State of the ART of ARV Therapy

Manuel Battegay

Basel, Switzerland

UNI BASEL

EACS European AIDS Clinical Society

Universitätsspital Basel

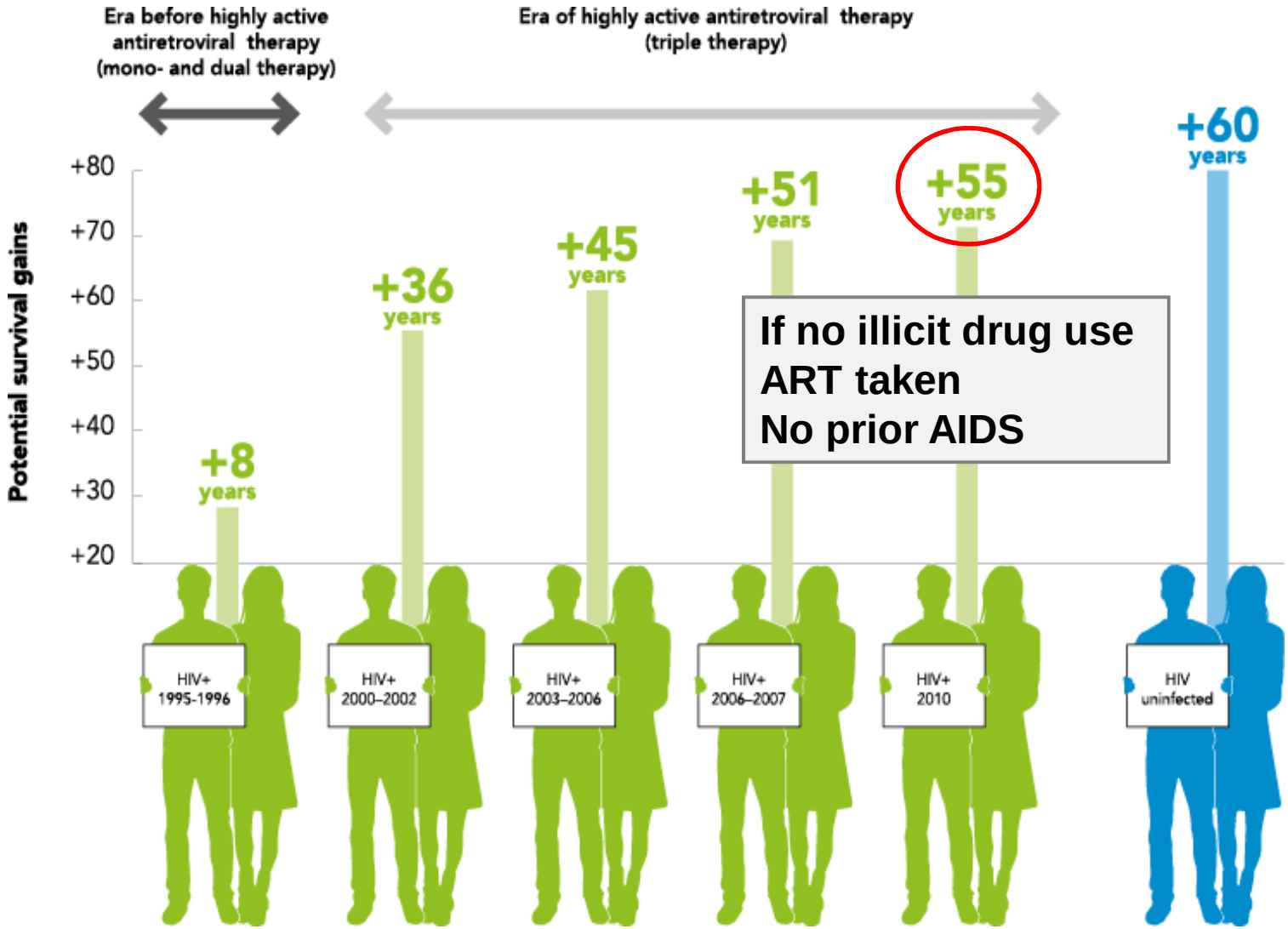
Conflict of Interest

- None
  - No participation in Speakers Bureau at any time ever
  - No stocks or stock options of pharmaceutical or biotech companies at any time ever
  - No participation in Satellite Meetings since 2011
  - No participation in Advisory Boards since 2014

State of the ART of ARV Therapy

- **When to start antiretroviral therapy**
- **Treatment as prevention - TASP**
- **What to start with**
- **Perspectives**

Mortality - Almost no Difference to HIV-Negative Persons



UNAIDS / Lohse et al / Hoog et al / May et al / Hogg et al

LIFE EXPECTANCY BY HIV STATUS AND EDUCATION IN SWITZERLAND

16,532 HIV-positive patients (72% male); 1,328,985 people from the SNC

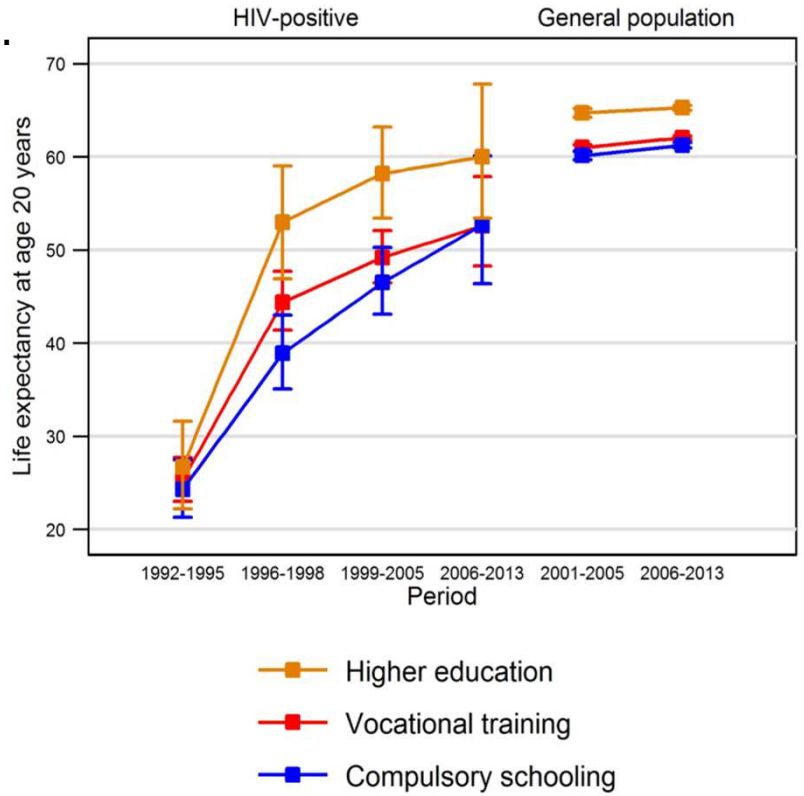
11,304 (68.4%) treatment naïve at enrolment

4,707 (28.5%) history of current or past IDU.

HIV-positive individuals with higher education have a life expectancy similar to individuals from the general population with compulsory education.

Life expectancy increased most when cART was introduced (1996-1998) and continued to increase thereafter.

Greater life expectancy among those with higher education compared to those with compulsory education only.



Additional life expectancy at age 20 years in the SHCS and the general Swiss population by level of education.

A. Gueler et al, and M. Egger for the Swiss HIV Cohort Study and Swiss National Cohort

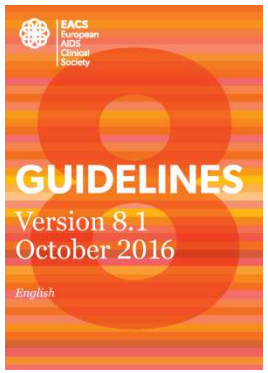
AIDS 2016
DURBAN, SOUTH AFRICA

Aims of ART

Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons ***HIV Medicine, 2016***

L Ryom,[1] C Boesecke,[2] V Gisler,[3] C Manzardo,[4] JK Rockstroh,[2] M Puoti,[5] H Furrer,[3] JM Miro,[4] JM Gatell,[4] A Pozniak,[6] G Behrens,[7] M Battegay[8] and JD Lundgren[1] on behalf of the EACS Governing Board

EACS European AIDS Clinical Society



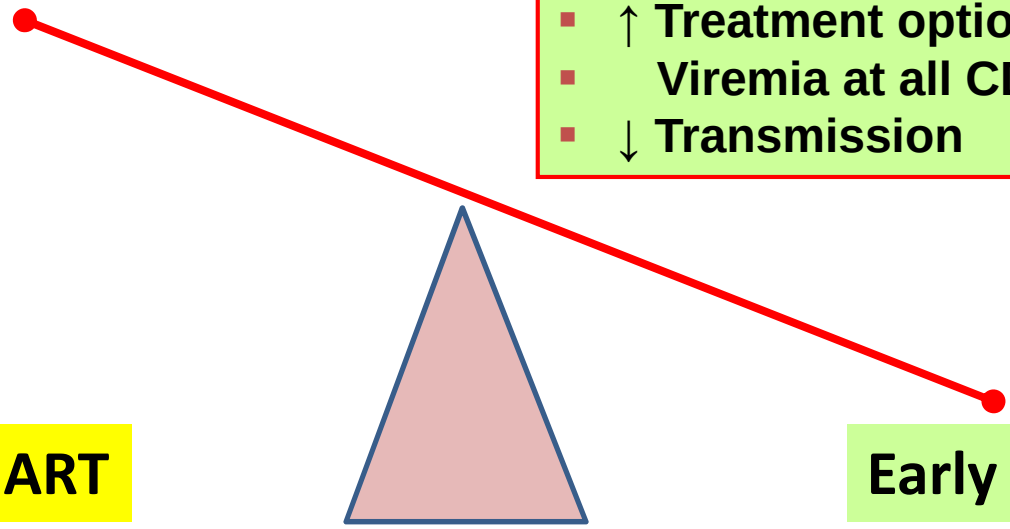
1. Suppression of HIV viral load in >>90%!
2. Immunological function close to normal
3. **Reduction of HIV morbidity and mortality**
4. **Reduction of transmission**

http://www.eacsociety.org, Coordinator Lundgren JD, Medical Assistant Ryom L. et al.

When to Start Therapy: Balance now Favors Early ART

- Drug toxicity
- Preservation of ART options
- Risk of resistance
- Risk of transmission of resistant virus

- ↑ Potency, durability, simplicity, safety of ART
- ↓ Resistance
- ↓ Toxicity with earlier therapy
- ↑ Treatment options
- Viremia at all CD4 levels
- ↓ Transmission

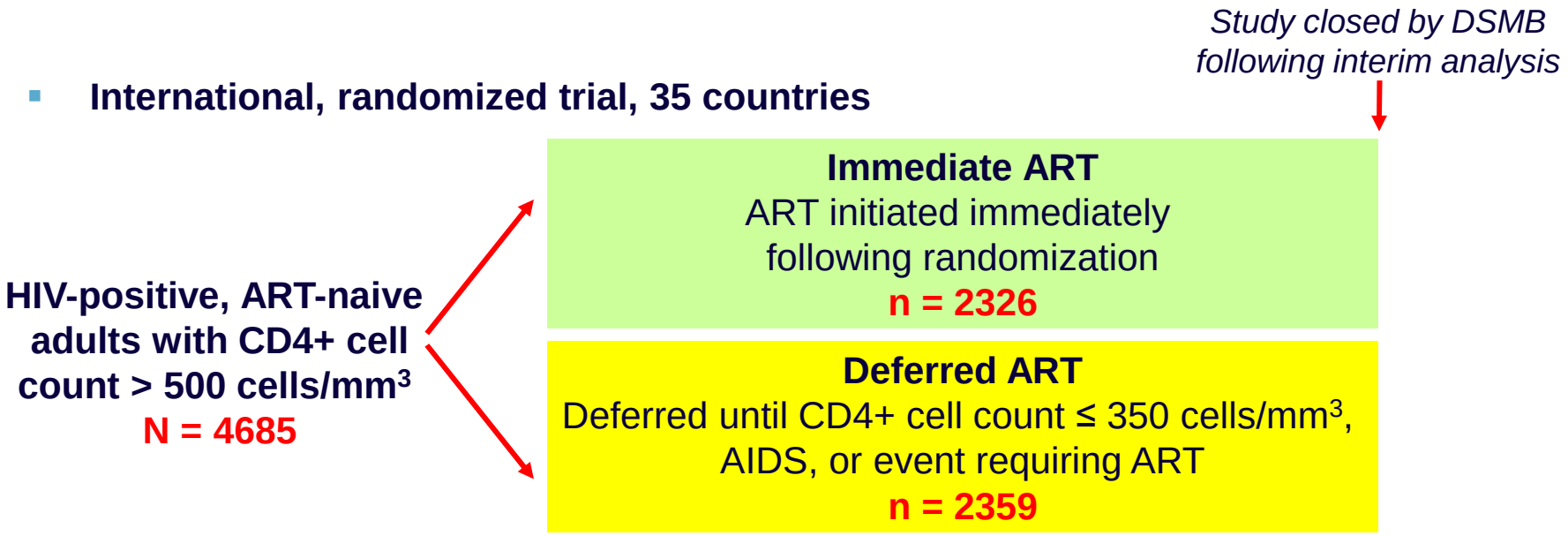


Delayed ART

Early ART

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Patients

- **International, randomized trial, 35 countries**

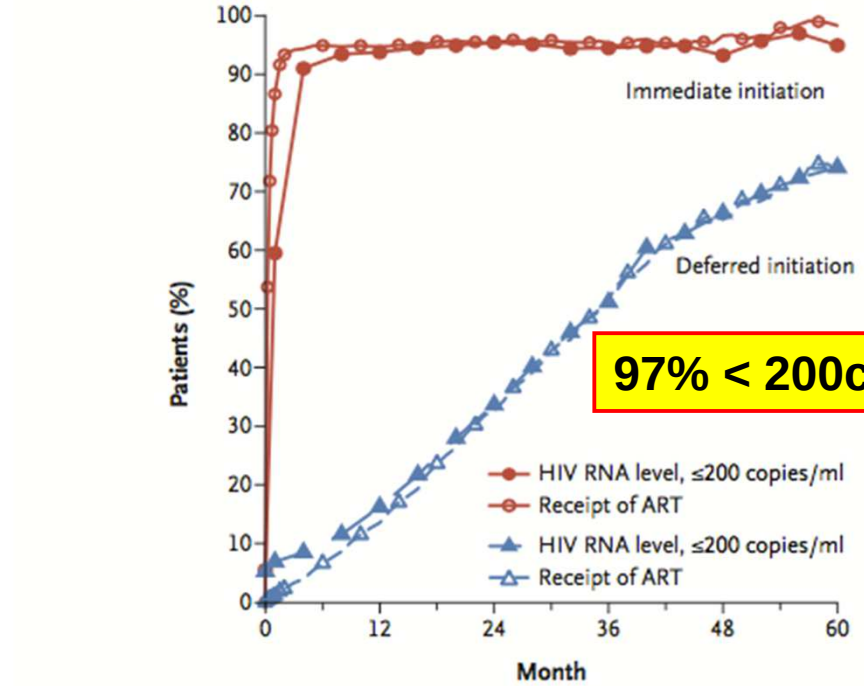


- **Composite primary endpoint**: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- **Mean follow-up**: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm^3

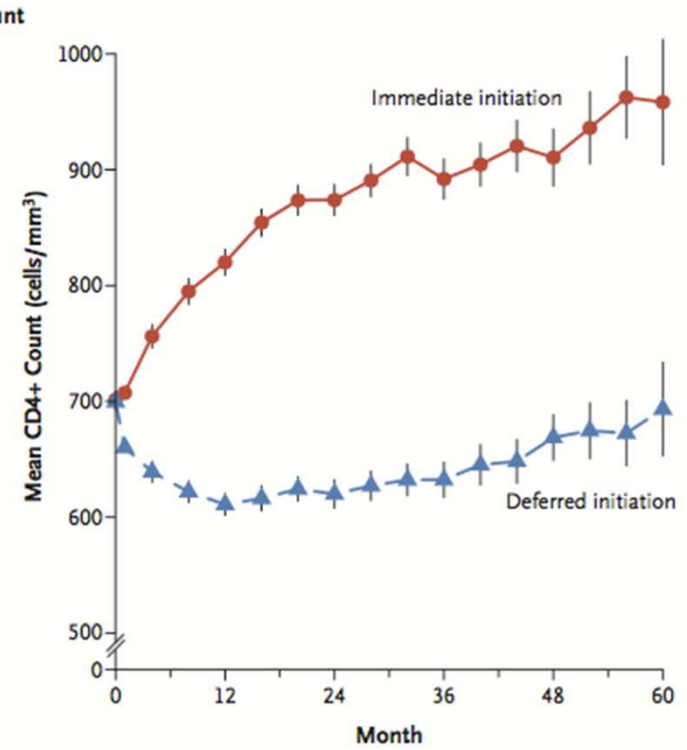
INSIGHT START Study Group, Lundgren JD et al., N Engl J Med. 2015

ART, HIV RNA and CD4 Course

98% < 200c/mL



97% < 200c/mL



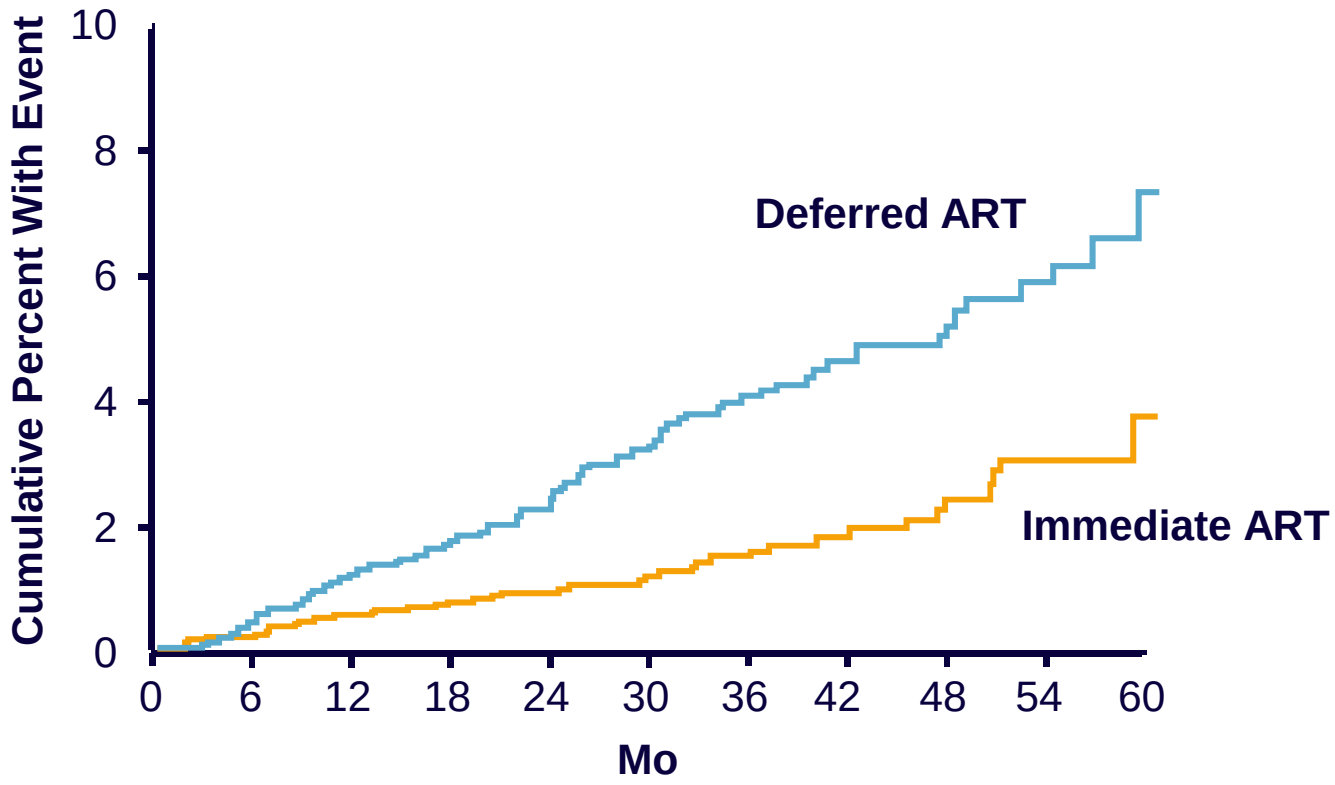
No. of Patients						
Immediate initiation	2326	2287	1809	1040	551	115
Deferred initiation	2359	2303	1837	1055	546	109

No. of Patients						
Immediate initiation	2326	2205	1853	1075	574	157
Deferred initiation	2359	2190	1829	1077	549	162

INSIGHT START Study Group, Lundgren JD et al., N Engl J Med. 2015

START: 57% Reduced Risk of Serious Events or Death with Immediate ART

4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; *P* < .001)



INSIGHT START Study Group, Lundgren JD et al., N Engl J Med. 2015

START: Primary Endpoint Components with Immediate vs Deferred ART

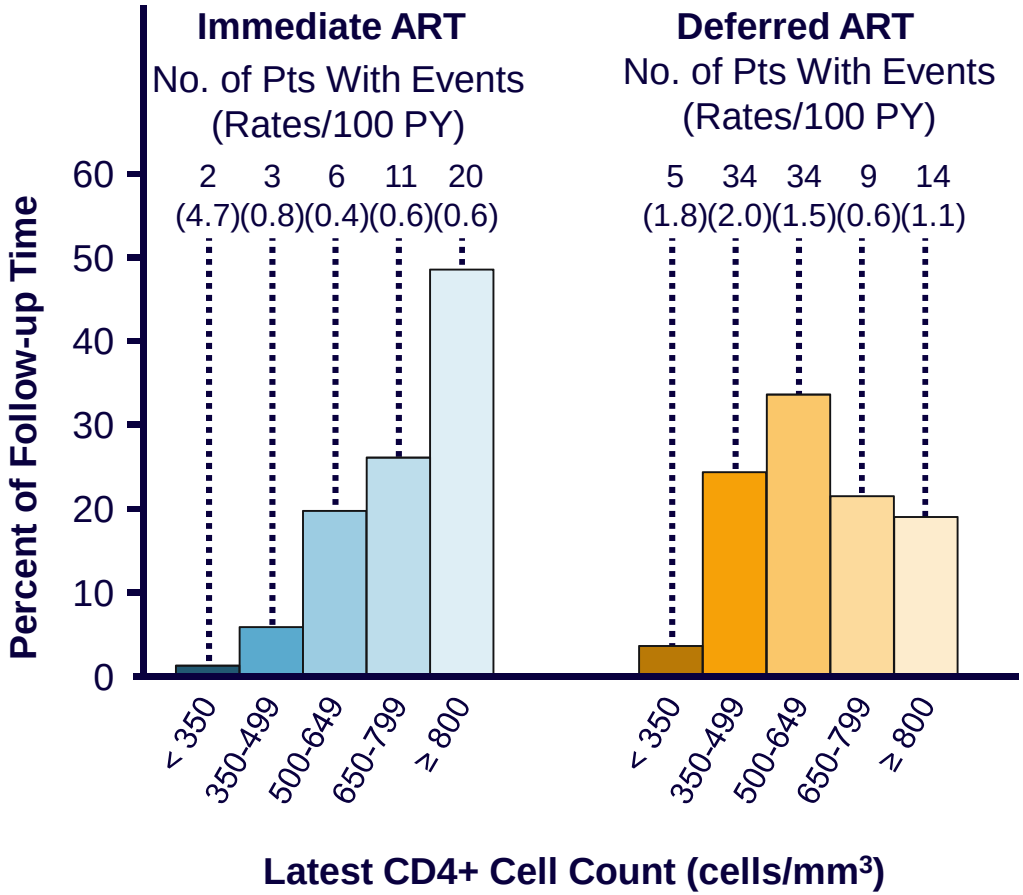
Endpoint	Immediate ART (n = 2326)		Deferred ART (n = 2359)		HR (95% CI)	*P* Value
	N	Rate/100 PY	N	Rate/100 PY		
Serious AIDS-related event	14	0.20	50	0.72	**0.28 (0.15-0.50)**	< .001
Serious non-AIDS–related event	29	0.42	47	0.67	**0.61 (0.38-0.97)**	.04
All-cause death	12	0.17	21	0.30	**0.58 (0.28-1.17)**	.13
Tuberculosis	6	0.09	20	0.28	**0.29 (0.12-0.73)**	.008
Kaposi's sarcoma	1	0.01	11	0.16	**0.09 (0.01-0.71)**	.02
Malignant lymphoma	3	0.04	10	0.14	**0.30 (0.08-1.10)**	.07
Non-AIDS–defining cancer	9	0.13	18	0.26	**0.50 (0.22-1.11)**	.09
CVD	12	0.17	14	0.20	**0.84 (0.39-1.81)**	.65

INSIGHT START Study Group, Lundgren JD et al., N Engl J Med. 2015

START: Primary Endpoint Events by Latest CD4+ Cell Count

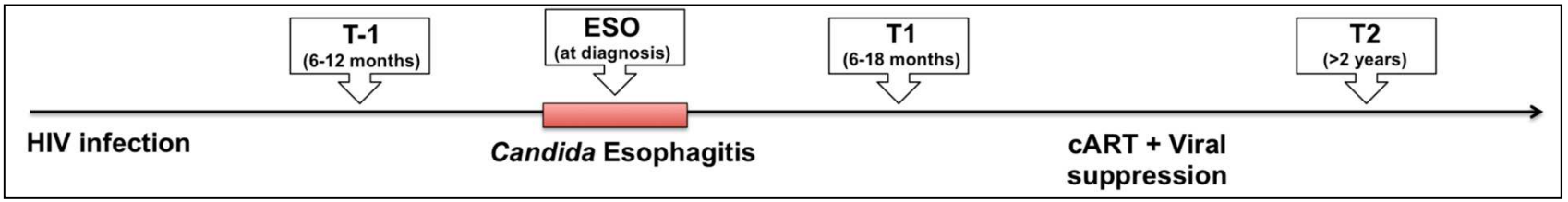
Latest CD4+ count > 500 cells/mm³

	Immediate ART	Deferred ART
Primary events, % (n/N)	88 (37/42)	59 (57/96)
Rate/100 PY	0.6	1.1

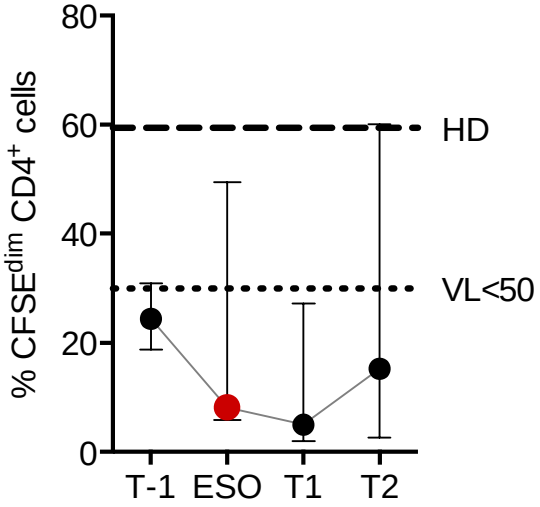


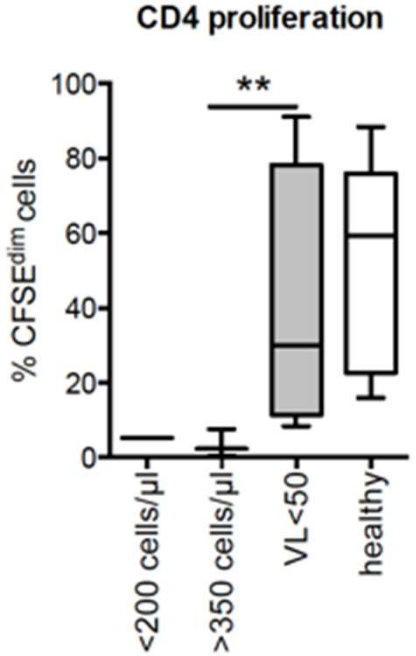
INSIGHT START Study Group, Lundgren JD et al., N Engl J Med. 2015

Immunological Gaps Persist despite ART



Proliferation of *Candida*-specific CD4





- **Case control study**
- n= 33 cases with *Candida* ESO
- Swiss HIV Cohort

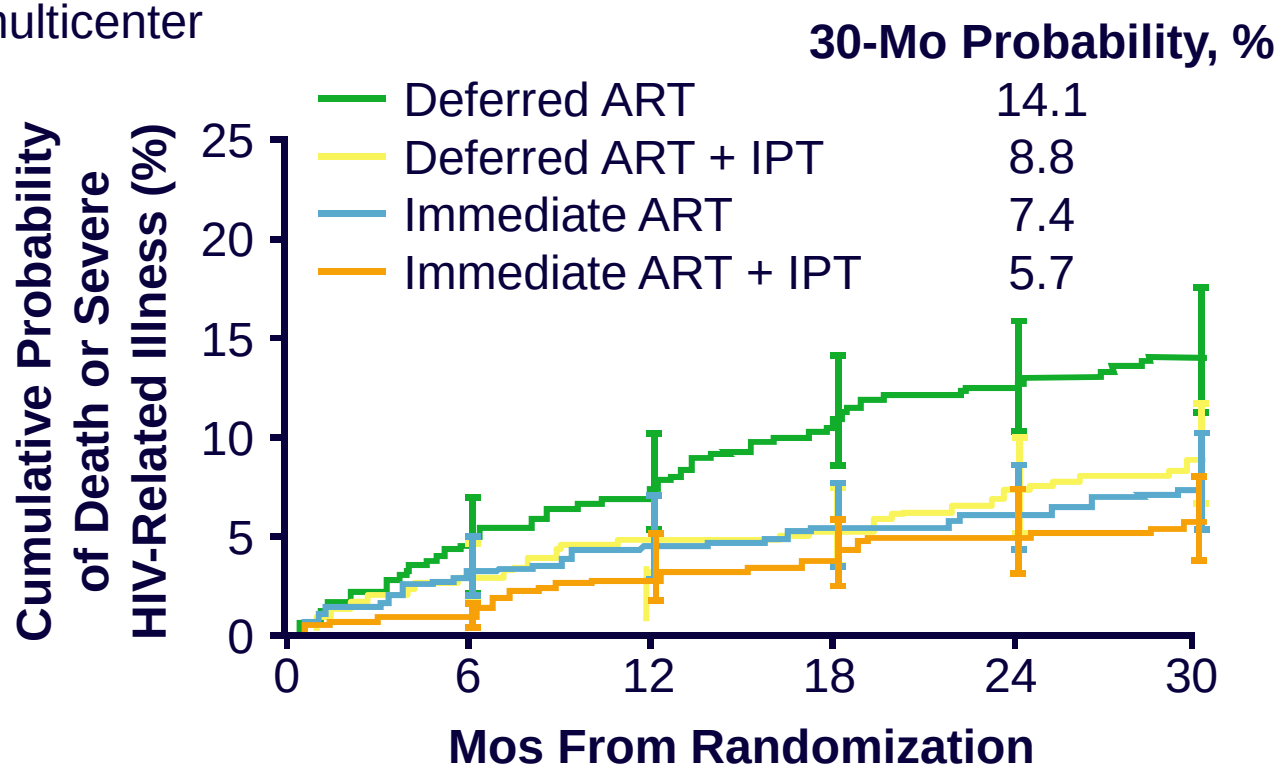
Specific gaps are present regardless of absolute CD4 cell counts at diagnosis and persist despite successful ART

Stuehler C, Battegay M and Khanna N et al., EACS 2015

TEMPRANO: Immediate or Deferred ART Initiation ± Isoniazid Preventive Therapy for African Patients

RCT, unblinded, multicenter

Pts with HIV infection and CD4+ cell count < 800 cells/mm^3 who did not meet WHO criteria for initiating ART (N = 2056)



TB 42% and bacterial diseases 27% of primary endpoints

TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015

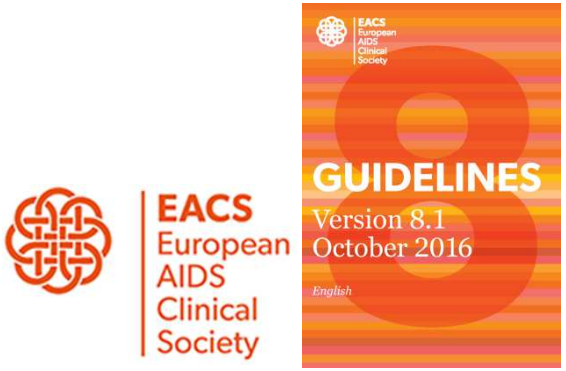
Start at any CD4 vs < 350

- Reduction of Morbidity +++
- Reduction of Mortality +
- Prevention if immunological Damage
- Well tolerated ARVs
- Lifetime duration versus short saving of drugs, approx. 3 years
- Transmission reduced
- Drug toxicity (+)
- Drug resistance +
- Number needed to treat high at early stage with high CD4

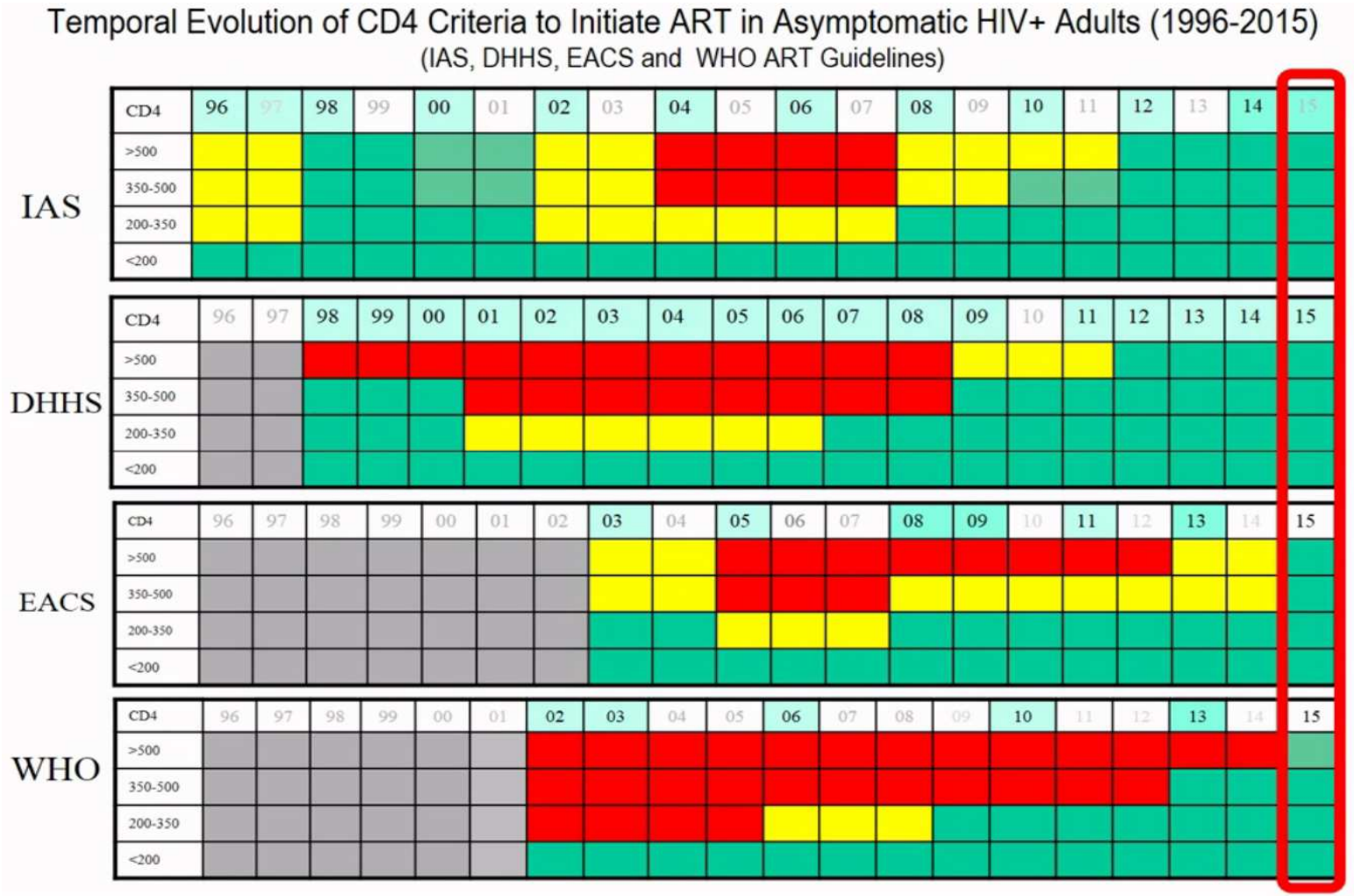
Impact on Guidelines

ART is recommended in all adults with chronic HIV infection

ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately.



CD4 at Start – Guidelines in Agreement



Slide courtesy Marco Vittoria

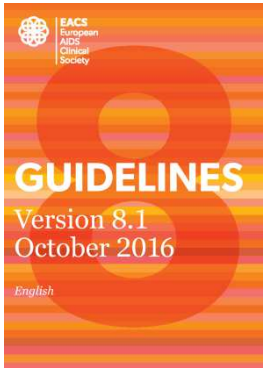
Starting ART during Primary HIV-infection

- Reduce severity of acute symptoms
- Limit neurological damage: **persons with neurological involvement should be treated without delay**
- Preserve immune function and integrity of lymphoid tissue (gut)
- Reduce immune activation and inflammation
- Reduced risk of transmission, anxiety, and facilitated disclosure
- Short interval between PHI and a CD4 count <500 cells/µL
- Before the results of resistance testing become available, preference should be given to starting a PI/r- or II based regimen

- Potential disadvantages: uncertain long-term clinical benefit; low likelihood of post-treatment control: possible adverse of treatment interruptions or consequences of long-term ART (toxicity, resistance)

Starting ART during Primary HIV-infection

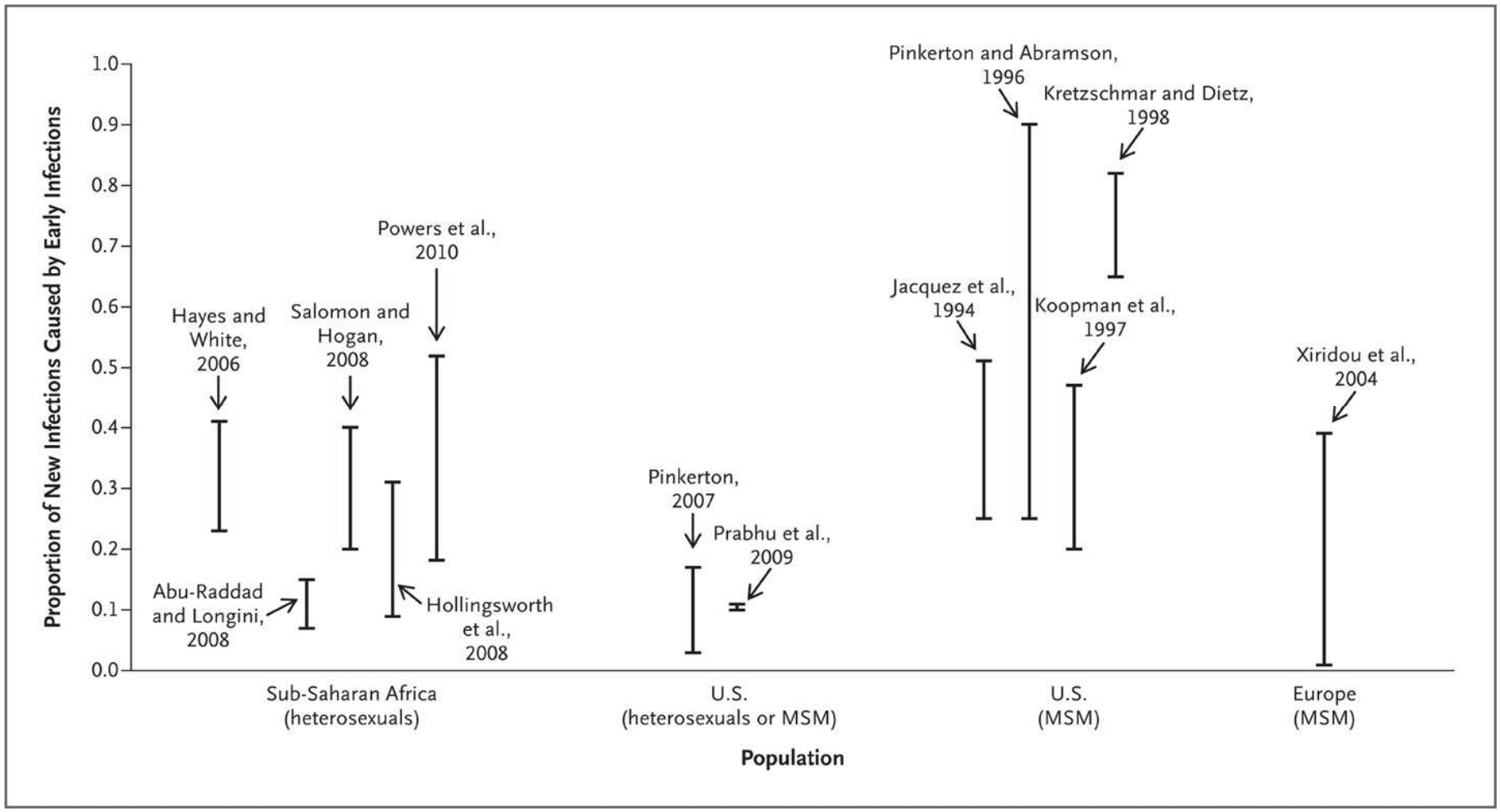
Immediate treatment initiation should be advised, when:
Acute infection
Severe or prolonged symptoms
Neurological disease
Age ≥ 50 years
CD4 count < 350 cells/µL



State of the ART of ARV Therapy

- When to start antiretroviral therapy
- Treatment as prevention - TASP
- What to start with
- Perspectives

Acute HIV-Infection
% of HIV-Transmissions



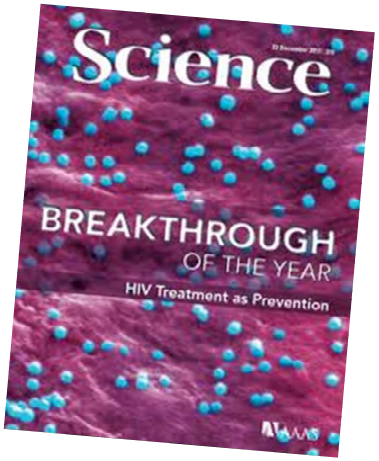
Cohen MS et al. N Engl J Med 2011

Reduction of Transmission with ART

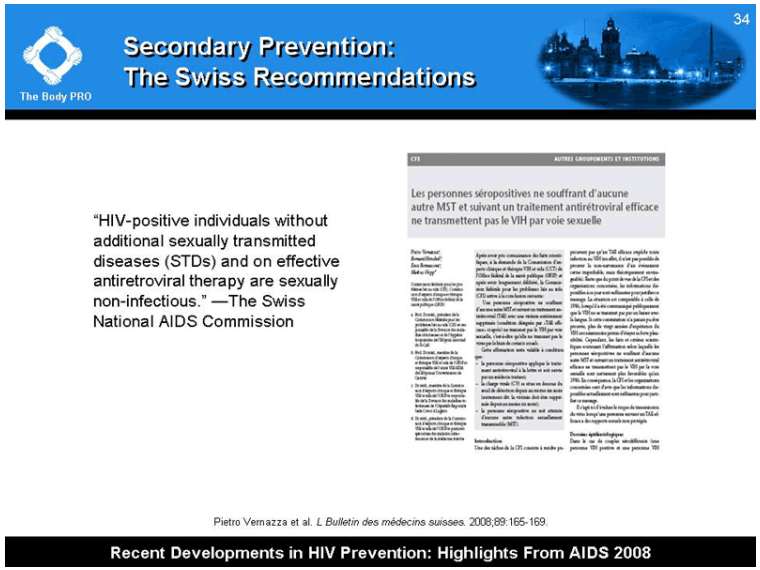
TASP = Treatment as Prevention

Myron S. Cohen et al, New England Journal of Medicine, 2011

Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe

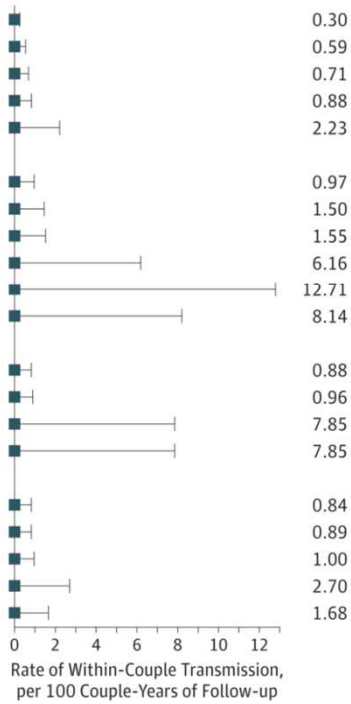


- 1763 serodiscordant couples (HIV+/HIV-)
- Reduction, with early therapy **96% !**
  - 1 Transmission in early therapy group
  - 27 Transmissions in standard therapy group



Sexual Activity without Condoms and Risk of HIV Transmission in Serodifferent Couples when the HIV+ Partner is using suppressive ART <200c/mL

	HIV-Negative Members of Eligible Couples Reporting Specific Sex Act, No./Total (%)	Couple-Years of Follow-up	Upper 95% Confidence Limit
All			
Any sex	863/866 (99.7)	1238	0.30
Vaginal sex	532/878 (60.6)	629	0.59
Anal sex	449/849 (52.9)	522	0.71
Insertive anal sex	363/862 (42.1)	417	0.88
Receptive anal sex with ejaculation	185/864 (21.4)	166	2.23
Heterosexual women			
Any sex	261/262 (99.6)	381	0.97
Vaginal sex with ejaculation	193/259 (74.5)	246	1.50
Vaginal sex without ejaculation	207/257 (80.5)	238	1.55
Anal sex	61/256 (23.8)	60	6.16
Receptive anal sex with ejaculation	37/255 (14.5)	29	12.71
Receptive anal sex without ejaculation	55/253 (21.7)	45	8.14
Heterosexual men			
Any sex	272/274 (99.3)	418	0.88
Vaginal sex	271/275 (98.5)	383	0.96
Anal sex	60/264 (22.7)	47	7.85
Insertive anal sex	60/264 (22.7)	47	7.85
Men who have sex with men			
Any sex	330/330 (100)	439	0.84
Anal sex	328/329 (99.7)	415	0.89
Insertive anal sex	303/329 (92.1)	370	1.00
Receptive anal sex with ejaculation	148/329 (45.0)	137	2.70
Receptive anal sex without ejaculation	217/324 (67.0)	220	1.68



HIV Transmission According to Sexual Behavior Reported

75 clinical sites,14 European countries

888: 548 heterosexual, 340 MSM, 1238 eligible couple-years of follow-up (1.3 yrs)

MSM	**22 000 sex acts**
heterosexuals	**36 000 sex acts**

11 HIV-negative partners became HIV-positive (10 MSM; 1 heterosexual)
No phylogenetically linked transmissions

Within-couple HIV transmission = 0
Upper 95%confidence limit of 0.30/100 couple-yrs of follow-up (condomless anal sex 0.71 per 100 couple-yrs of fup)

Longer-term follow-up is necessary to provide more precise estimates of risk

A. Rodger et al and JD Lundgren for the PARTNER Study Group, JAMA. 2016

Sexual Activity without Condoms and Risk of HIV Transmission in Serodifferent Couples when the HIV-Positive Partner is using suppressive ART <200c/mL

….this study provides informative data (especially for heterosexuals) for couples to base their personal acceptability of risk on.

In the absence of ART, receptive anal sex with ejaculation is recognized as carrying a higher risk than other forms and, despite an observed transmission rate of zero for this risk behavior, a clinically important rate of less than 2.2 per 100 couple-years of follow-up cannot be excluded.

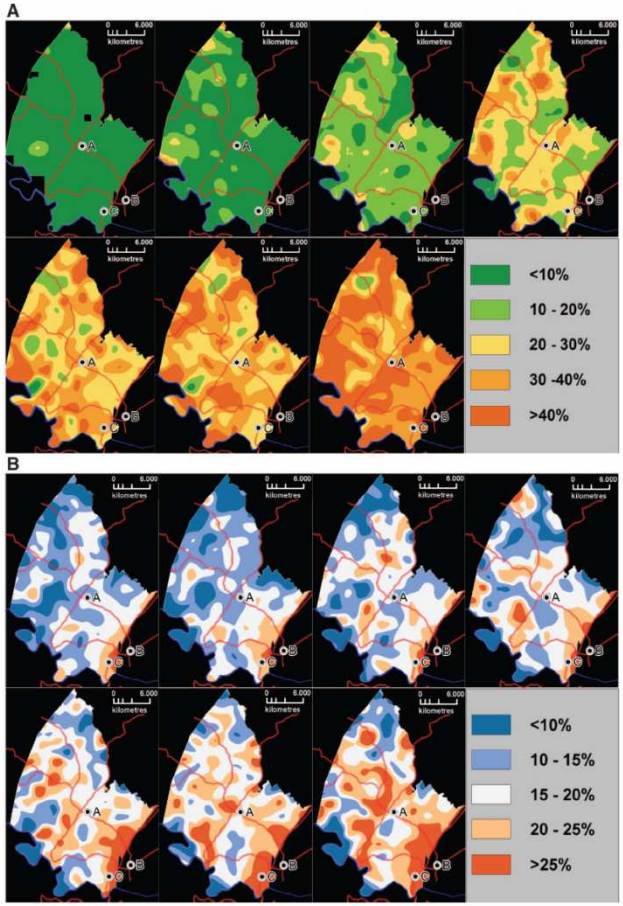
This translates into an upper limit estimate of 20% risk over 10 years. Because the upper limit of the 95% confidence interval is a function of the amount of couple-years of follow-up for that sexual act, additional follow-up in MSM is therefore needed through the second phase of the PARTNER study (PARTNER2).

A. Rodger et al and JD Lundgren for the PARTNER Study Group, JAMA. 2016

REPORTS www.sciencemag.org SCIENCE VOL 339 22 FEBRUARY 2013

High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser,[1*] Till Bärnighausen,[1,2] Erofili Grapsa,[1] Jaffer Zaidi,[1] Marie-Louise Newell[1,3]



A: ART coverage B: HIV prevalence

ART coverage = proportion of the total HIV-infected population receiving ART at <200 – 350 CD4 cells

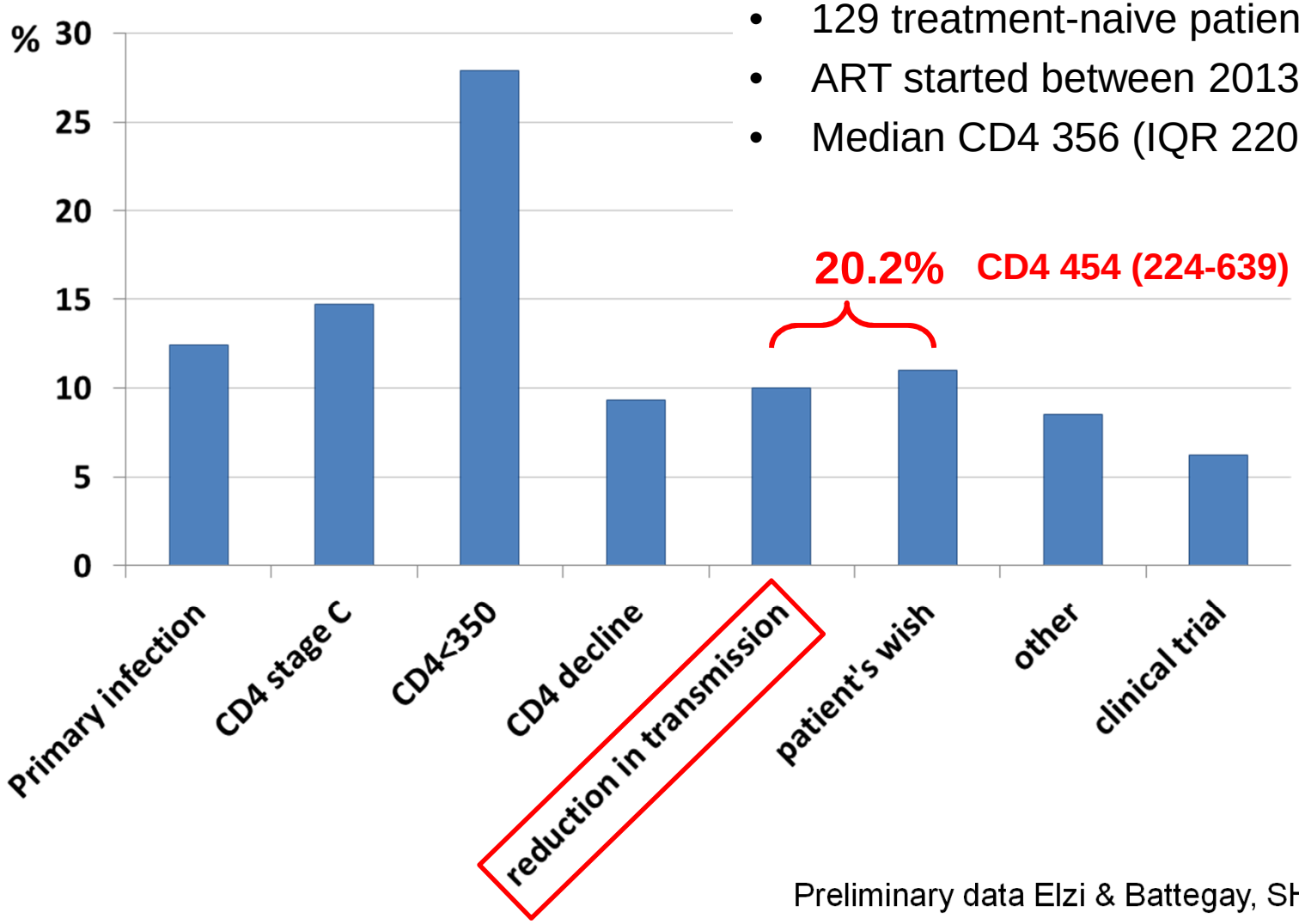
Population: approx. 60’000 persons

16’667 patients, each geolocated, 3 km

HIV-uninfected individual in community with high ART coverage (30 to 40%) 38% less likely to acquire HIV than someone living in community with low ART coverage (<10%)

Tanser et al. Science 2013

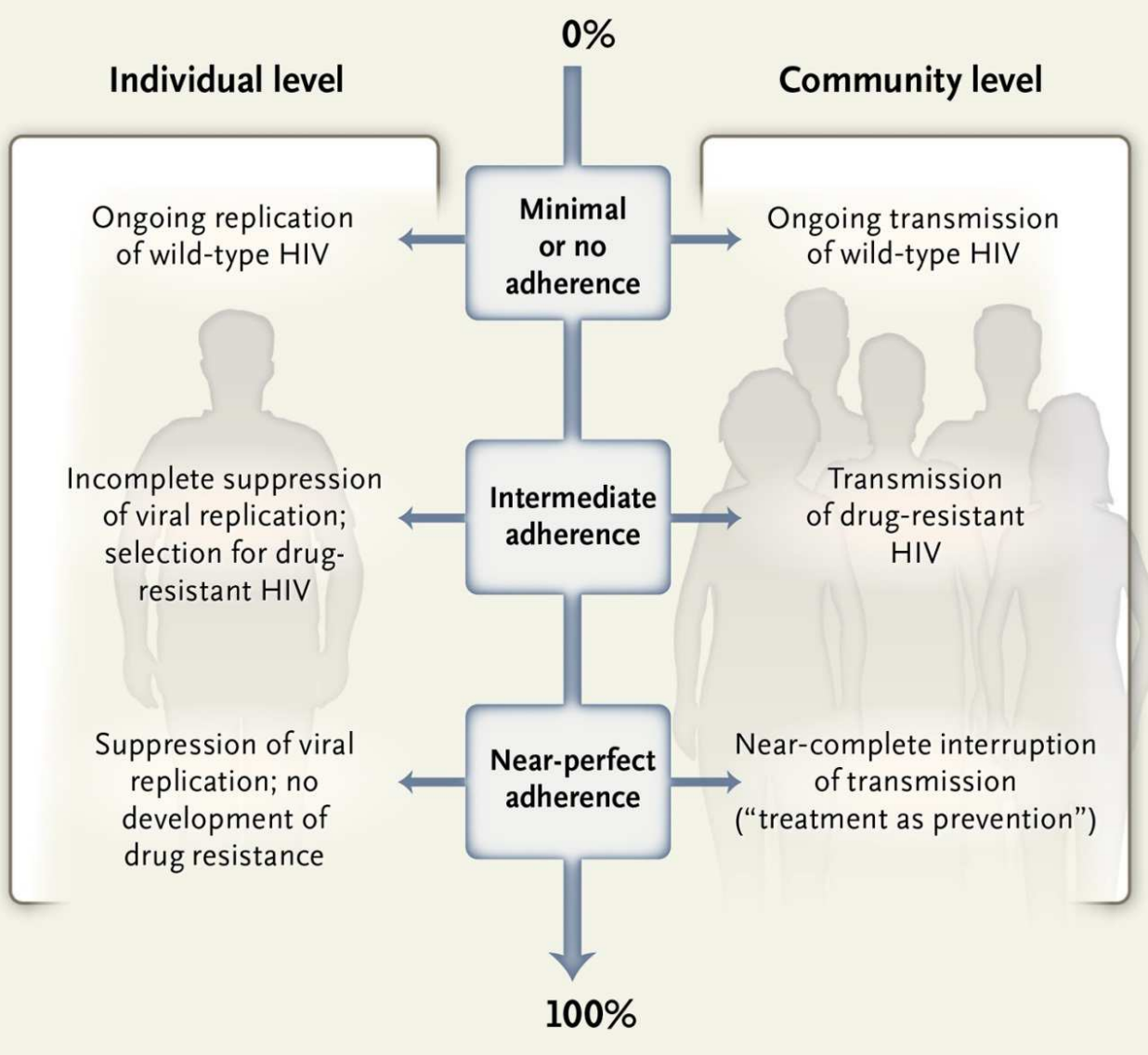
Main Reason for Starting ART



- 129 treatment-naive patients
- ART started between 2013-2014
- Median CD4 356 (IQR 220-495)

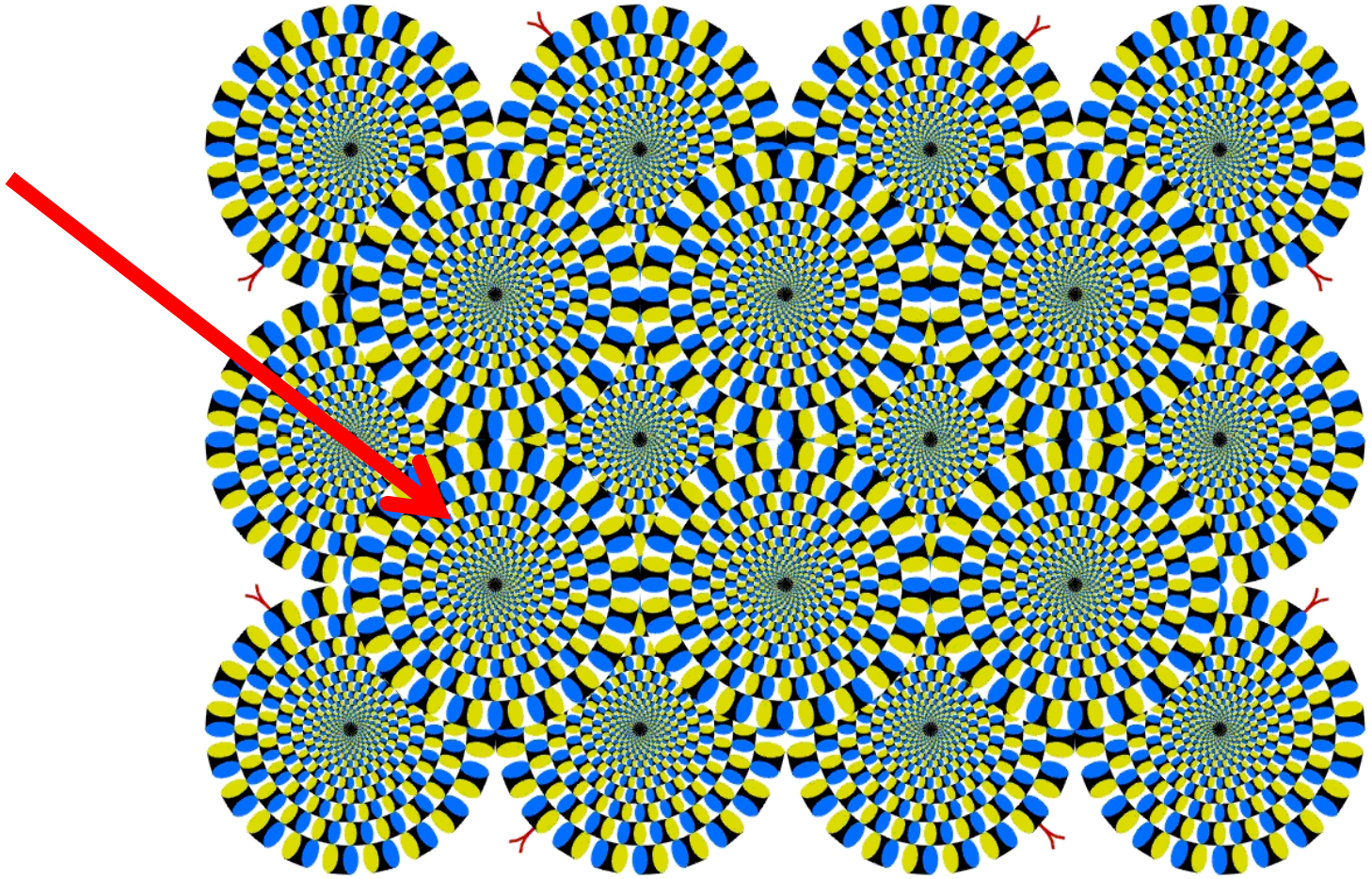
Preliminary data Elzi & Battegay, SHCS #644

Effects of Various Levels of Adherence on the Individual and Community



Gandhi M, Gandhi RT. N Engl J Med 2014

Perception versus Reality



Slide courtesy Mark Nelson, London

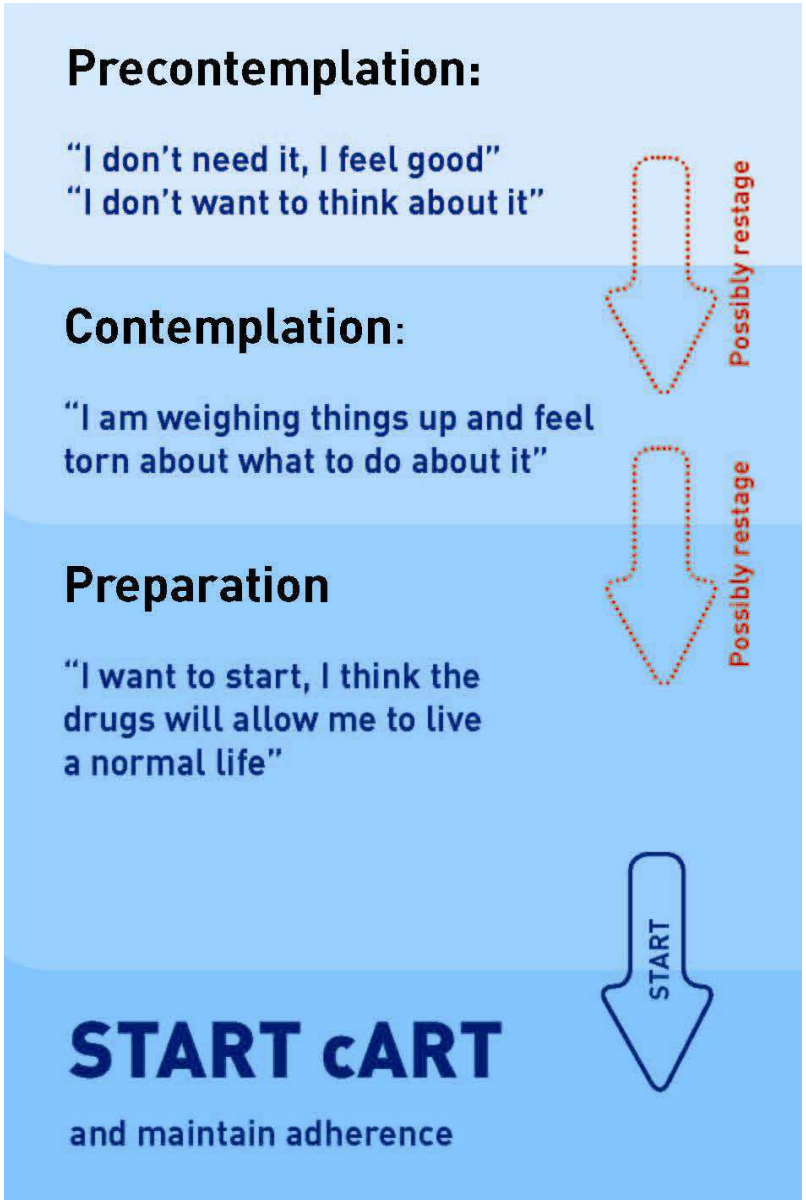
Is the patient ready for ART ?

«I would like to talk about HIV medication»

… please wait …

«What do you think about it?»

Patient	Depression Drug, alcohol addiction Cognitive problems Low health literacy
System	Health insurance Continuity drug supply Low social support

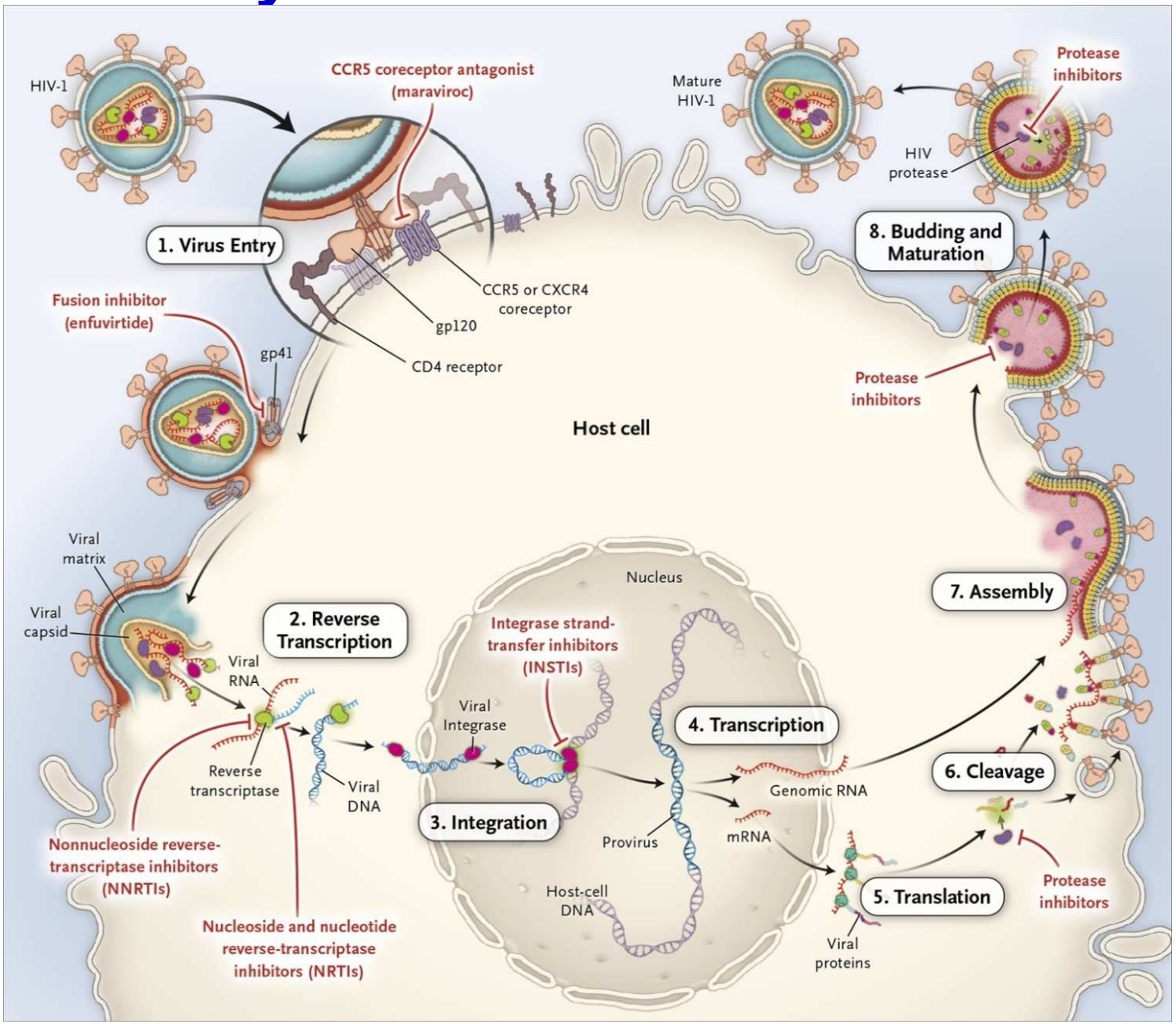


Fehr et al. Infection 2005, EACS Guidelines: www.eacsociety.org

State of the ART of ARV Therapy

- When to start antiretroviral therapy
- Treatment as prevention
- What to start with
- Perspectives

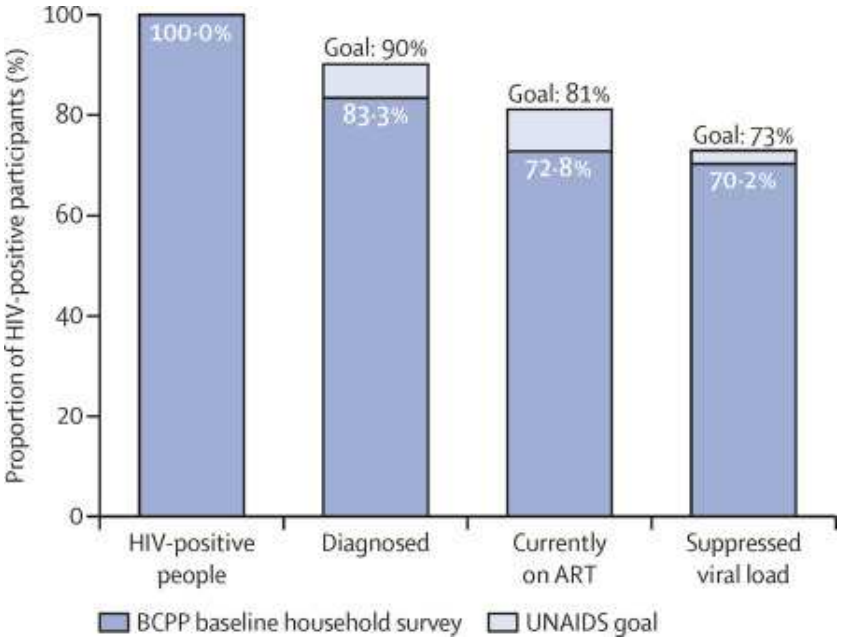
HIV-1 Cycle and Sites of Action ART

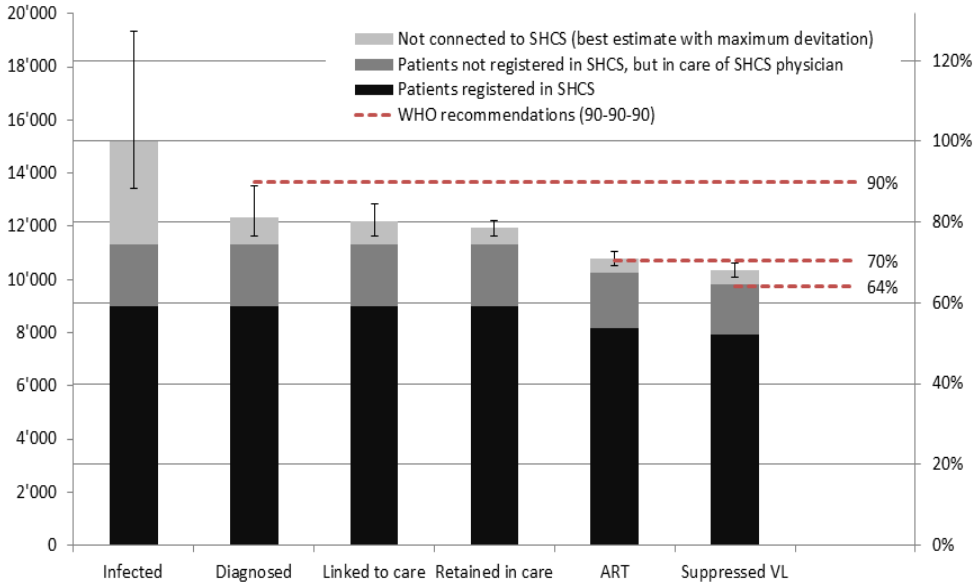


Gandhi M, Gandhi RT. N Engl J Med 2014

Rates of Viral Suppression are High

1’932	Individuals in Botswana receiving ART	
1’837	HIV-1 RNA <400 copies/mL	**95.1%**
10’800	Individuals in the SHCS receiving ART	
10’400	HIV-1 RNA <200 copies/mL	**96.3%**





Gaolathe T et al, Lancet HIV 2016, Kohler et al, AIDS, 2015

Recommended intial regimens

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2016 Recommendations of the International Antiviral Society–USA Panel

Huldrych F. Günthard, MD; Michael S. Saag, MD; Constance A. Benson, MD; Carlos del Rio, MD; Joseph J. Eron, MD; Joel E. Gallant, MD, MPH; Jennifer F. Hoy, MBBS, FRACP; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Melanie A. Thompson, MD; Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Davey M. Smith, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

- Dolutegravir/abacavir/lamivudine (evidence rating AIa)
- Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[b]
- Elvitegravir/cobicistat/TAF/emtricitabine (evidence rating AIa)[b]
- Raltegravir plus TAF/emtricitabine (evidence rating AIII)

Günthard HF1 et al. JAMA July 2016

Newer Antiretroviral Drugs for HIV

	Dolutegravir	Elvitegravir/COBI	Rilpivirine
Study	**SPRING-2, SINGLE, FLAMINGO**	**Study 102, 103**	**Echo-Thrive Study**
Convenience	Small pill once-daily	Single tablet regimen	Small pill once-daily
Efficacy (HIV-RNA<50 at week 48, 96)	• **Non-inferior to RAL** (81% vs 76%) • **Superior to EFV*** (80% vs 72%) • **Superior to DRV/r** (81% vs 76%)	• **Non-inferior to EFV** (83% vs 82%) • **Non-inferior to ATV/r** (84% vs 83%)	• **Non-inferior to EFV if HIV-RNA <100,000** (84% vs 80%)
Resistance	No DTG resistance detected	2% failure with EVG/c resistance	Cross-resistance with etravirine
Toxicity	Rapid increase in serum creatinine	Rapid increase in serum creatinine	Fewer CNS AE and rash than EFV
Interactions	Few DDI	Potential DDI through COBI	Caution with PPI, H2-Blockers

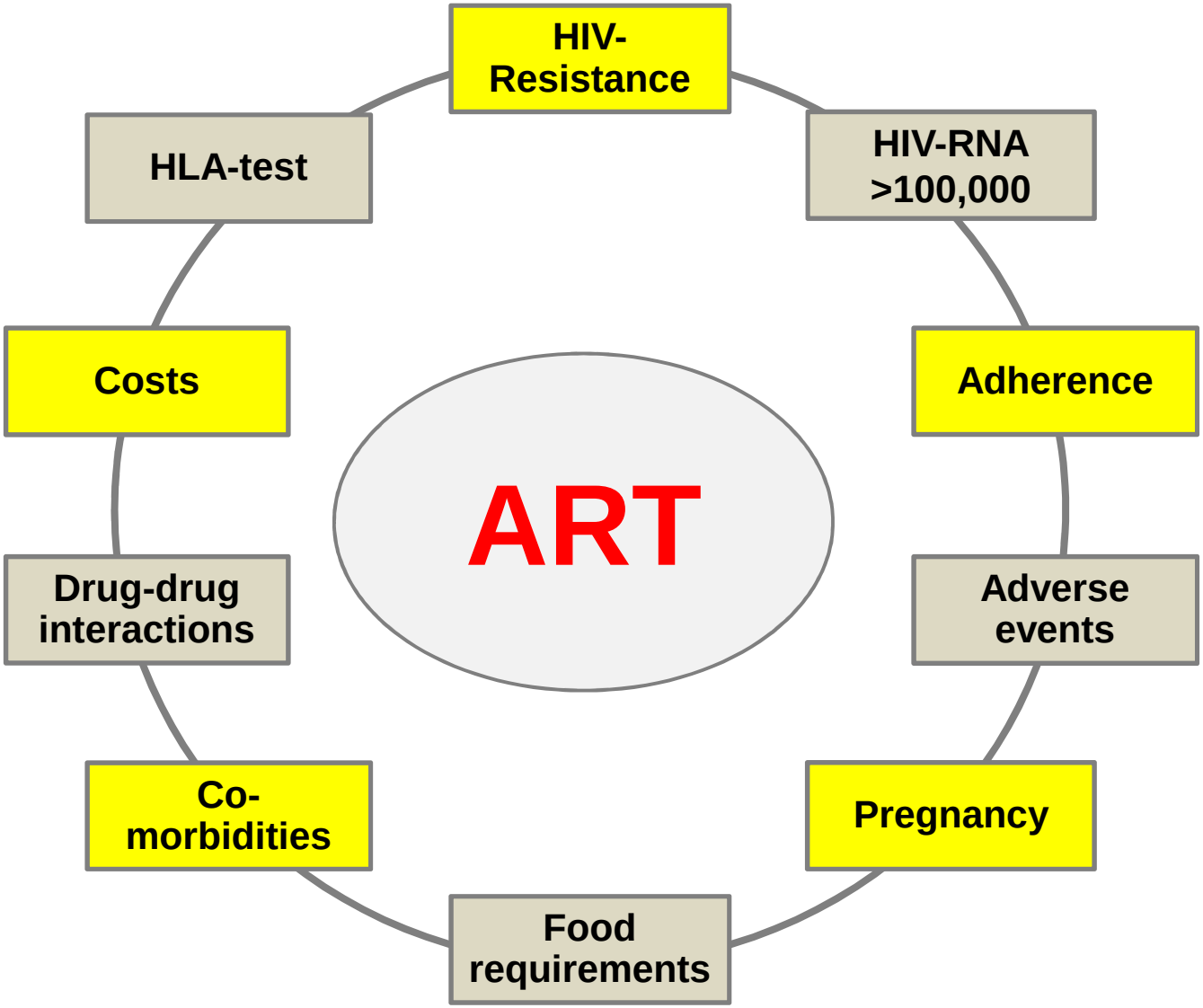
*In the SINGLE trial DTG was combined only with ABC/3TC

Sax PE, et al. Lancet. 2012; Zolopa A, et al. JAIDS, 2013; Wohl D, et al. ICAAC 2013; DeJesus E, et al. Lancet. 2012; Rockstroh J, et al. JAIDS; 2013; Clumeck N, et al. EACS 2013; Cohen CJ, AIDS 2013

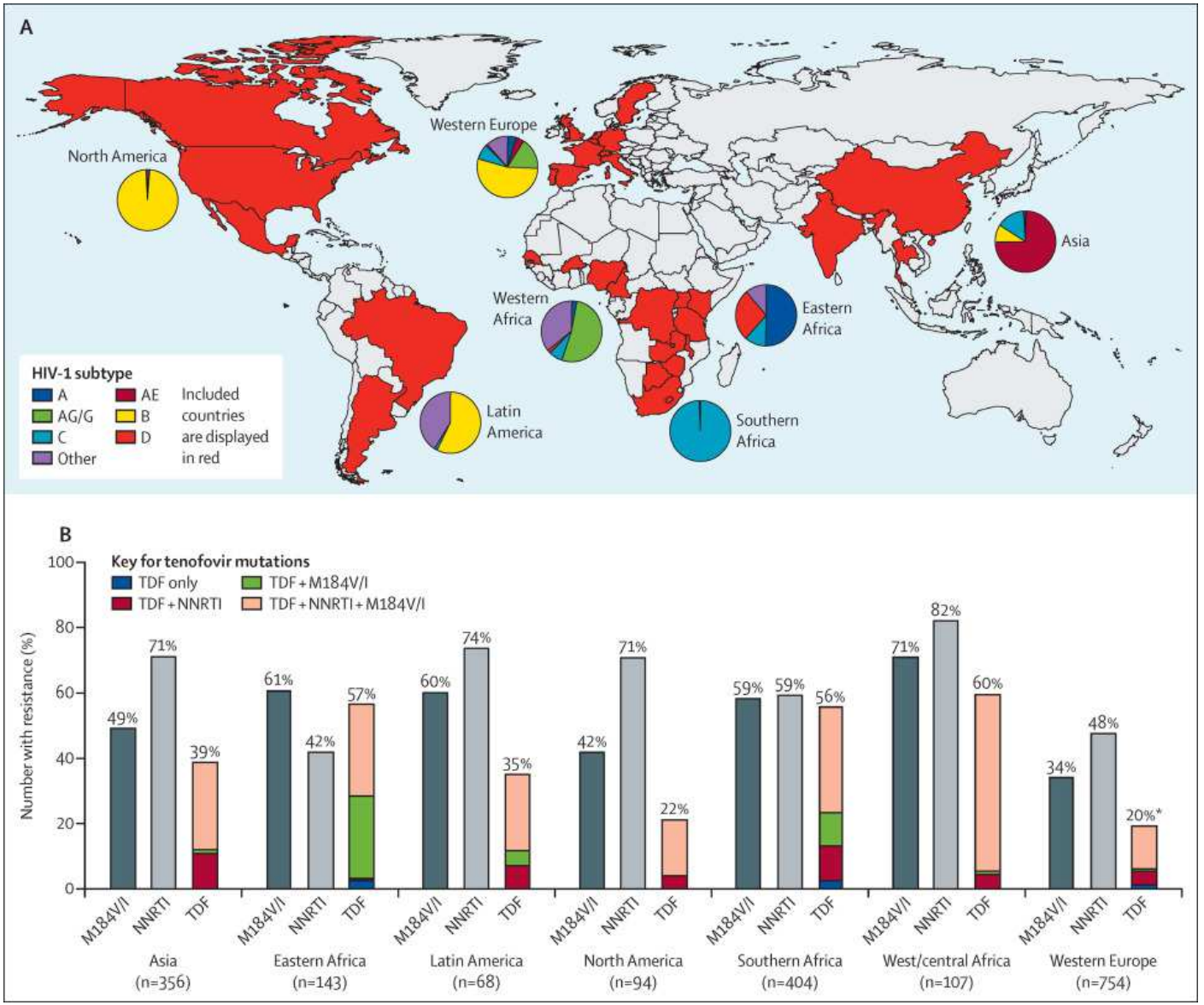
Which Drugs to Use

Drug	Considerations IN FAVOR	Considerations AGAINST
Dolutegravir	• Well-tolerated • Once-daily without boosting • Few drug-drug interactions • Almost absent resistance	• n.a.
Elvitegravir/ COBI	• Well tolerated • Co-formulation, 1 pill OD	• Cross-resistance with RAL • Drug-drug interactions • Concern of renal monitoring with COBI
Raltegravir	• Well tolerated • Few drug-drug interactions • Limited effect on lipids	• No coformulation with NRTI • Twice daily • Higher risk of resistance
Rilpivirine	• Well tolerated • Co-formulation, 1 pill OD	• Less effective at high VL (>100,000) • CD4 count < 200 cells/µL • Restricted use with PPI, H2-Blockers
Darunavir/r	• Little risk of resistance • Can be given with low adherence • Preferred in pregnancy	• No coformulation yet with NRTI • Variable lipid effect, hyperbilirubinemia • Drug-drug interactions

Considerations for ART Choice

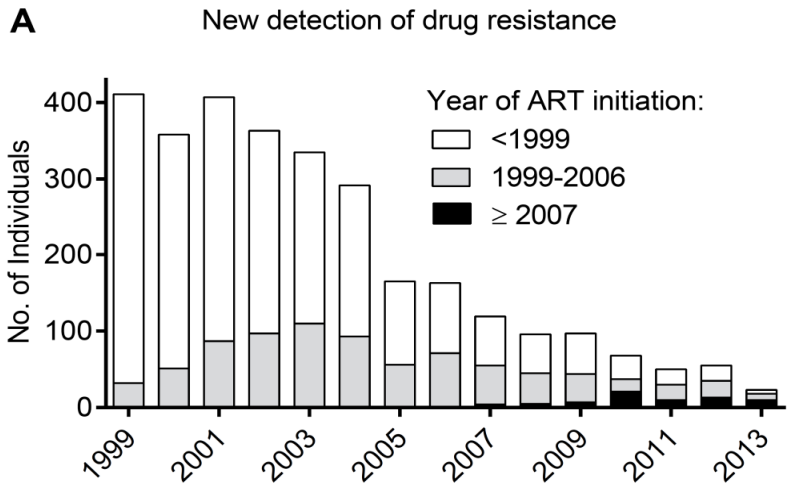


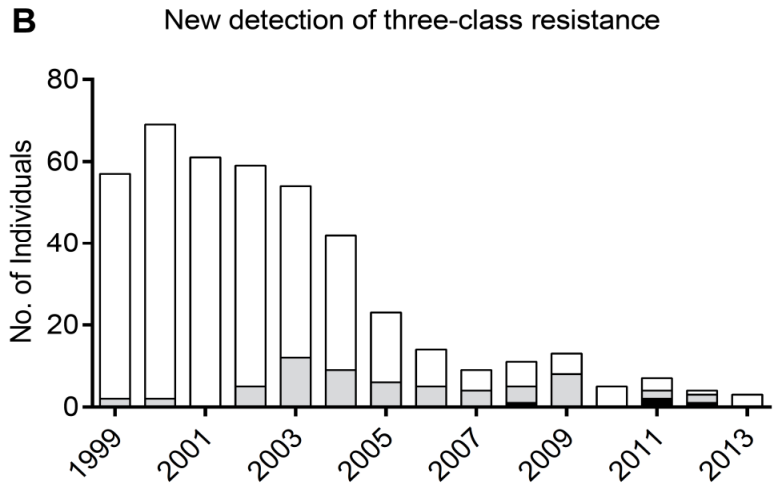
Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection



Lancet Infect Dis; Volume 16, Issue 5, 2016, 565-575

Emergence of Acquired HIV-1 Drug Resistance has Stopped in Switzerland

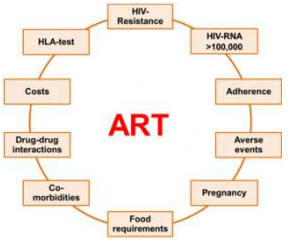




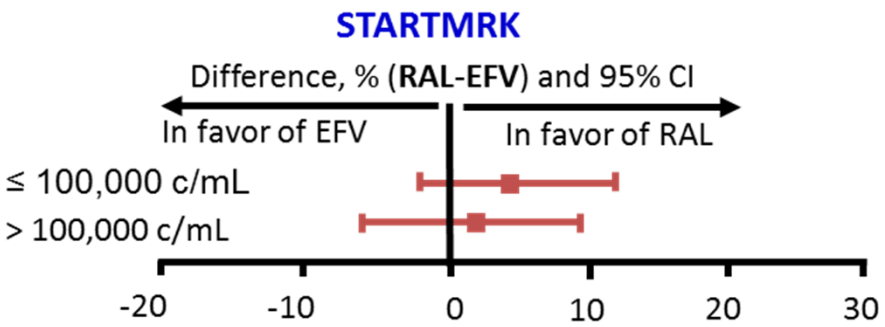
		Year of first ART initiation		
Characteristics	**All** n=11,084	**<1999** n=3,730	**1999-2006** n=3,910	**2007-2013** n=3,444
NNRTI resistance, No. (%)	**1120 (10.1)**	**667 (17.9)**	**326 (8.3)**	**127 (3.7)**
NRTI resistance, No. (%)	**2794 (25.2)**	**1994 (53.5)**	**621 (15.9)**	**179 (5.2)**
PI resistance, No. (%)	**1409 (12.7)**	**1058 (28.4)**	**271 (6.9)**	**80 (2.3)**

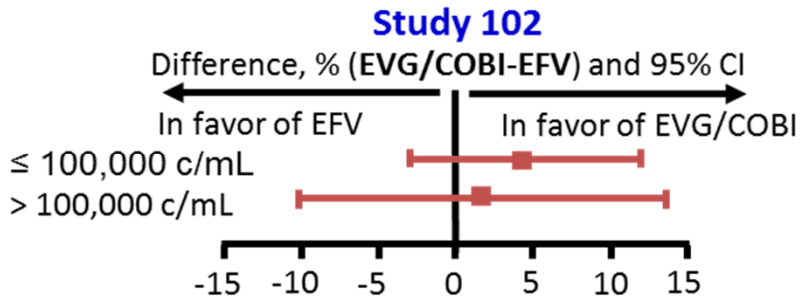
Scherrer AU, Günthard HF et al.; Swiss HIV Cohort Study, Clin Infect Dis. 2016 Epub ahead of print

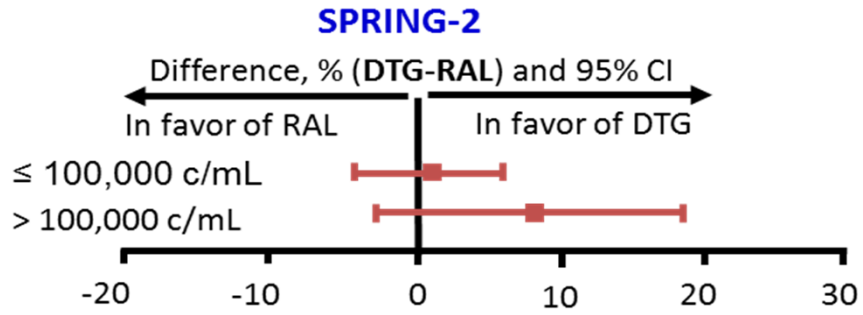
HIV-RNA >100,000 copies/ml



HIV-RNA >100,000





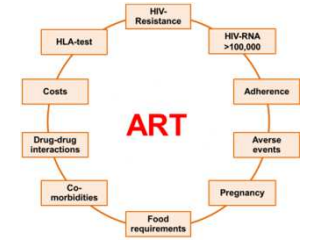


Inferior virologic response for

- **ABC + 3TC** + EFV
- **ABC + 3TC** + ATV/r
- **RPV-based regimens**

Sax PE et al., NEJM 2009; Sax PE et al., J Infect Dis, 2011;Post FA et al., JAIDS 2010; Lennox J, et al. Lancet. 2009; Sax PE, et al. Lancet. 2012; Brinson C, et al. CROI 2013

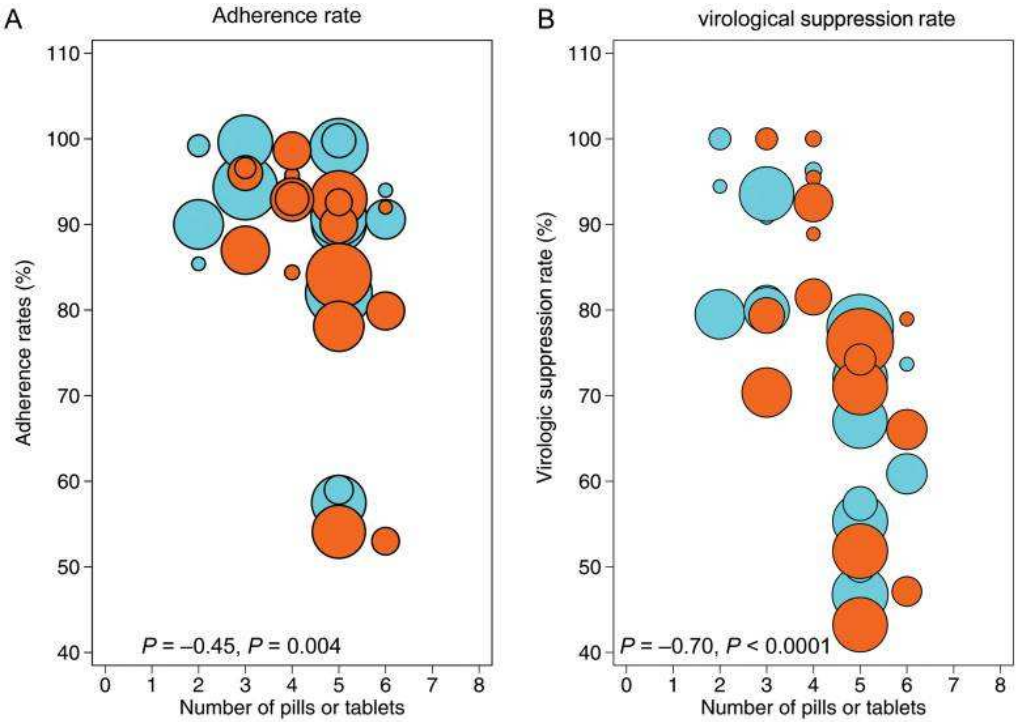
Adherence



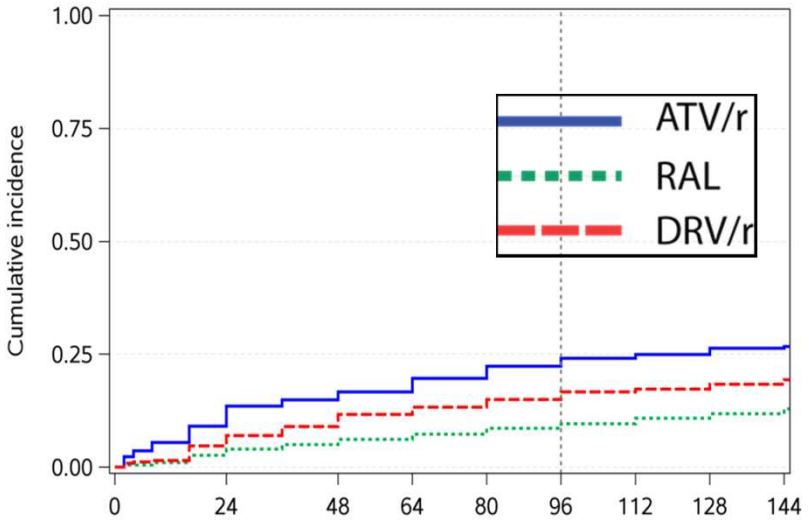
Adherence

Meta-analysis, n=6312

Once daily
Twice daily



ACTG A5257
RCT, n=600 each arm



Low pill burden → better adherence and virological suppression in OD and BID

OD *versus* BID → better adherence, but similar virological suppression to BID

BID vs OD regimens

RAL was superior to both PI/r regimens for combined tolerability and virologic efficacy

Nachega et al., Clin Infect Dis, 2014; Landovitz, Abstract CROI 2014

Adverse events*

AE (>5%)		Drug
Skin	Rash	all
GI-tract	Nausea, diarrhea	DRV/r, ATV/r, DTG, EVG/r
Liver	Hepatitis	EFV, RPV, ATV/r, DRV/r, MVC
	Jaundice	ATV/r
Metabolic	Bone density loss	TDF
	Dyslipidemia	EFV, ATV/r, DRV/r, EVG/c
CNS	Depression	EFV, RPV, EVG/c, RAL, ATV/r,
	Sleep disturbances	EFV, RAL, EVG/c, DTG
Renal	Proximal tubulopathy	TDF
	Nephrolithiasis	ATV/r
	Increase of creatinine	EVG/c, DTG
Muscle	CK increase	RAL

*AE occuring > 5% in RCT's. No AE led to a stop of treatment in more than 10% of patients.

Pregnancy and HIV

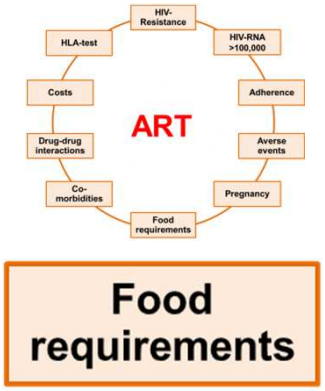
13,124 live births; 1994 and 2010, 42% (n=5,388) ART exposed in first trimester of pregnancy. Significant association between efavirenz and neurological defects (n=4) using the MACDP classif., p=0.04, absolute risk +0.7% (95% CI +0.07%; +1.3%), but not significant using the less inclusive EUROCAT classif., p=0.16[1]

Antiretroviral regimen in pregnancy	Same as non pregnant
	NVP not to be initiated but continuation is possible if started before pregnancy
	EFV can be started if other options are not available or suitable. Continuation of EFV is possible if already started before pregnancy
	Among PI/r, prefer LPV/r or ATV/r
	If RAL, EVG/c, RPV or DRV/r: could be continued (class B).
	Limited experience with TAF and DTG in pregnancy: use with caution.

[1]Association between Prenatal Exposure to Antiretroviral Therapy and Birth Defects: An Analysis of the French Perinatal Cohort Study (ANRS CO1/CO11), Sibiude et al, PLoS Medicine, 2014

http://www.eacsociety.org,

Food requirements



550 Kcal

- Rilpivirine

375 Kcal

- Elvitegravir/COBI
- Darunavir/r
- Atazanavir/r

Fasting

- Efavirenz

Independent

- Dolutegravir
- Raltegravir

Multimorbidity and HIV

SWISS HIV COHORT STUDY

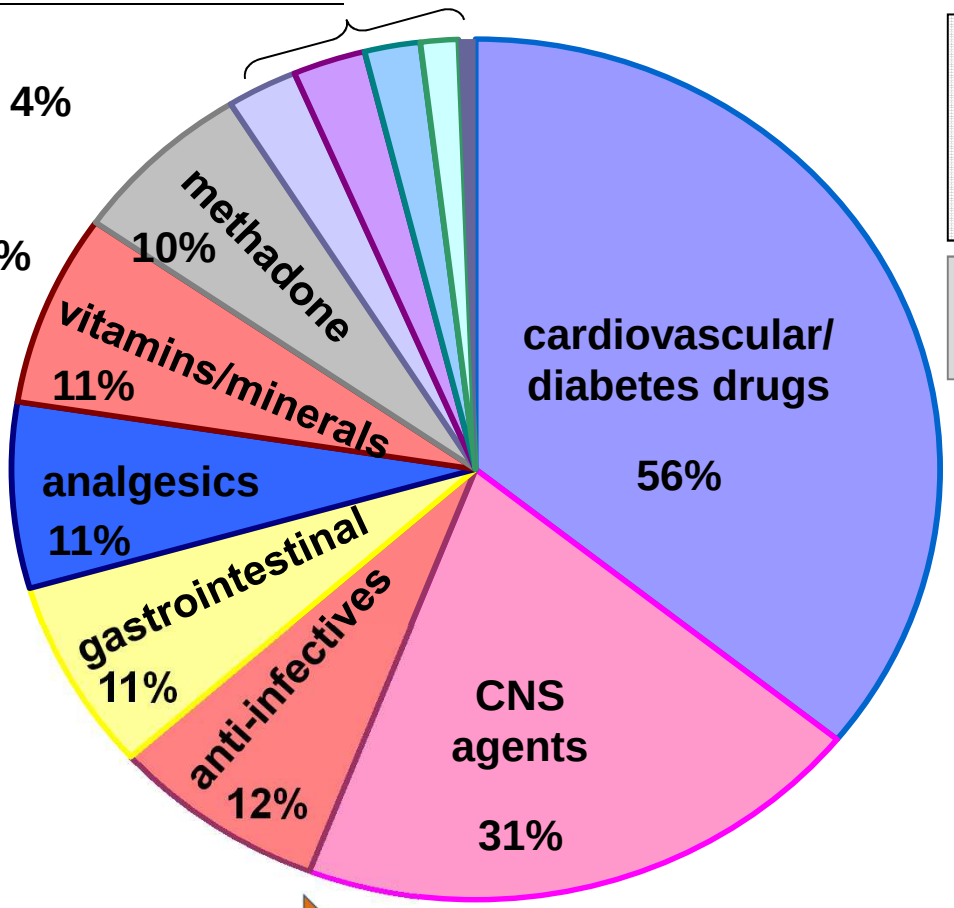
immunosuppressants 4%

hormones 3%

bronchodilatators 3%

antihistamines 2%

herbals 1%



Hypertension, Diabetes, Dementia, CVD, Tumors, Hepatitis, IVDU

Interactions more frequent >50 y

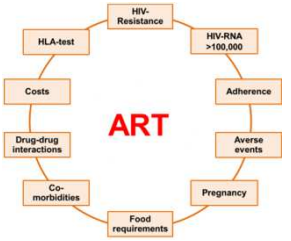
www.eacsociety.org/guidelines

www.hiv-druginteractions.org

- **1497 patients**
- **68% with ≥ 1 co-medication**
- **40% ≥ 1 drug-drug interaction**

Marzolini & Battegay et al., Antiviral Therapy, 2010, Marzolini C et al. J Antimicrob Chemother 2011

Drug-drug interactions



Drug-drug interactions

Co-morbidities

non HIV drugs	ATV/r	DRV/r	EFV	RPV	RAL	EVG/c	DTG	TDF
atorvastatin	↑	↑	↓43%	↔	↔	↑	↔	↔
pravastatin	↔	↑81%	↓44%	↔	↔	↔	↔	↔
rosuvastatin	↑213%	↑48%	↔	↔	↔	↑38%	↔	↔
simvastatin	↑	↑	↓68%	↔	↔	↑	↔	↔
amlodipine	↑iii	↑	↓	↔	↔	↑	↔	↔
diltiazem	↑iii	↑	↓69%	E	↔	↑	↔	↔
metoprolol	↑iii	↑	↔	↔	↔	↑	↔	↔
warfarin	↑or ↓	↓	↑or ↓	↔	↔	↑or ↓	↔	↔
diazepam	↑	↑	↓	↔	↔	↑	↔	↔
midazolam (oral)	↑	↑	↑	↔	↔	↑	↔	↔
citalopram	↑iii	↑	↓	↔	↔	↑	↔	↔
mirtazapine	↑	↑	↓	↔	↔	↑	↔	↔
p								
c								
c								
it								
rifabuti								
rifampi								
voricon								
antacid								
PPIs	D	↔	↔	D	E	↔	↔	↔
H2 blockers	D	↔	↔	D	E	↔	↔	↔

Legend

- no DDI
- contra-indicated
- potential DDI requiring monitoring
- DDI predicted to be of weak i nsity

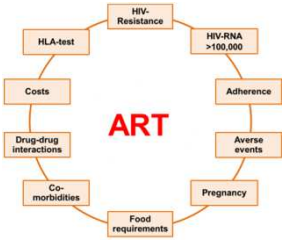
dication
ication
ug
drug
AUC

www.eacsociety.org/guidelines

www.hiv-druginteractions.org

www.hiv-druginteractions.org, EACS guidelines

Gastroesophageal reflux



Co-morbidities

Drug-drug interactions

- **Antacids:**

  → **caution** with:

  Rilpivirine, Atazanavir, all INSTIs

- **H_2 antagonists:**

  → **caution** with:

  Rilpivirine, Atazanavir

  AUC ↓ 76% **AUC ↓ 23-41%**

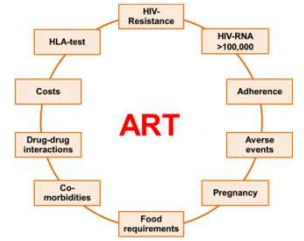
- **Proton pump inhibitors:**

  → **caution Rilpivirine, Atazanavir**

  Cmin ↓37% **Cmin ↓ 78-93%**

If coadministration unavoidable, close monitoring. Doses of PPI comparable to omeprazole 20 mg should not be exceeded and taken approximately 12 hours prior to ATV/r.

Effects on lipids



Adverse events

- **Efavirenz**

  ΔTChol +33 mg/dL

- **Darunavir/r, Atazanavir/r**

  ΔTChol +11 mg/dL ΔTChol +12 mg/dL

- **Rilpivirine**

  ΔTChol +5 mg/dL

neutral

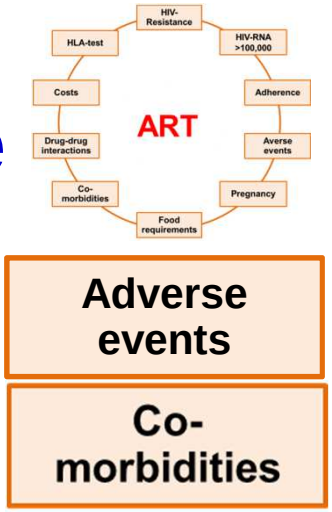
- **Raltegravir, EVG/COBI, Dolutegravir**

  ΔTChol -2 mg/dL ΔTChol ≈0 mg/dL ΔTChol ≈0 mg/dL

Significantly increased risk of MI with cumulative exposure of abacavir, lopinavir/r <u>but not</u> of efavirenz or atazanavir/r. Abacavir should be used with caution in persons with a high CVD risk. The D:A:D Study

Lennox J, et al. Lancet 2009; Daar ES, et al. Ann Intern Med 2011;Martinez et al., HIV Med 2014; Tebas et al., Clin Infect Dis 2014; Molina JM, et al. Lancet 2008; Ortiz R, et al. AIDS 2008, Westring Worm S et al., JID 2010, Monforte Ad et al. AIDS 2013

Renal function and kidney disease



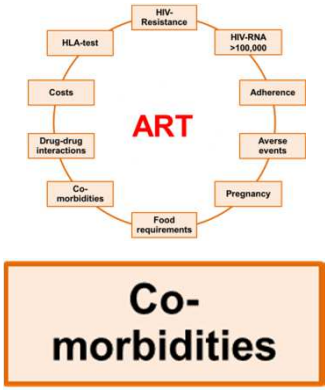
- **Tenofovir**: Proximal tubulopathy
  Associated w. chronic renal impairment
  Impairment greater when TDF paired with a boosted PI
- **Atazanavir/r:** Associated w. chronic renal impairment
  rarely nephrolithiasis
- **Rilpivirine:** rarely small, rapid ↑ serum creatinine*
- **Elvitegravir/c:** small, rapid ↑ serum creatinine*
- **Dolutegravir:** small, rapid ↑ serum creatinine*

*inhibition of tubular secretion of creatinine, renal function not altered

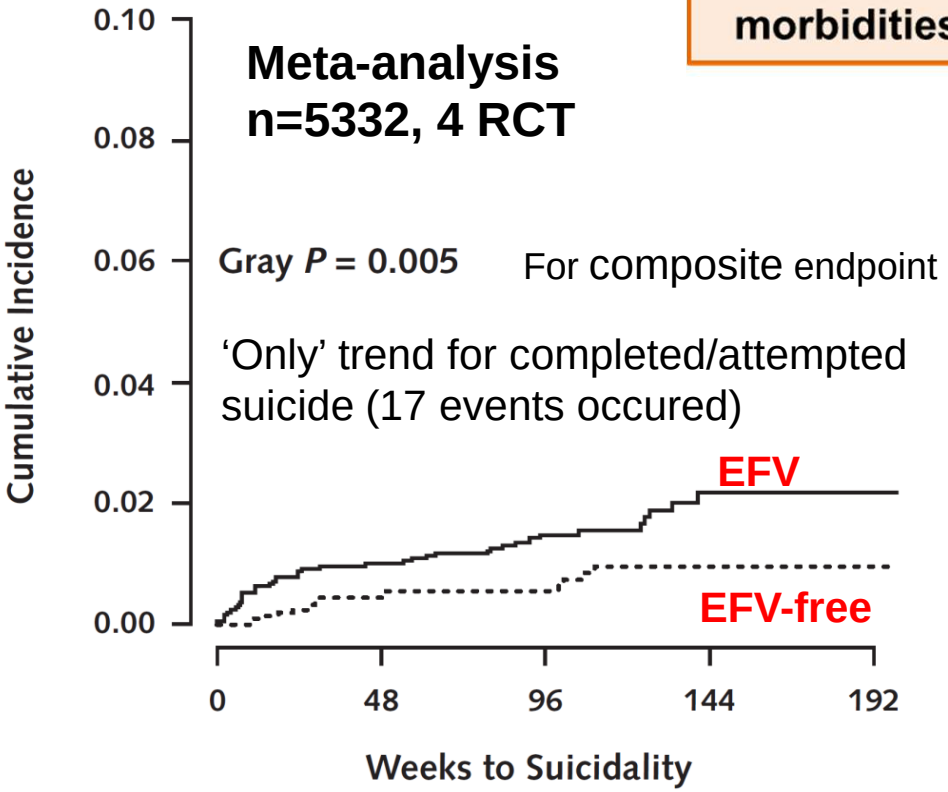
TDF: caution and/or dose reduction with existing kidney disease (eGFR <50mL/min). DDI with NSAID, especially diclofenac.
EVG/COBI/TDF/FTC: should not be initiated in persons with eGFR <70 mL/min

Morlat P, et al. IAS 2011. Young J et al, AIDS 2012, Ryom L et al. JID 2013, Gallant JE, et al. AIDS. 2009; Mocroft A, et al. AIDS. 2010

Depression



- **Efavirenz** (6%)
  2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)



But Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study
C. Smith; L. Ryom; A. d'Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

Cohen et al., Lancet 2011; Molina et al, Lancet 2011; Elion et al., JAIDS 2013; Mollan et al, Ann Intern Med 2014

New Strategies for HIV Care

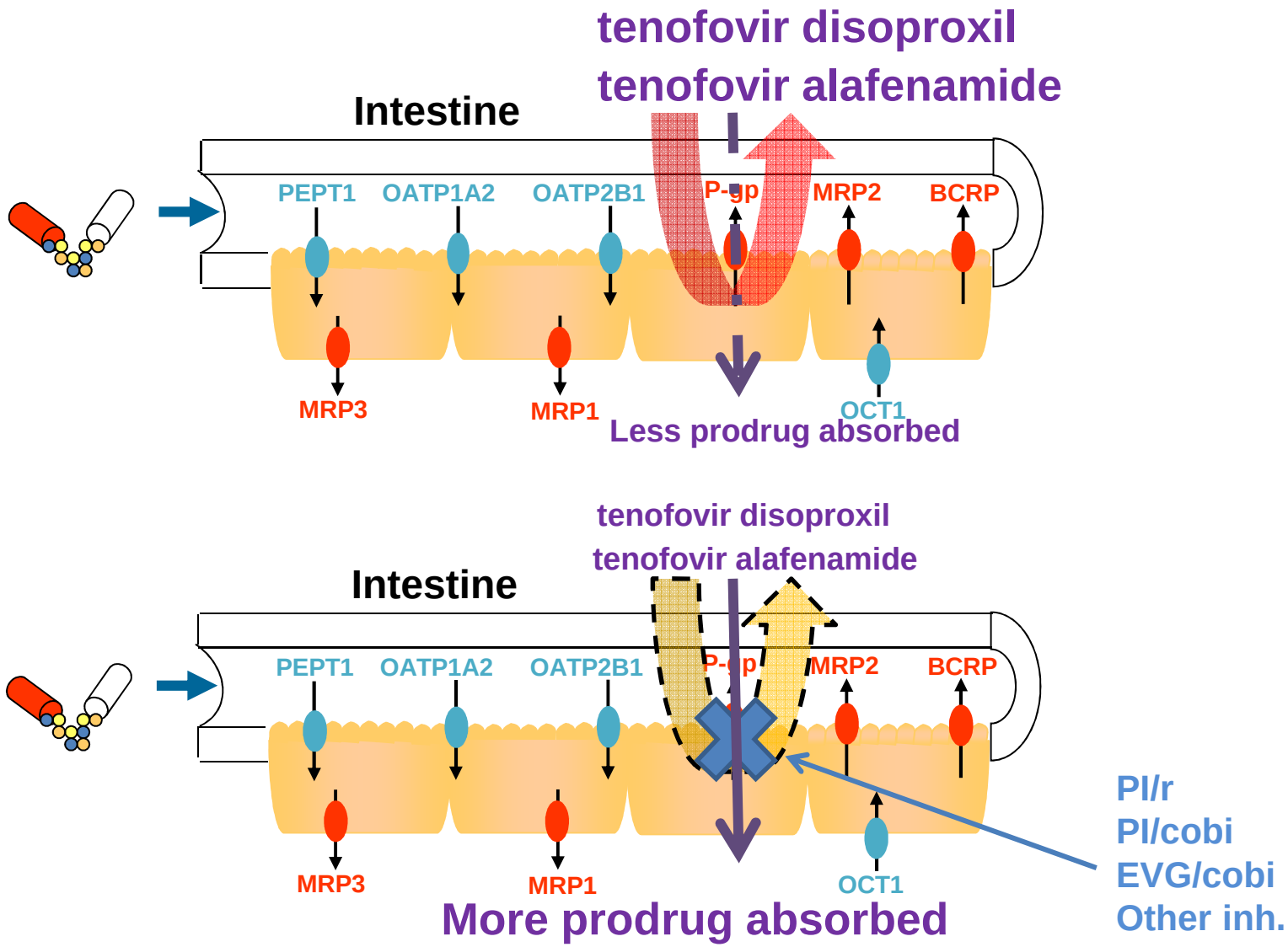
- When to start antiretroviral therapy
- Treatment as prevention - TASP
- What to start with
- Perspectives

Simplicity Across All Classes

- **PI/c**
  - DRV/c
  - ATV/c
- **QD RAL** new formulation (NCT02131233)
- **Single tablet regimen**
  - Efavirenz/TDF/FTC
  - Rilpivirine/TDF/FTC
  - Elvitegravir/cobicistat/TDF/FTC
  - Dolutegravir/ABC/3TC
  - Elvitegravir/cobicistat/TAF/FTC
- **Soon**
  - Darunavir/cobicistat/TAF/FTC
- **Long acting**
  - CBTG + RPV (NCT01593046)

Arribas J, EACS 2015

TDF/TAF are victim of DDI at the intestinal level



Tong L et al. AAC 2007, Mathias A. IWCPHT 2015, German P et al. CROI 2015
Slide Courtesy Catia Marzolini

Tenofovir alafenamide and Cobi products

TAF (10 mg)	+ FTC + EVG/cobi	Genvoya®	Complete STR
	+ FTC	Descovy®	
TAF (25 mg)	+ FTC	Descovy®	
	+ FTC + RPV	Odefsey®	Complete STR

Cobi (150 mg)	+ EVG + FTC + TDF	Stribild®	Complete STR
	+ EVG + FTC + TAF	Genvoya®	Complete STR
	alone	Tybost®	
	+ ATV	Evotaz®	
	+ DRV	Rezolsta®	

Slide Courtesy Catia Marzolini

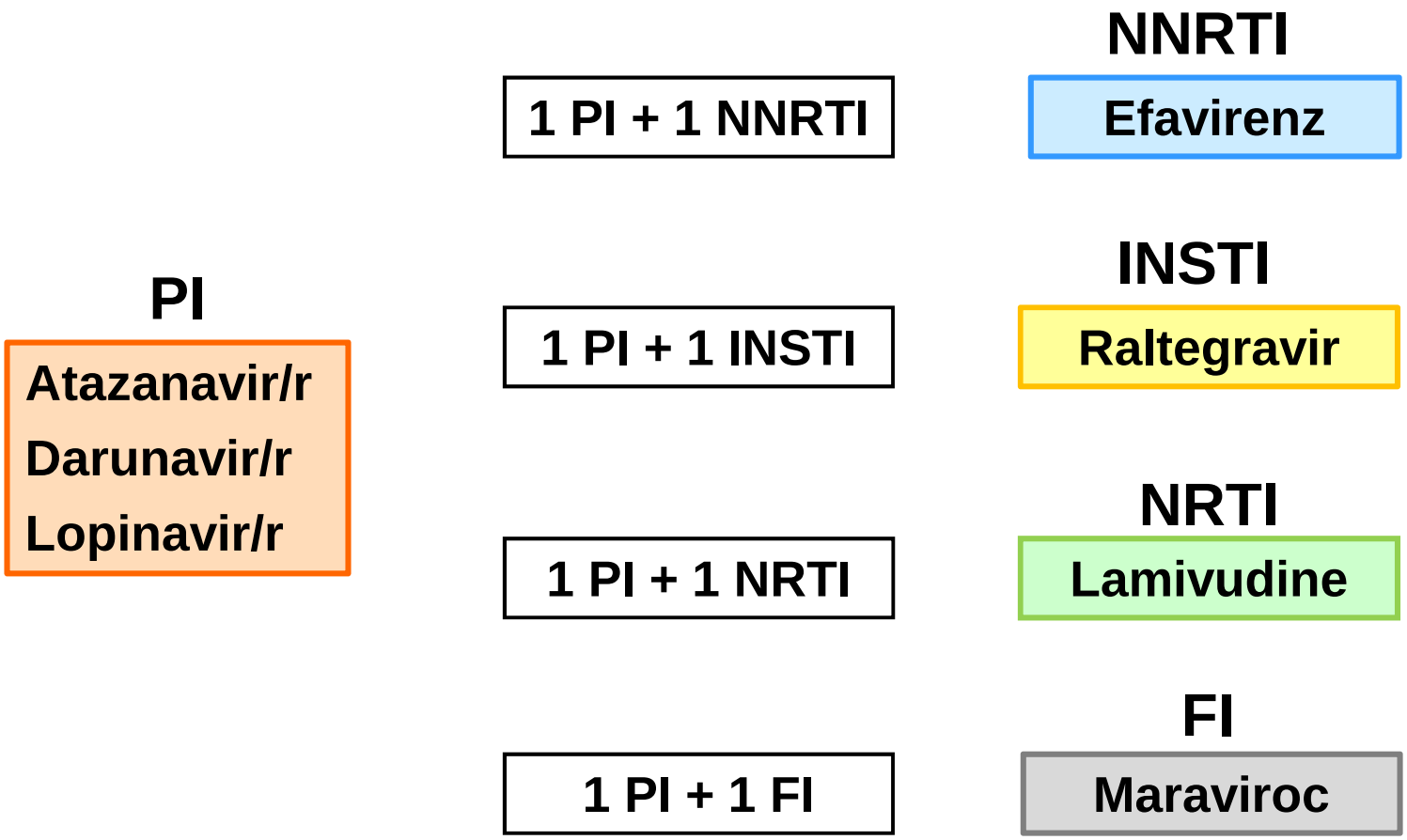
Side Effects and New Compounds

Tenofovir Alafenamide:

- GS 104 and 111[1], RCT 144-Wk studies of E/C/F/**TAF** vs E/C/F/**TDF** in 1744 ART-naive pts with eGFR ≥ 50 mL/min
  - Improved renal outcomes with **TAF** vs **TDF**
  - Fewer discontinuations for renal AEs with **TAF**
- GS-1089[2]: Switch From suppressive **TDF**- to **TAF**-containing ART: Wk 48 efficacy improved renal parameters
- GS-1089[2]: Bone mineral densitiy: improved with switch from **TDF**- to **TAF**-containing ART

[1]Sax PE, et al. Lancet. 2015, [2]Gallant JE, et al. CROI 2016

Nuke free/sparing initial ART



Nuke Free/Sparing Initial ART

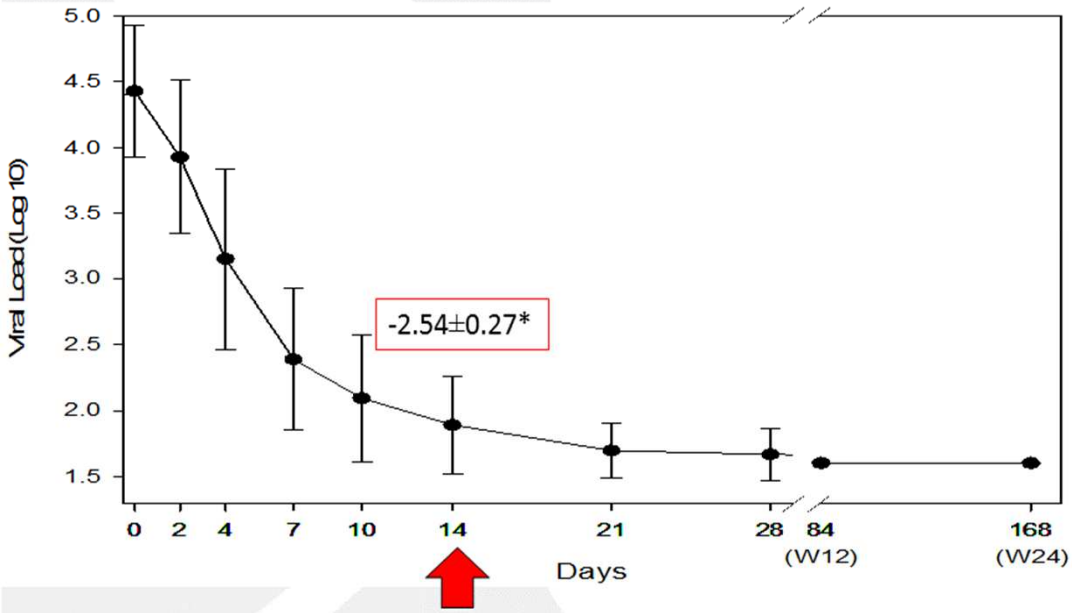
Study	Regimen	Comparison	Efficacy
SPARTAN	**ATV/r + RAL**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 24: 74.6% vs 63.3% → **non-inferior** (but high bilirubinemia and resistance to RAL)
A4001078	**ATV/r + MVC**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 48: 74.6% vs 83.6% → **non-inferior**
NEAT001/ ANRS143	**DRV/r + RAL**	DRV/r + TDF-FTC	Virological or clinical failure at wk 96: 17.8% vs 13.8% → **non-inferior** significantly inferior to standard therapy if CD4 <200/ml; trend for >100 000 c/mL
MODERN	**DRV/r + MVC**	DRV/r + TDF-FTC	HIV-RNA <50 at wk 48: 77.3% vs 86.8% → **inferior**
ACTG 5142	**LPV/r + EFV**	LPV/r + 2NRTI or EFV + 2NRTI	HIV-RNA<50 at wk 96: 83% vs 77% vs 89% → **non-inferior**
PROGRESS	**LPV/r + RAL**	LPV/r + TDF-FTC	HIV-RNA <40 at wk 96: 66.3% vs 68.6% → **non-inferior**
GARDEL	**LPV/r + 3TC**	LPV/r + 2 NRTI	HIV-RNA <50 at wk 48: 88.3% vs 83.7% → **non-inferior,** also >100 000 c/mL

Raffi et al., Lancet 2014; Riddler et al., NEJM 2008; Mills et al., JAIDS 2013;Kozal et al., HIV Clin Trials 2012; Reynes et a., AIDS Res Hum Retroviruses 2013; Cahn et al., Lancet Infect Dis 2014; Stellbrink, AIDS 2014

Dual Therapy with Dolutegravir in HIV-infected ART-naive Patients

- PADDLE Pilot Antiretroviral Design with Dolutegravir (50mg) Lamivudine (300mg)
- 20 patients, ART naive > 5‘000 ≤ 100‘000 c/mL, because of differences of screening to baseline values, 4 patients had VL > 100‘000 c/mL

Results: Viral load decay



*Day 14: Early evolution of viral load (log 10) (mean ± standard deviation).

From week 8 onwards all patients had VL < 50 c/mL

18/20 pts achieved HIV-1 RNA < 50 c/mL at Wk 48

1 pt committed suicide

1 pt experienced PDVF at Wk 36 (BL HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit (Wk 52)

Figueroa MI, et al., et al, AIDS 2016

Investigational Agents

- **Nucleosides**
  - EFdA
- **Non nucleosides**
  - Doravirine (NNRTI)
- **CCR5 Inhibitors**
  - Cenicriviroc
- **INSTI**
  - GS-9833
- **Maturation inhibitors**
  - BMS-955176
  - GSK2838232
- **CD4 attachment inhibitors**
  - BMS-66308
- **Broadly neutralizing monoclonal antibodies**

Arribas J, EACS 2015

Clinical Management of HIV – e-learning Online Course

iversity.org

With Russian translation

Main topics

- Epidemiology and surveillance of HIV
- Opportunistic infections and co-morbidities
- Antiretroviral therapy and complications of ART
- Continuum of HIV Care
- Key affected populations
- Treatment as prevention of HIV

EACS European AIDS Clinical Society
www.eacsociety.org

Course organizer CHIP, EACS,

Course instructors Jens D. Lundgren, Manuel Battegay

New Strategies for HIV Care

- Mortality and morbidity will continue to decrease due to more effective and better tolerated ART, started early (START trial) including ART started during primary HIV-infection.
- Treatment as prevention - TASP – is most effective to reduce the risk of transmission to HIV-uninfected partners and near-complete interruption of transmission at the community level.
- In this context, the HIV-test to limit late presentation and thereby improve individual prognosis and impair long-term transmission becomes even more essential.

New Strategies for HIV Care

- Recommended initial ART regimens demonstrate excellent potency and low but existing risk for adverse events. ART should take resistance, comorbidities, drug-drug interactions, adherence, convenience and other into consideration.
- Newer drugs and drug regimens as well as alternative regimens add to the excellent possibilities of initial choice of ART.