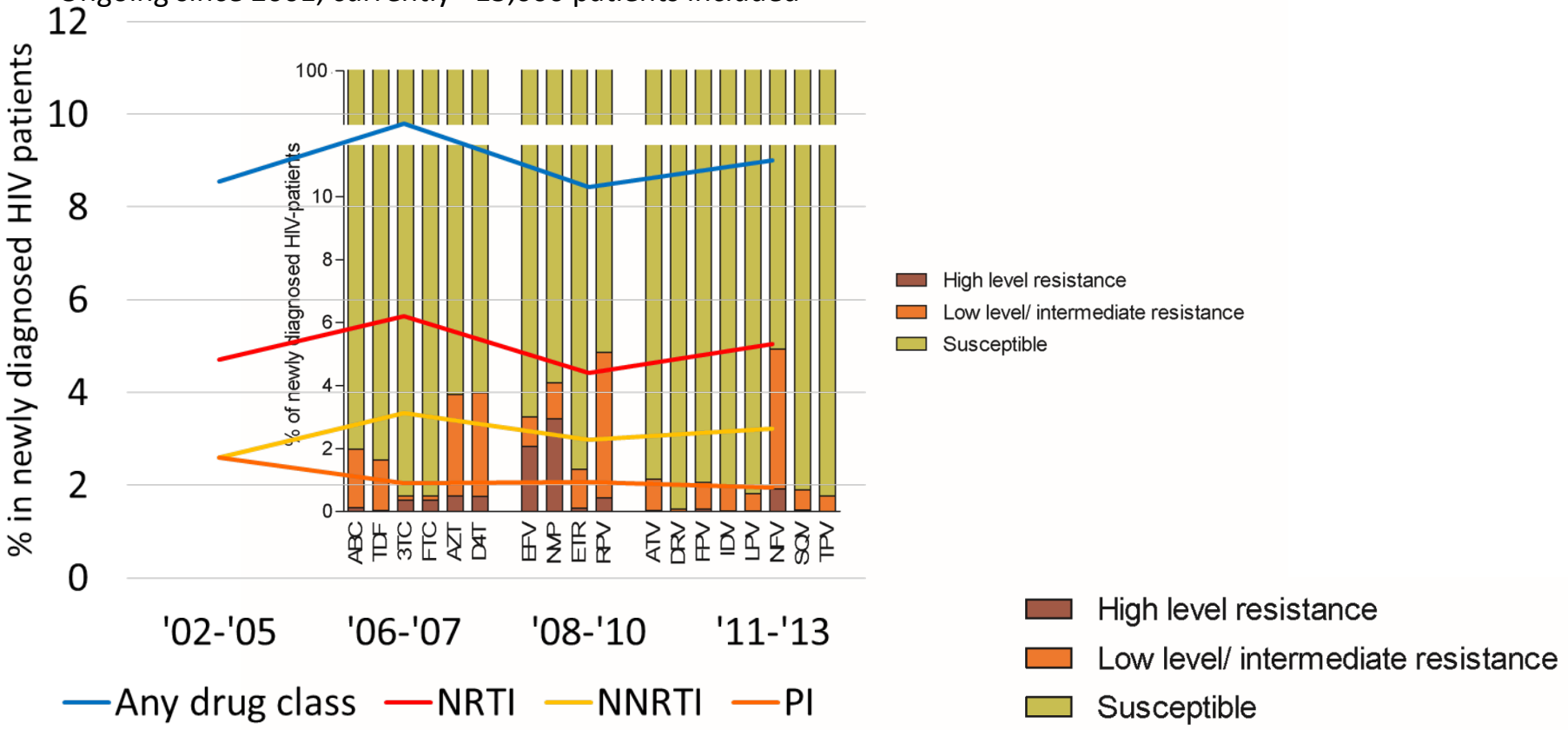
* provisional

Vitoria, & Ford,/2015

Prevalence of TDRM is stable in Europe

SPREAD Program:

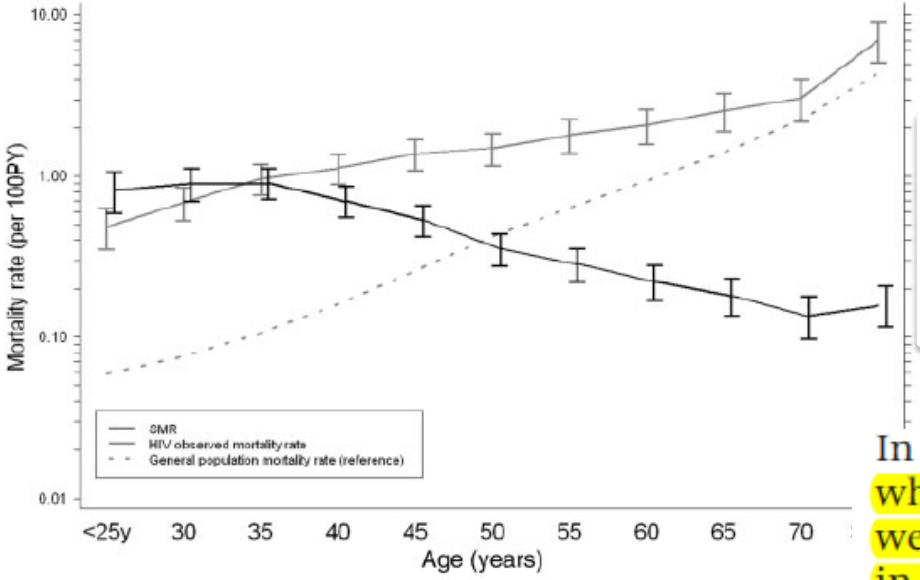
- Pan European surveillance program (28 countries involved)
- Monitor transmitted drug resistance in newly diagnosed ART naive patients
- Ongoing since 2001, currently >15,000 patients included



Hofstra LM et al on behalf of the SPREAD Program , CID 2015

All-cause mortality in treated HIV-infected adults with CD4 $\geqslant$500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration†

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord



International Journal of Epidemiology 2012;41:433–445

31 countries, 33 cohorts; 80,642 individuals
Overall mortality rate higher in HIV +, except if CD4 count reaches ≥ 500/mm3

In conclusion, among treated HIV-infected individuals who attained a CD4 count $\geqslant$500/mm^3, mortality rates were similar to those of the general population in non-IDU men and after 3 years in this CD4 strata in non-IDU women. Among IDUs, mortality rates remained higher than those in the general population, even after 5 years spent with a CD4 count $\geqslant$500/mm^3, though SMRs tended to decrease with longer durations above this threshold. Further studies will be necessary to confirm this trend across several decades of cART. The persistent influence of a prior AIDS diagnosis even among those attaining a high CD4 count, underlines the importance of the current public health calls for earlier identification of HIV infection and entry into care.

HIV-drugs 2016

NRTI/NtRTI	NNRTI	Proteaseinhibit	Fusionsinhibit.
AZT	Nevirapine	Saquinavir	Fuzeon
3TC	Efavirenz	Indinavir	
DDI	Etravirine	Nelfinavir	Integraseinhib.
D4T	Rilpivirine	Ritonavir	Raltegravir
Abacavir		Fosamprenavir	Elvitegravir/c
Tenofovir		Lopinavir/r	Dolutegravir
FTC		Atazanavir	CCR5-Inhibitor
		Tipranavir	Maraviroc
		Darunavir	

Comparing preferred and alternative 1st line ARV options (DHHS, IAS, EACS and WHO ART guidelines)

GUIDELINES	NRTI BACKBONE			NNRTI			INSTI			PI		
	TDF/ XTC	ABC/ 3TC	AZT/3TC	EFV	NVP	RIL	DTG	EVG	RQL	ATV	DRV	LPV
IAS (2014)												
DHHS (2015)												
EACS (2015)												
WHO (2015)												

preferred

alternative

not recommended/ special situations

GUIDELINES	preferred 1st line options	alternative 1st line options
IAS (2014)	**11**	**16**
DHHS (2015)	**05**	**07**
EACS (2015)	**06**	**13**
WHO (2015)	**01**	**05**

M Vitoria, 2015,

What to Start
Times are changing

Comparison of International Guidelines 2015

Regimen	Draft BHIVA	GESIDA	EACS
EFV/TDF/FTC	Alternative	Alternative	Recommended
ATV/r + TDF/FTC	Recommended	Alternative	Recommended
DRV/r + TDF/FTC	Recommended	Alternative	Recommended
EVG/COBI/TDF/FTC	Recommended	Alternative	Recommended
RAL + TDF/FTC	Recommended	Recommended	Recommended
DTG + ABC/3TC DTG + TDF/3TC	Recommended	Recommended	Recommended

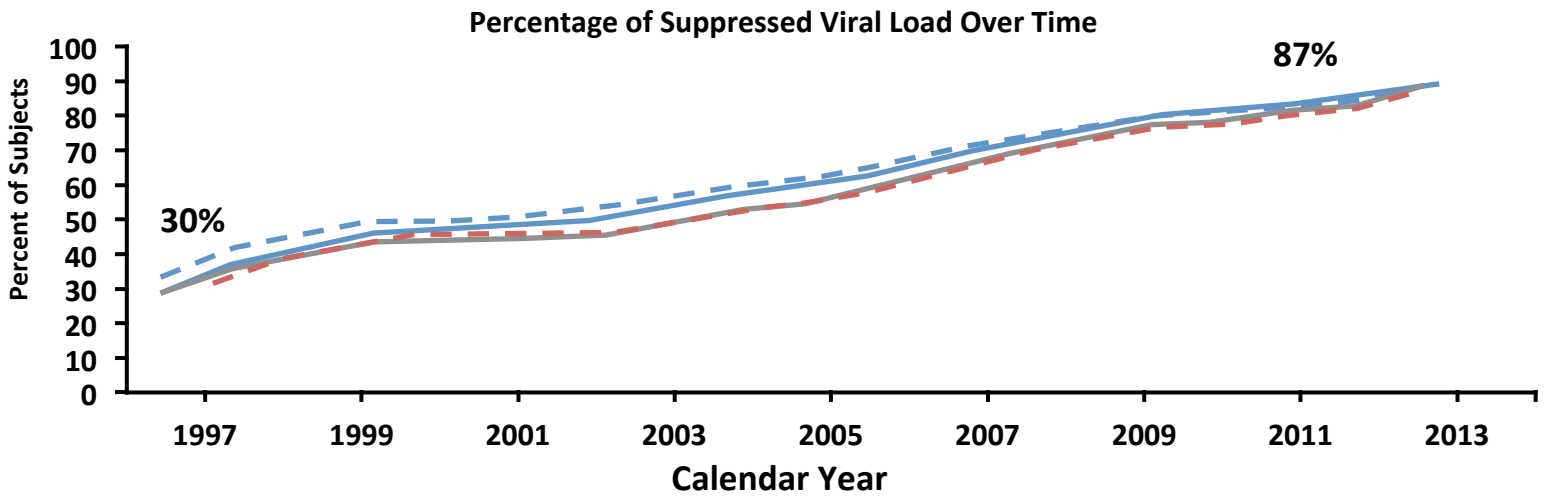
Perspectives in ARV optimization

ART Optimization Strategy	Tolerability	Robust	Convenient	PW, TB, children	Cost Reduction	What is needed?	Timeline
Low dose EFV	✓	?	✓	?	✓	• pK studies (PW & TB)	**1-2 yrs**
Low dose DRV/r (as FDC)	✓	?	✓	?	✓	• pK studies (DRV:RTV ratio) • RCT (standard vs low dose)	**1-2 yrs**
Use of DTG (as FDC)	✓	✓	✓	?	✓	• Studies in PW, TB & children • Comparative trials • RCT (DRV/r + DTG in 2nd line)	**2-5 yrs**
Use of TAF	✓	?	✓	?	✓	• Comparative trials using DTG • Studies in PW, TB & children	**2-5 yrs**
Long-acting formulations	✓	?	✓	✓	✓	• Phase II/III studies (treatment & preventive trials)	**> 5 yrs**

WHO Think Tank, on Treatment Optimization (meeting report), 2014

US Clinics: Changes in Viral Load Over Time

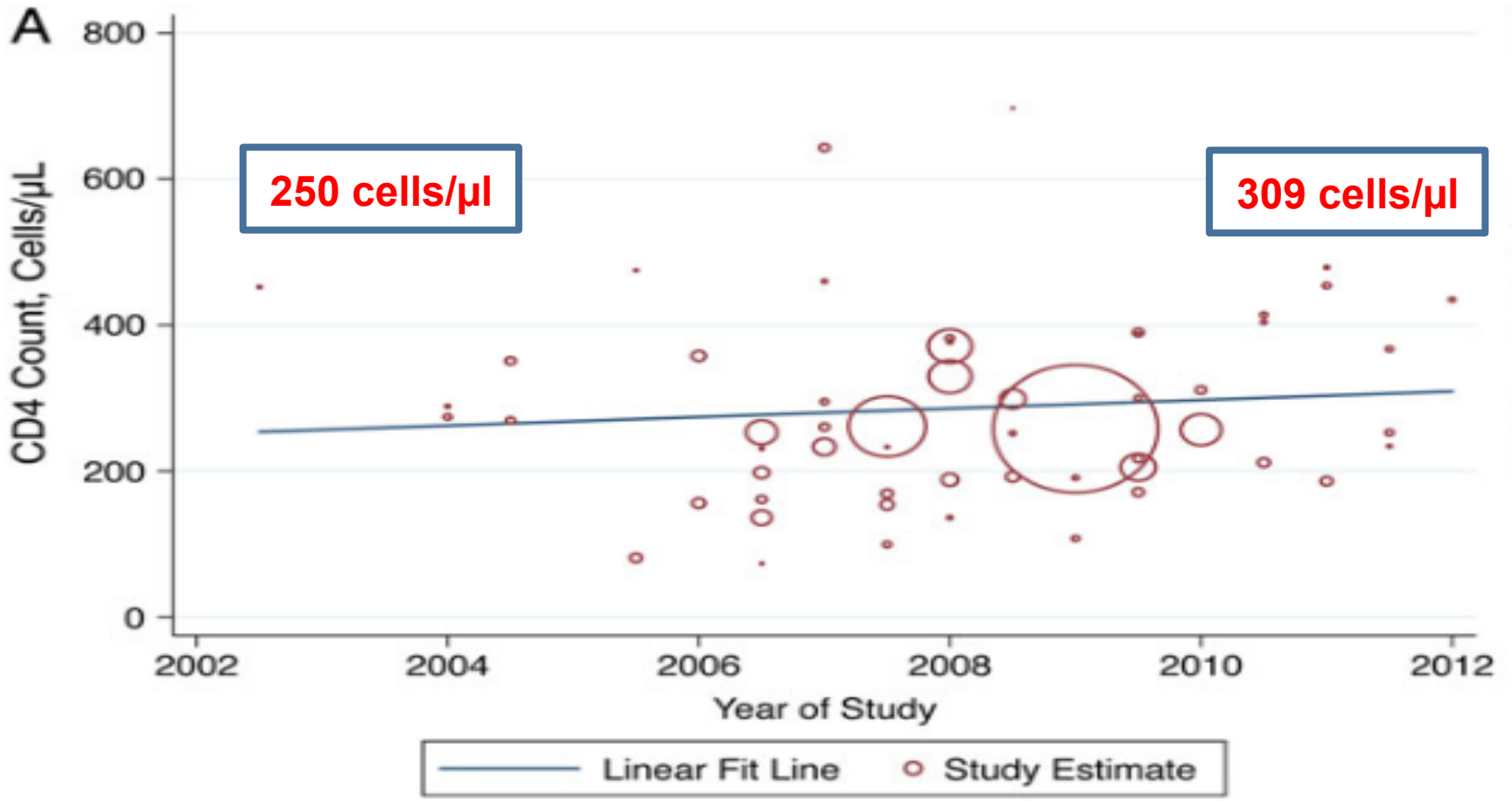
CFAR Network of Integrated Clinical Systems (CNICS)
Cohort 29,467 Participants at 8 HIV Clinics



	OR	Std Err	95% CI	P-value
Integrase Use	2.40	0.12	[2.17-2.66]	<0.01
Male	1.42	0.09	[1.23-1.61]	<0.01
Age (per year)	1.05	0.00	[1.04-1.05]	<0.01
Race (White=Ref)				
Black	0.48	0.03	[0.43-0.53]	<0.01
Hispanic	1.09	0.08	[0.94-1.26]	0.27
Other/Missing	1.24	0.14	[0.99-1.55]	0.06
Years from Baseline	2.95	0.10	[2.76-3.14]	<0.01

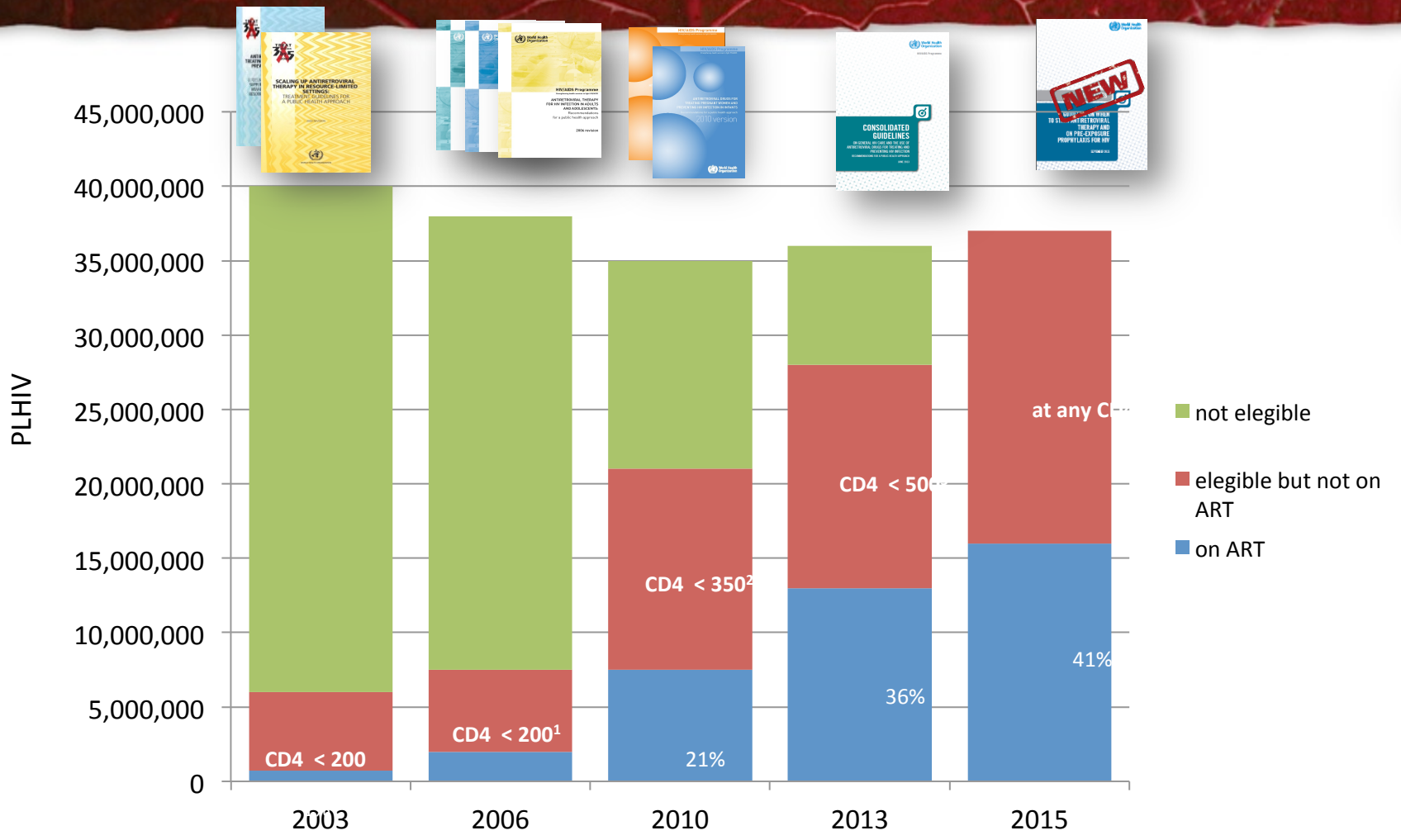
Simoni J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 1034.

Trends in CD4 Count at Presentation to Care and Treatment Initiation in Sub-Saharan Africa, 2002–2013: A Meta-analysis



Siedner MJ, *CID* 2015

Evolution of global ART coverage and eligibility criteria according WHO guidelines (2003-2015)



Source WHO rand UNAIDS reports

1. At CD4 < 350: active TB disease and HIV+ pregnant women
2. At any CD4: active TB disease and HBV co-infection requiring HBV treatment"
3. At any CD4: active TB disease, HBV co-infection with severe liver disease, HIV+ pregnant women and HIV serodiscordant couples