HIV – when and what to start – antiretroviral therapy principles

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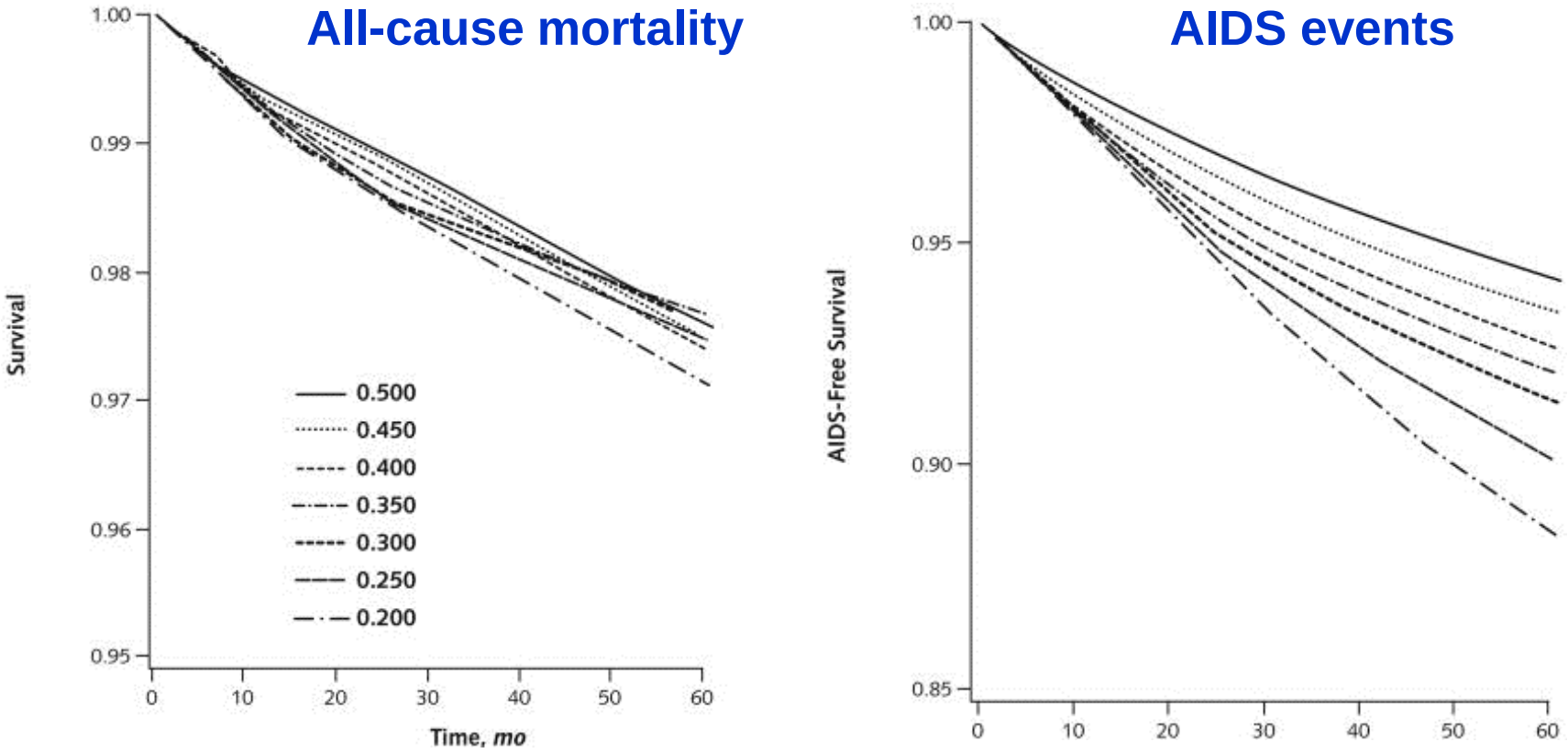
5-year outcome by CD4 at starting ART



No changes in mortality but in AIDS-defining events with starting ART at increasing CD4 (>450 cells/µl)

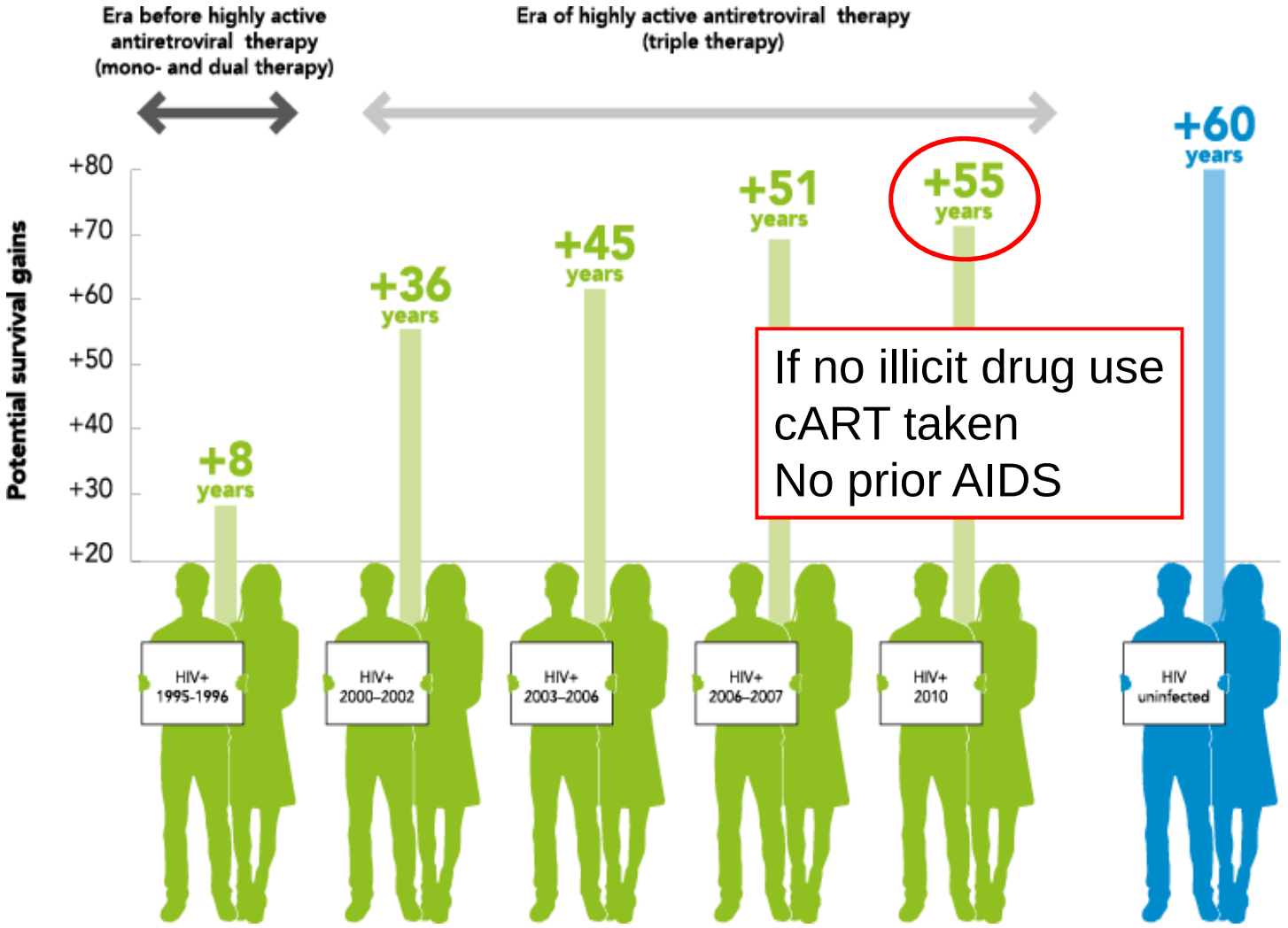
Cain et al., Ann Intern Med, 2011:154:509-115

International Guidelines 2014
when to start

Guideline	AIDS or HIV-related symptoms	Asymptomatic CD4 cell count		
		<350	350-500	>500
EACS	Yes	Yes	Consider	Consider
US DHHS	Yes	Yes	Yes	Yes
IAS-USA	Yes	Yes	Yes	Yes
WHO	Yes	Yes	Yes	Not addressed

EACS. February 2013. DHHS. Guidelines. February 2013. IAS-USA. Guidelines. July 2012. WHO. ART Guidelines. June 2013.

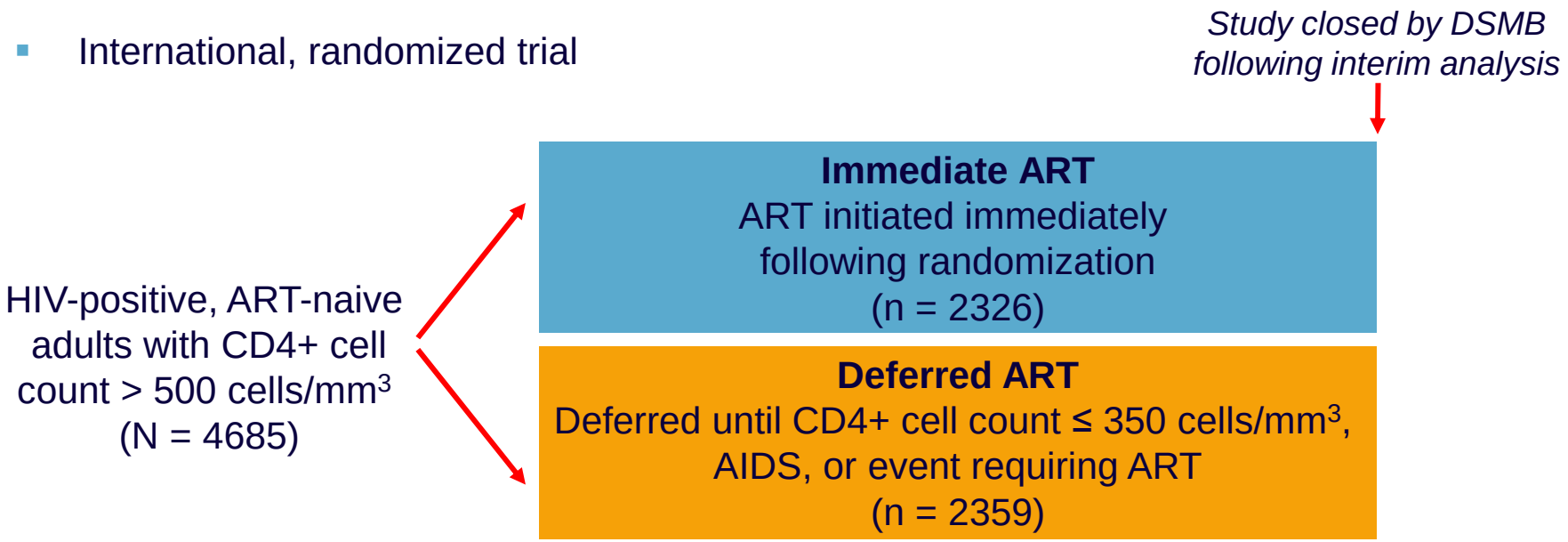
Mortality - almost no difference



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

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

- International, randomized trial

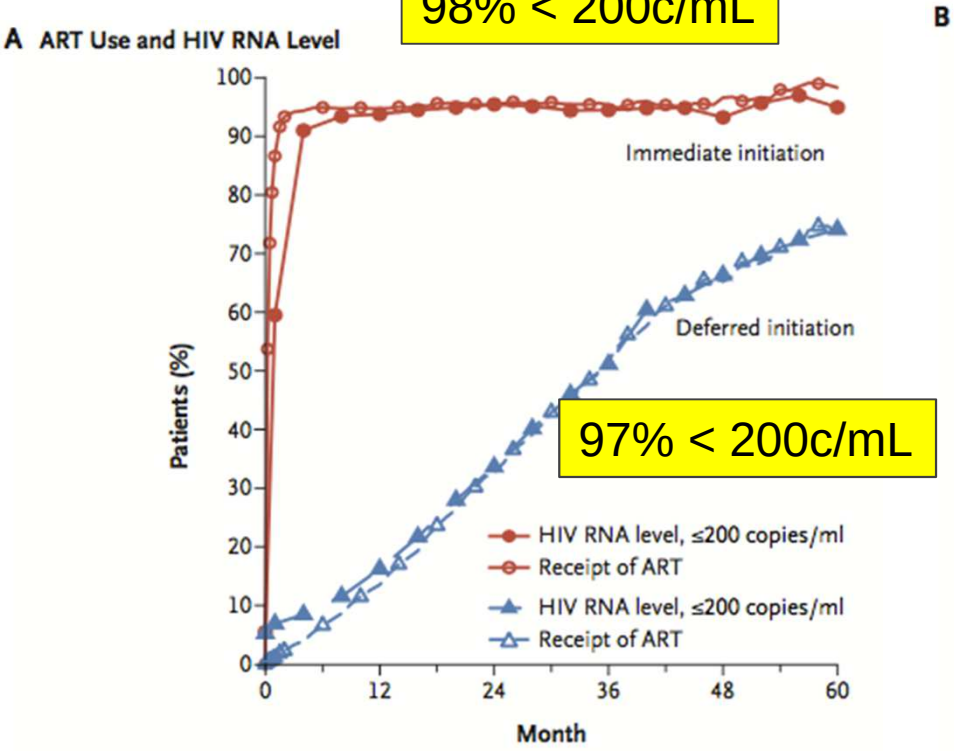


- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3;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

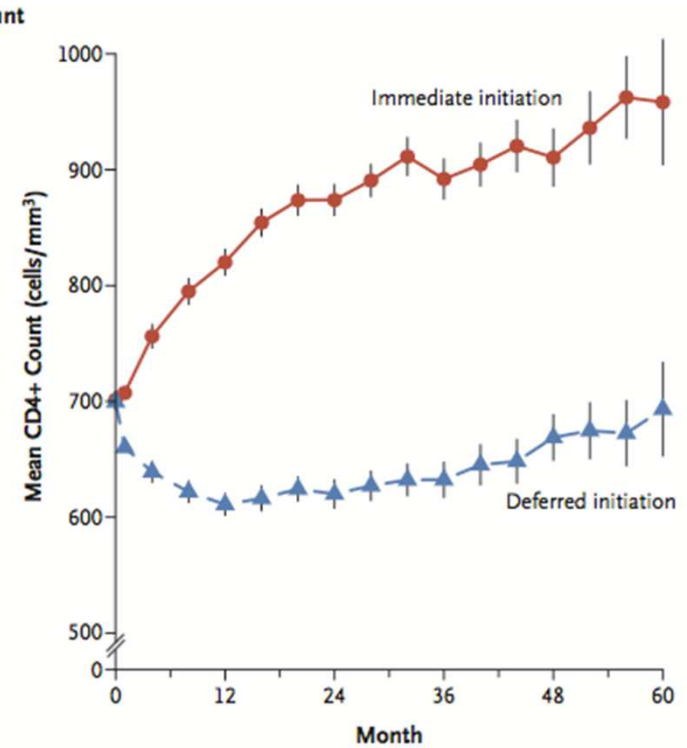
INSIGHT START Study Group. N Engl J Med. 2015; Lundgren J, et al. IAS 2015

ART, HIV RNA and CD4 course

98% < 200c/mL



97% < 200c/mL

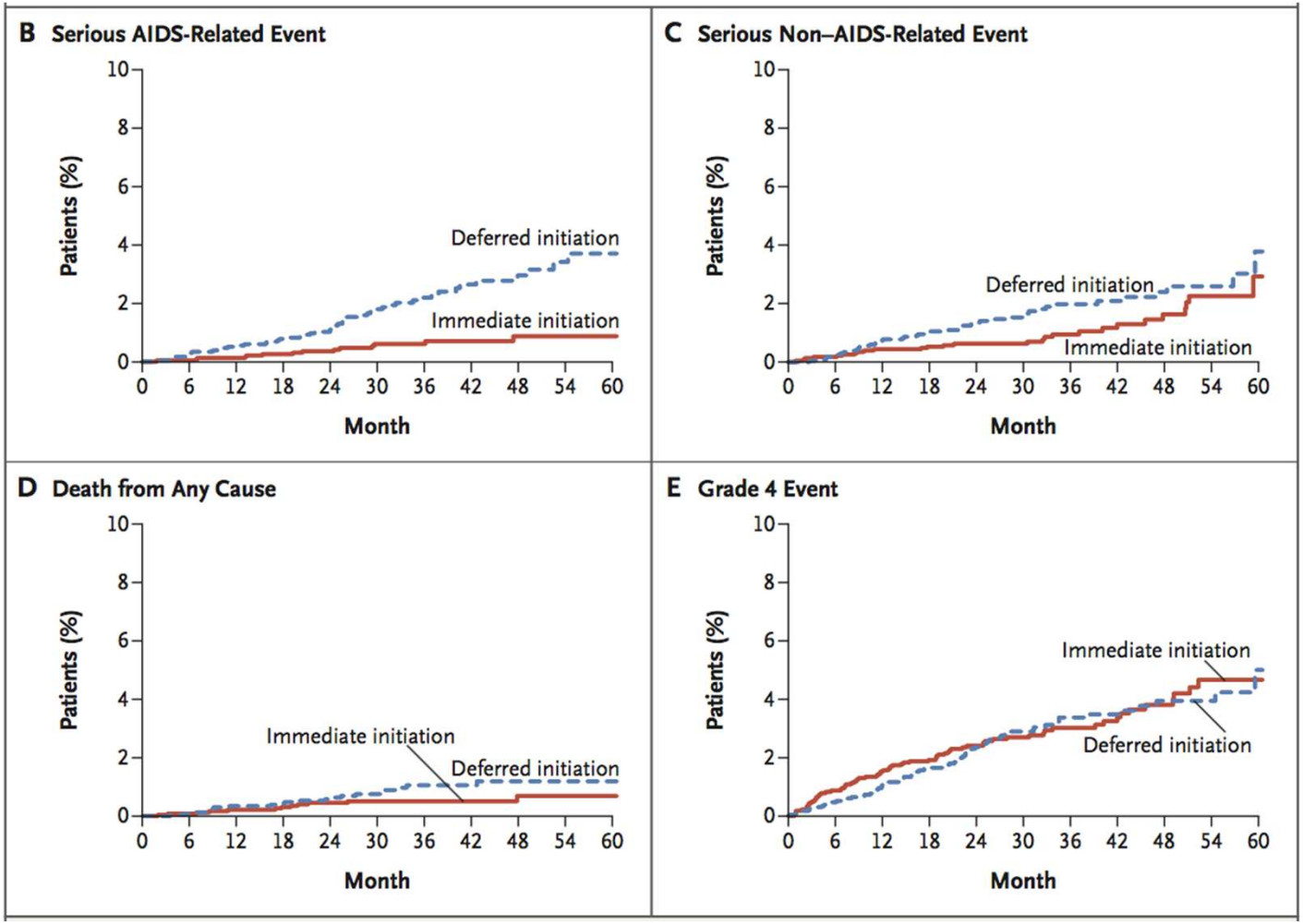


No. of Patients						
Immediate initiation	2326	2287	1809	1040	551	115
Deferred initiation	2359	2303	1837	1055	546	109

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

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

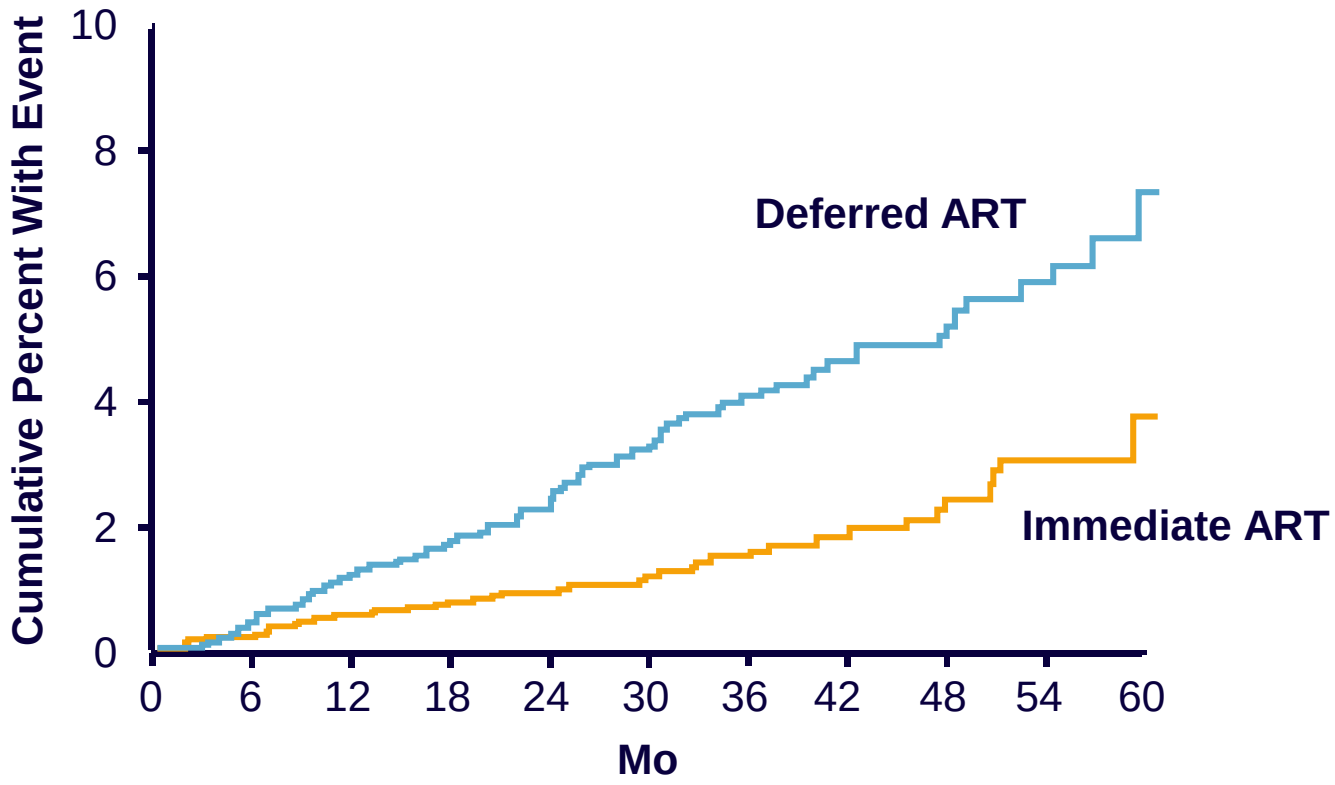
Events / Death



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

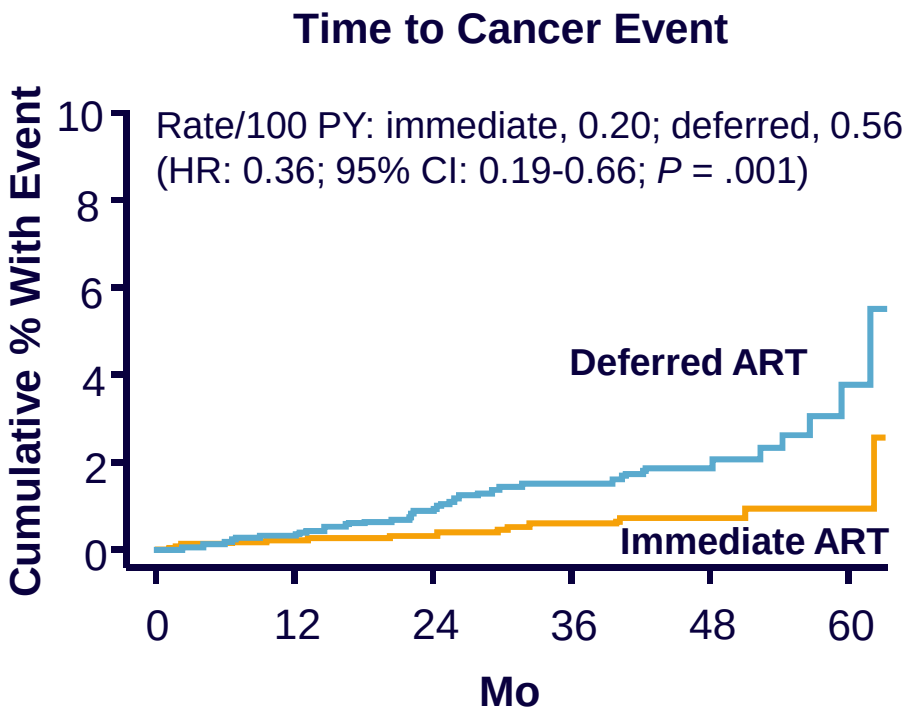
START: Primary Endpoint Components With Immediate vs Deferred ART

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. N Engl J Med. 2015; Lundgren J, et al. IAS 2015

START: Cancer Events With Immediate vs Deferred ART

Cancer Event, n	Immediate ART (n = 2326)	Deferred ART (n = 2359)
Total	**14**	**39**
Kaposi's sarcoma	1	11
Lymphoma, NHL + HL	3	10
Prostate cancer	2	3
Lung cancer	2	2
Anal cancer	1	2
Cervical or testis cancer	1	2
Other types*	4	9



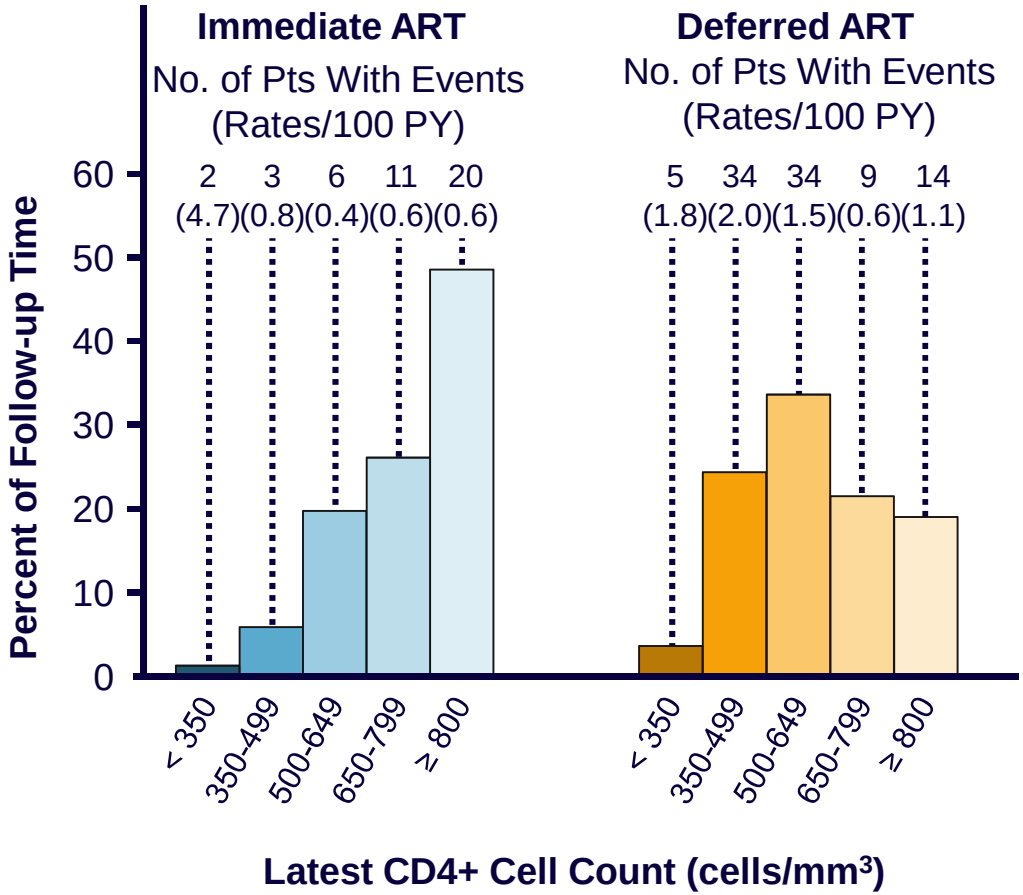
*Immediate ART: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma. Deferred ART: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

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

START: Primary Endpoint Events by Latest CD4+ Cell Count

Latest CD4+ count > 500 cells/mm³

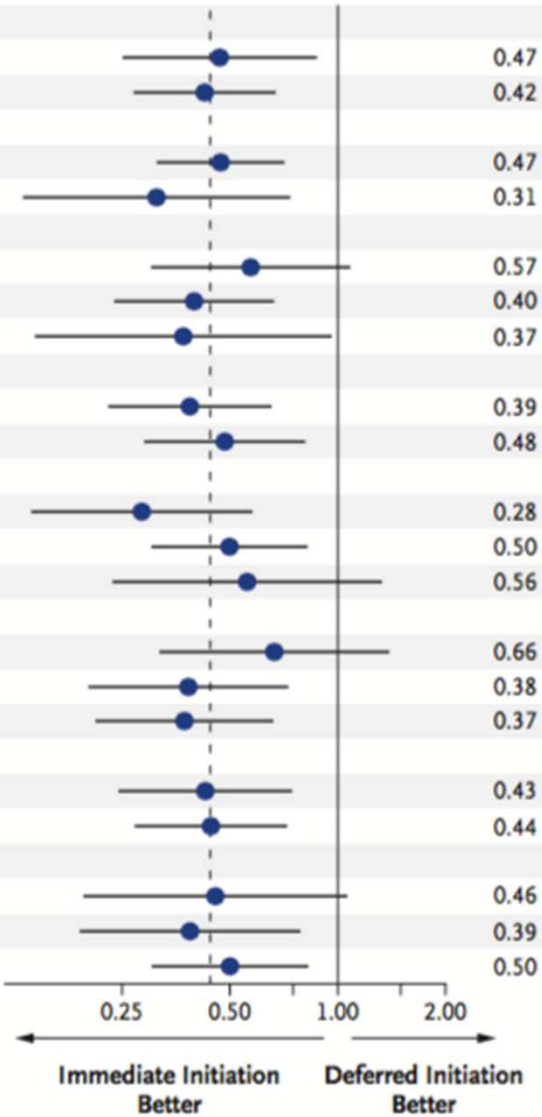
	Immediate ART	Deferred ART
Primary events, % (n/N)	88 (37/42)	59 (57/96)
Rate/100 PY	0.6	1.1



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

Subgroup Analyses for the Primary endpoint

Subgroup	Percentage in Group	Immediate Initiation	Deferred Initiation	Hazard Ratio (95% CI)	P Value for Interaction
		no. of patients with event (rate per 100 person-yr)			
Age					0.98
≤35 yr	48.8	15 (0.43)	31 (0.91)	0.47	
>35 yr	51.2	27 (0.78)	65 (1.85)	0.42	
Sex					0.38
Male	73.2	35 (0.66)	74 (1.40)	0.47	
Female	26.8	7 (0.42)	22 (1.34)	0.31	
Race					0.65
Black	30.1	15 (0.82)	28 (1.52)	0.57	
White	44.5	21 (0.63)	53 (1.54)	0.40	
Other	25.4	6 (0.34)	15 (0.91)	0.37	
Geographic region					0.55
High income	46.0	20 (0.56)	51 (1.42)	0.39	
Low or moderate income	54.0	22 (0.65)	45 (1.35)	0.48	
Baseline CD4+					0.71
<600 cells/mm³	31.5	10 (0.44)	35 (1.54)	0.28	
600–800 cells/mm³	48.6	24 (0.70)	46 (1.38)	0.50	
>800 cells/mm³	19.9	8 (0.63)	15 (1.14)	0.56	
Baseline HIV RNA					0.25
<5000 copies/ml	31.8	12 (0.56)	18 (0.83)	0.66	
5000–30,000 copies/ml	35.5	13 (0.53)	36 (1.41)	0.38	
>30,000 copies/ml	32.5	17 (0.72)	42 (1.92)	0.37	
Smoker					0.93
Yes	31.9	18 (0.78)	43 (1.81)	0.43	
No	68.1	24 (0.52)	53 (1.16)	0.44	
Framingham 10-yr CHD risk					0.56
<0.8	32.7	8 (0.35)	17 (0.77)	0.46	
0.8–3.6	32.3	11 (0.48)	27 (1.23)	0.39	
>3.6	33.5	23 (1.00)	50 (2.05)	0.50	



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

TEMPRANO: Immediate or Deferred ART Initiation ± IPT for African Pts

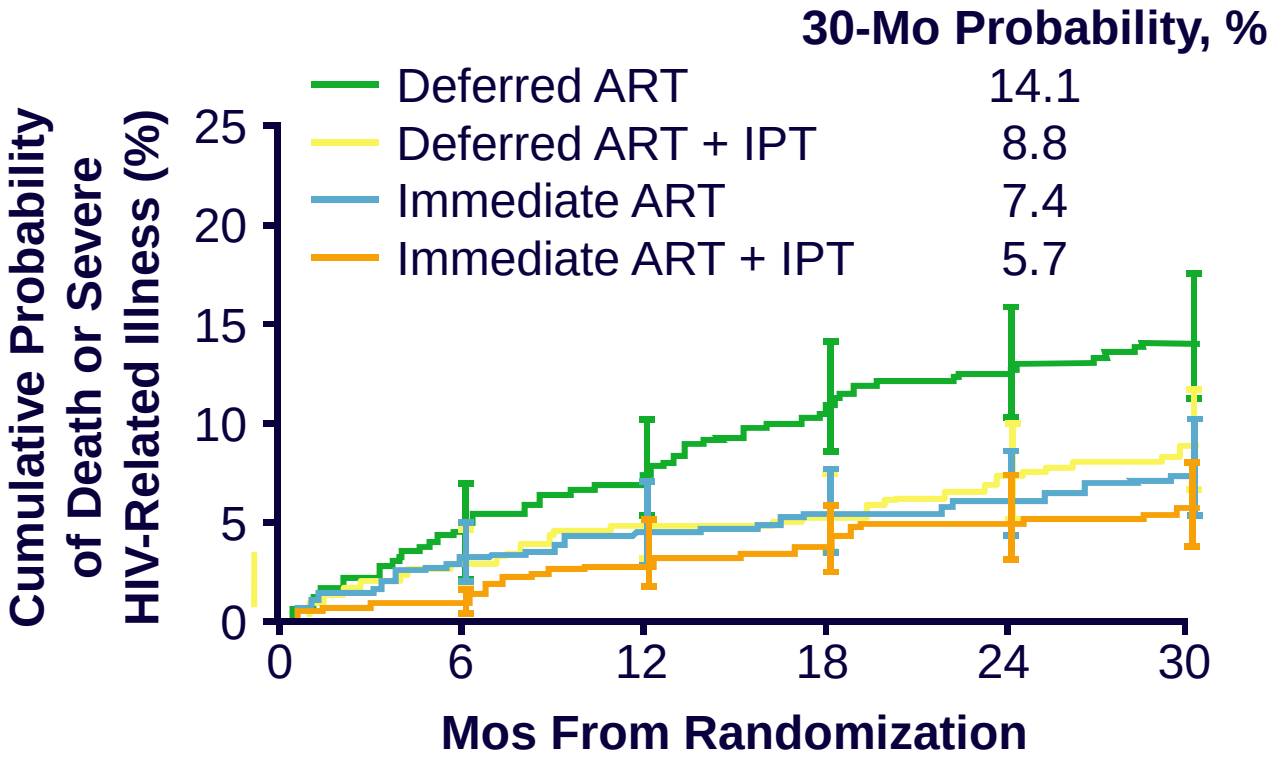
- Randomized, controlled, unblinded, multicenter (Ivory Coast), 2 x 2 factorial

*WHO criteria evolved during the study (updates 2006, 2010, 2013). †ART initiated immediately following randomization. ‡IPT = 300 mg daily isoniazid initiated 1 mo after enrollment and terminated 7 mos after enrollment. §Deferred until meeting WHO criteria for initiating ART.

- Pts in the treatment arms well matched at baseline
  - First-line ART primarily EFV + TDF/FTC (68% to 71%) or LPV/RTV + TDF/FTC (22% to 24%)
- Median duration of follow-up: 29.9 mos

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

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts



TB 42% and bacterial diseases 27% of primary endpoints

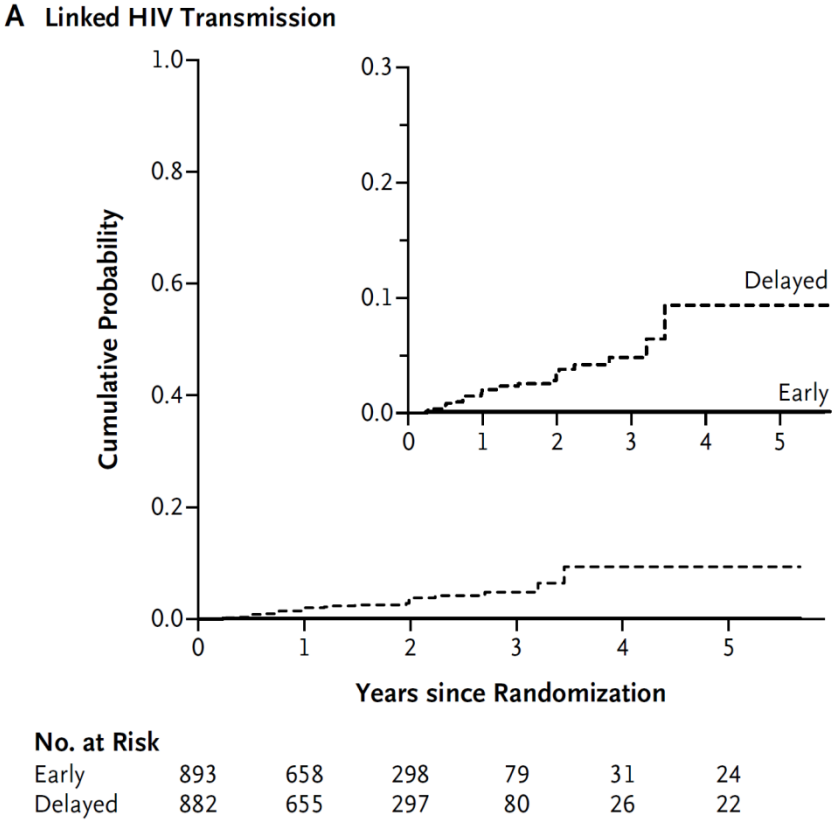
TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015

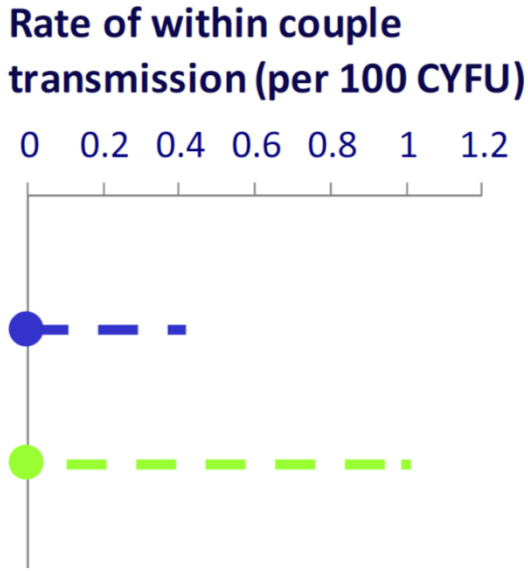
Conclusions

The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter.

Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)	Asymptomatic HIV infection	
Any CD4 count	Current CD4 count	
	< 350	≥350
SR	SR	R

Impact of prevention of transmission on when to start





RCT: Delayed vs Early ART

1763 serodiscordant couples

→ 28 vs 1 transmissions*

* Not virologically suppressed

Cohen, New Engl J Med, 2011

Partner-study (longitudinal study)

→ Interim results after 984 elegible serodiscordant couple-years of FUP: HIV transmission rate of zero through condomless sex with HIV-RNA <200 c/mL on ART

Rodger et al., CROI 2014

Start at any CD4 vs < 350

- Reduction of Morbidity +++
- Reduction of Mortality +
- Prevention of Damage caused by Primary HIV Infection, especially with meningo-encephalitis
- Prevention if immunological Damage
- Well tolerated ARVs
- Lifetime duration versus short saving of drugs, approx 3 years

- Drug toxicity (+)
- Drug resistance +
- Number needed to treat high at early stage with high CD4

Primary HIV

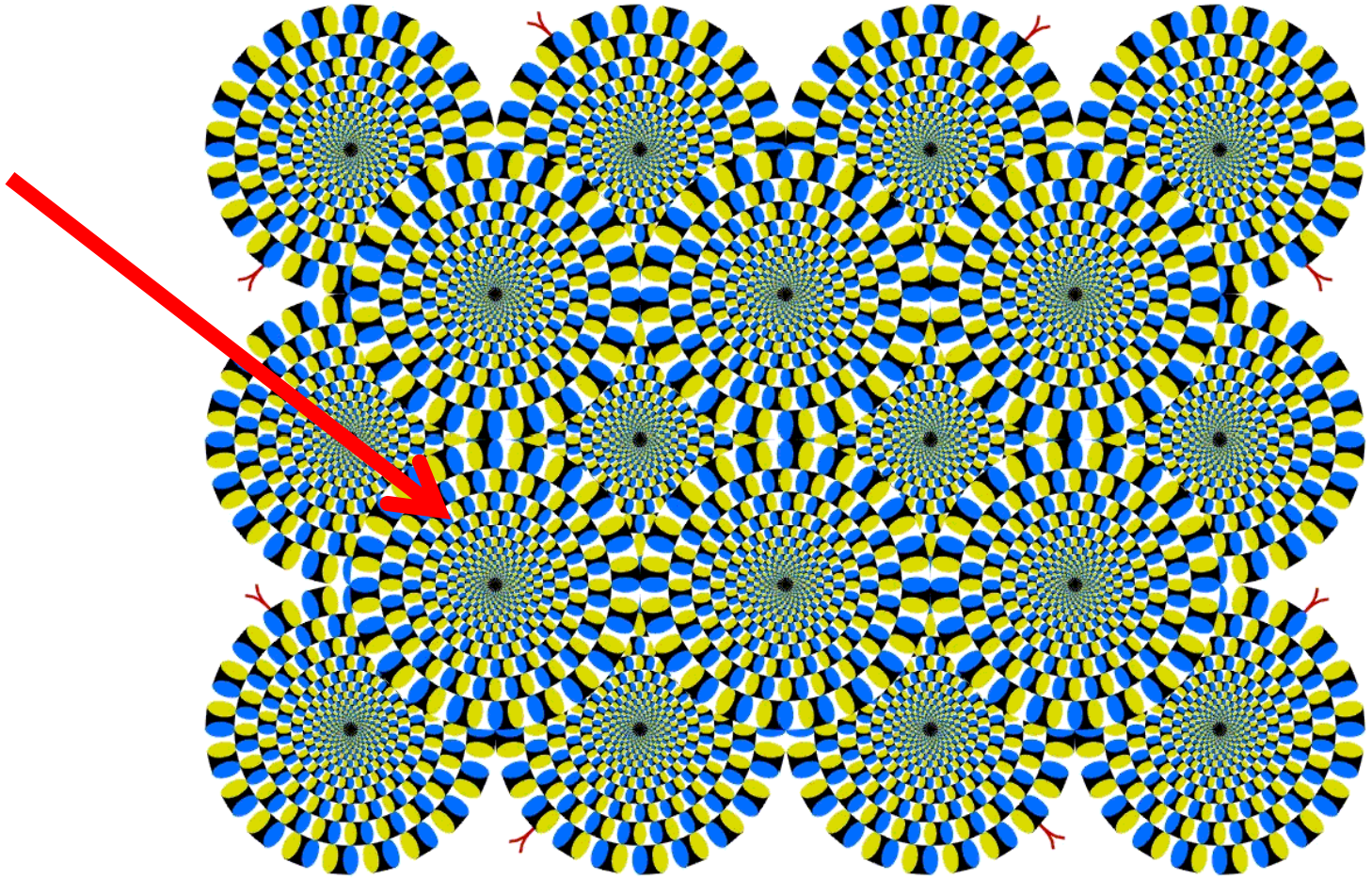
Pro ART

- Severity of acute symptoms; lower the VL set-point and size of the HIV DNA reservoir
- Reduce viral genetic evolution
- Reduce immune activation
- Preserve immune function
- Reduced risk of transmission
- Patients with PHI demonstrating symptoms of meningo-encephalitis should be treated urgently, if possible

Caveats

- Uncertain long-term clinical benefit
- Low likelihood of post-treatment control
- Treatment interruption leads to rebound of VL and inflammation markers
- Possible adverse consequences of long-term ART (toxicity, drug resistance)

Perception versus Reality



Slide courtesy Mark Nelson, London

Is the patient ready for ART ?

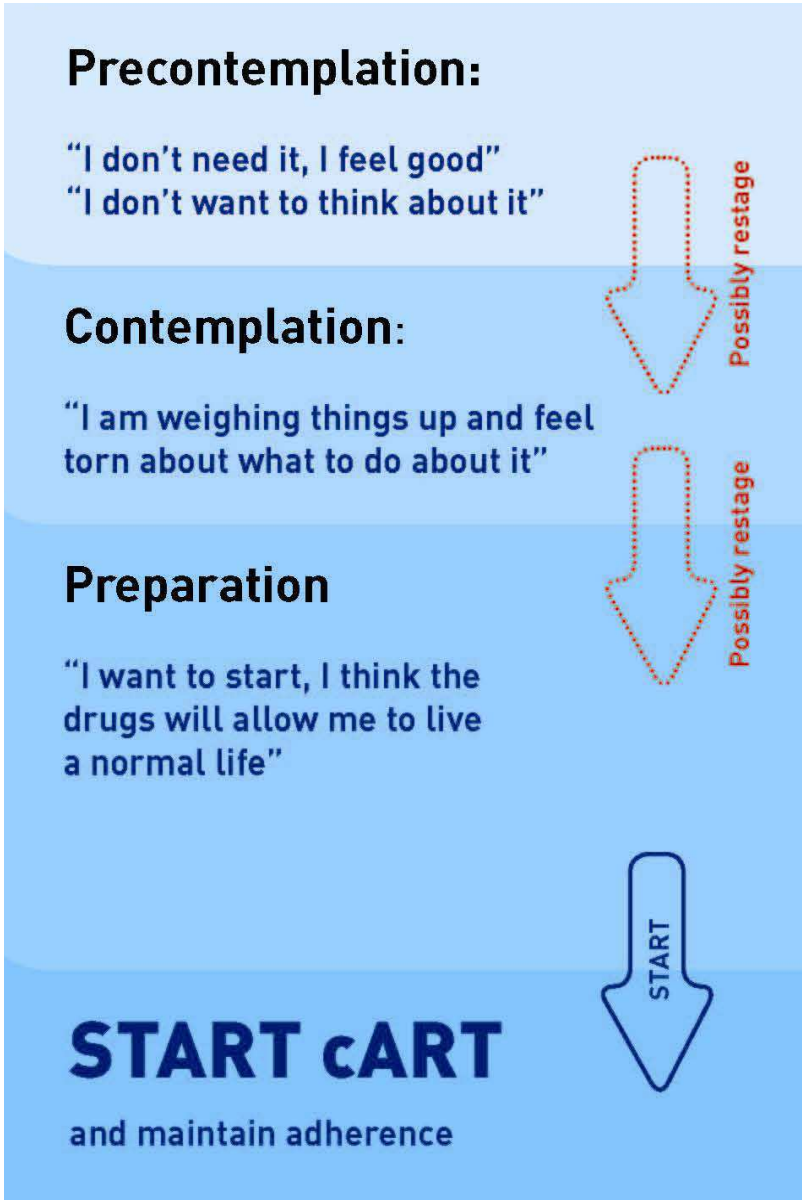
«I would like to talk about HIV medication»

… please wait …

«What do you think about it?»

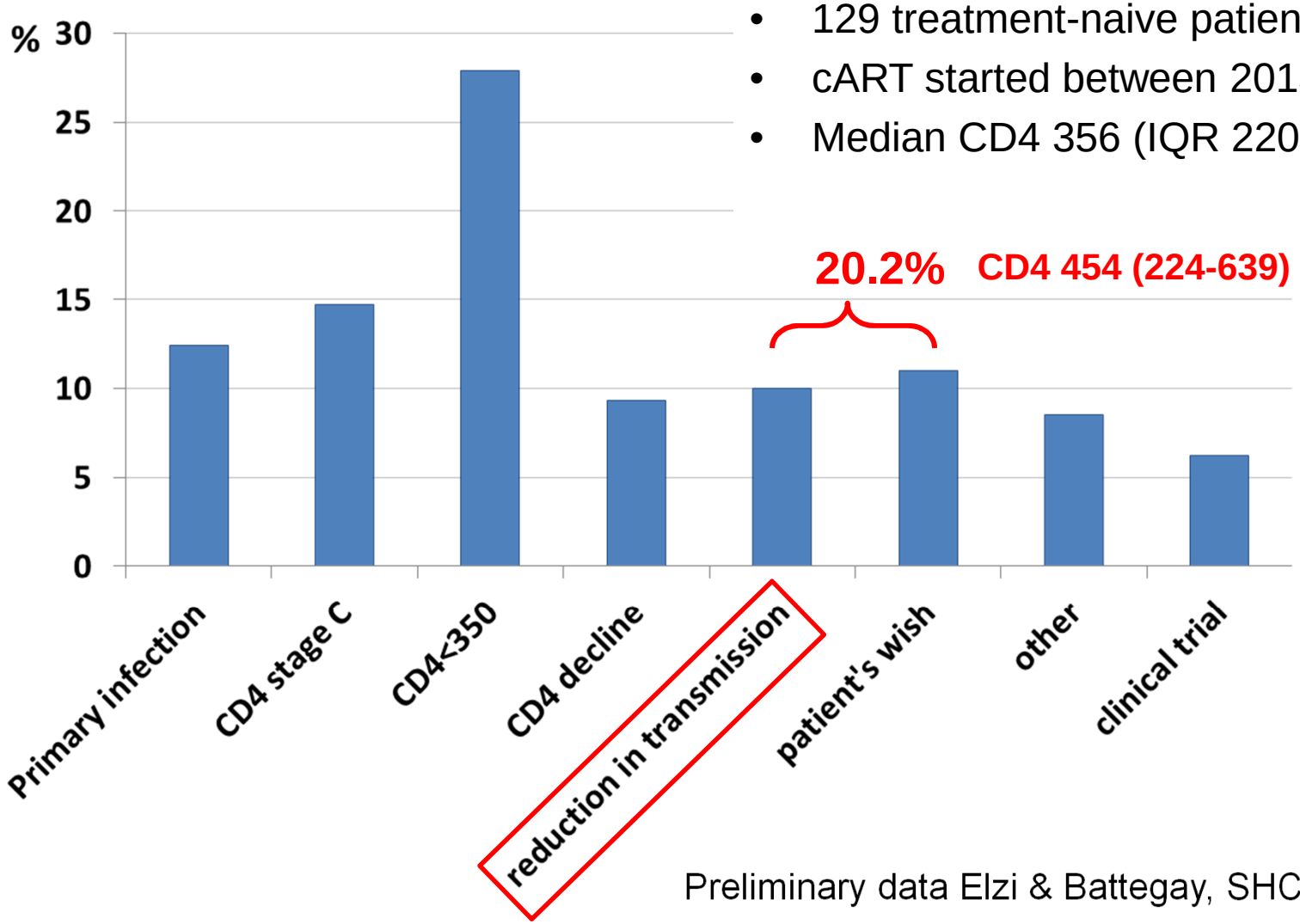
Patient
- Depression
- Drug, alcohol addiction
- Cognitive problems
- Low health literacy

System
- Health insurance
- Continuity drug supply
- Low social support



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

Main reason for starting ART

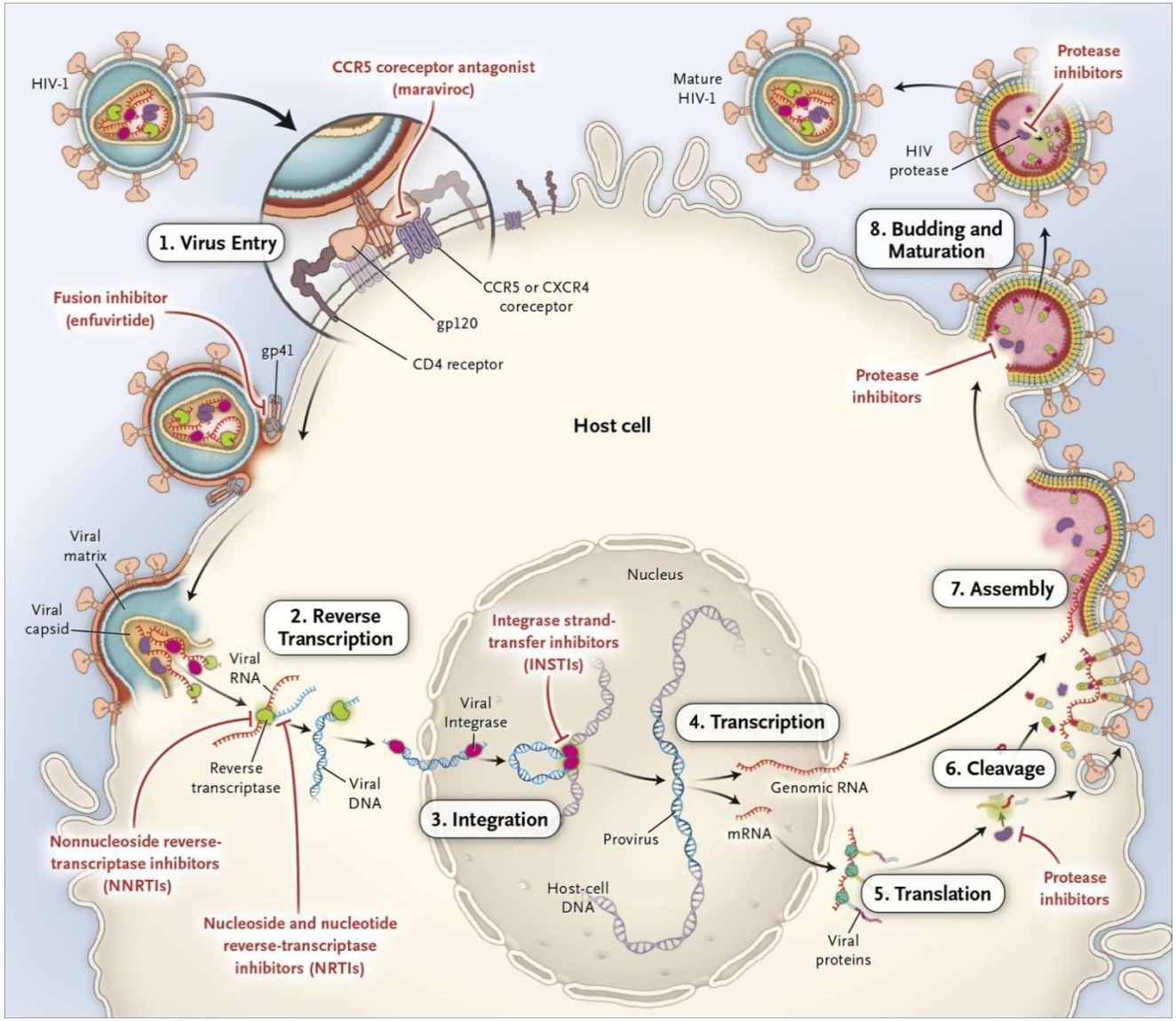


- 129 treatment-naive patients
- cART started between 2013-2014
- Median CD4 356 (IQR 220-495)

Preliminary data Elzi & Battegay, SHCS #644

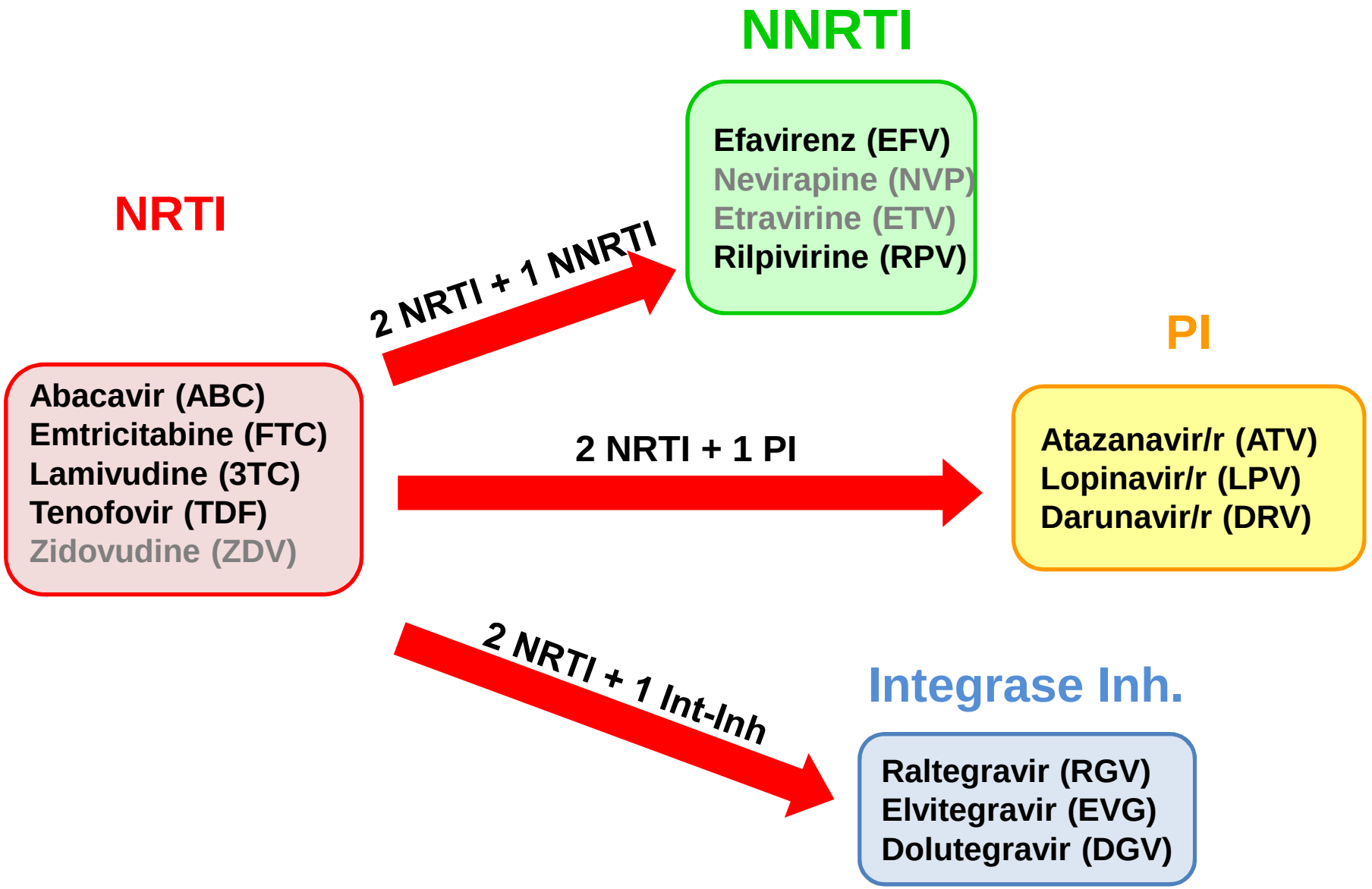
HIV – when and what to start – antiretroviral therapy principles

HIV-1 Cycle and Sites of Action ART

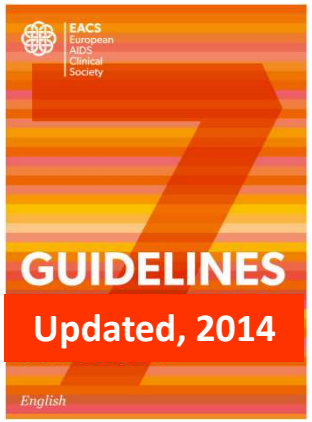


Gandhi M, Gandhi RT. N Engl J Med 2014

What to start



EACS Guidelines 2014/15



Initial *recommended* regimens for ART-naive Adult HIV-positive persons

Class	Drug	Backbone
NNRTI	Efavirenz	TDF-FTC or ABC-3TC
	Rilpivirine	TDF-FTC or ABC-3TC
Boosted PI	Atazanavir/r	TDF-FTC or ABC-3TC
	Darunavir/r	TDF-FTC or ABC-3TC
INSTI	Elvitegravir/COBI	TDF-FTC
	Raltegravir	TDF-FTC or ABC-3TC
	Dolutegravir	TDF-FTC or ABC-3TC

ABC contra-indicated if HLA B*5701 positive

www.eacssociety.org

Gatell J, Pozniak A and the ART Panel; Coordinator Lundgren JD, Lene Ryom, Medical Secretary, EACS Guidelines, 2014 updated

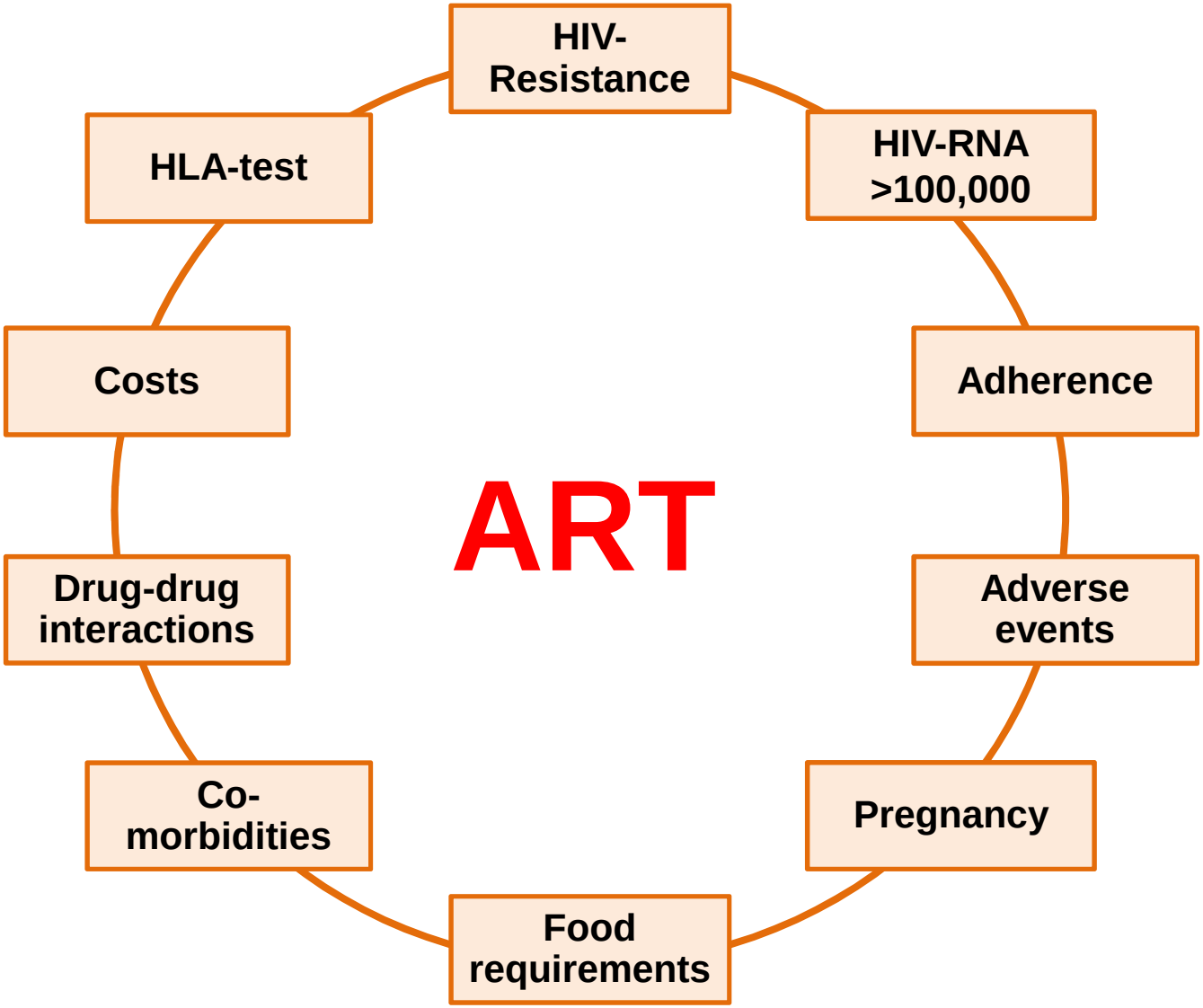
Newer antiretroviral drugs for HIV

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

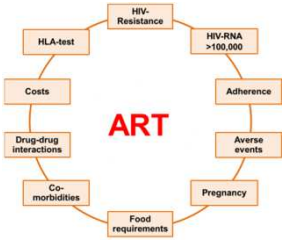
*In the SINGLE trial DTG was combined only with ABC/3TC

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

Considerations for ART choice



Resistance



HIV-Resistance

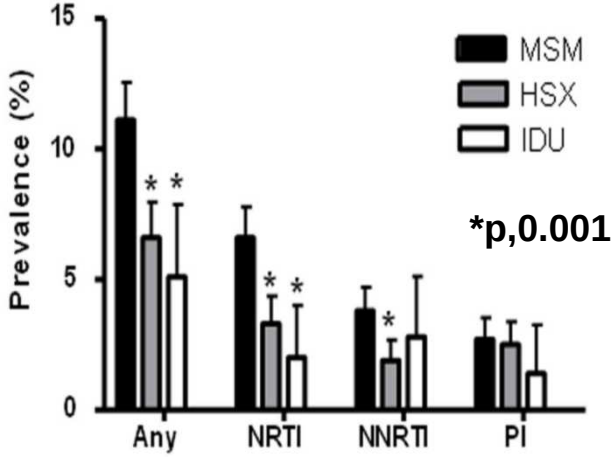
Transmitted HIV Drug Resistance in Europe

HIV-1 new diagnoses; 27 countries, 2002-2007

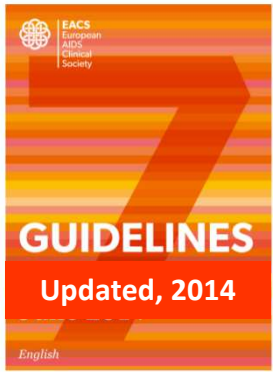
4317 patients

<u>Prevalence of TDRM</u>

MSM	**11.1%**
Heterosexuals	**6.6%**
PWID	**5.1%**

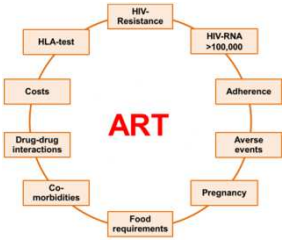


Genotypic resistance test recommended prior to ART (at HIV diagnosis); otherwise before initiation of ART. If ART needs to be initiated before results available, include a ritonavir-boosted PI in the first-line regimen.

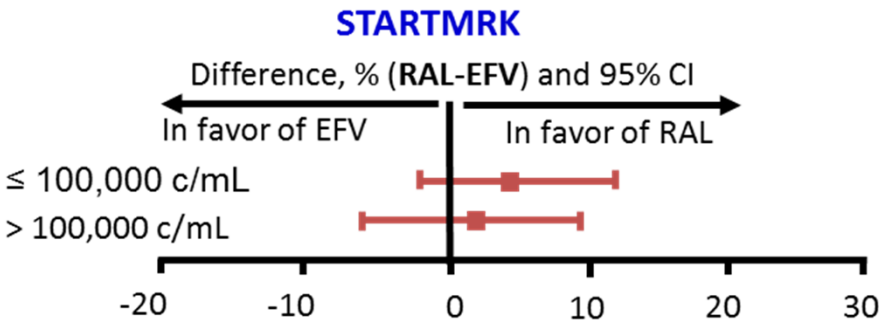


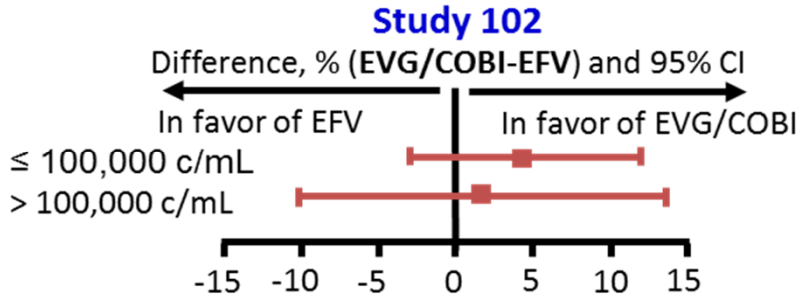
Frentz D, et al on behalf of the SPREAD Programme, PLoS One, 2014

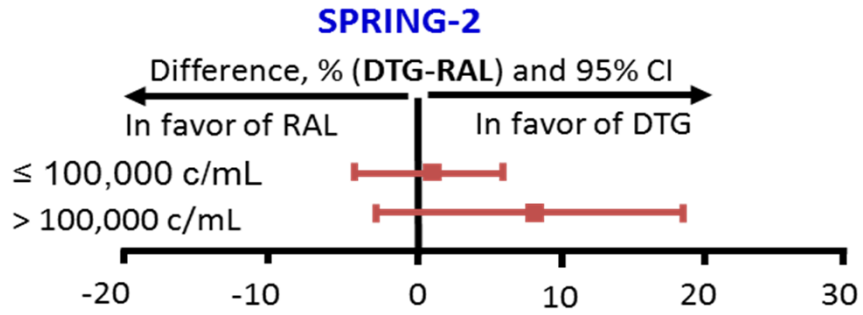
HIV-RNA >100,000 copies/ml



HIV-RNA >100,000





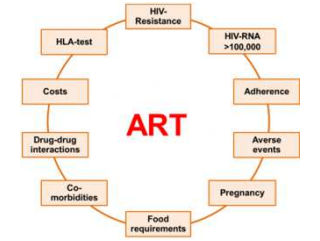


Inferior virologic response for

- **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

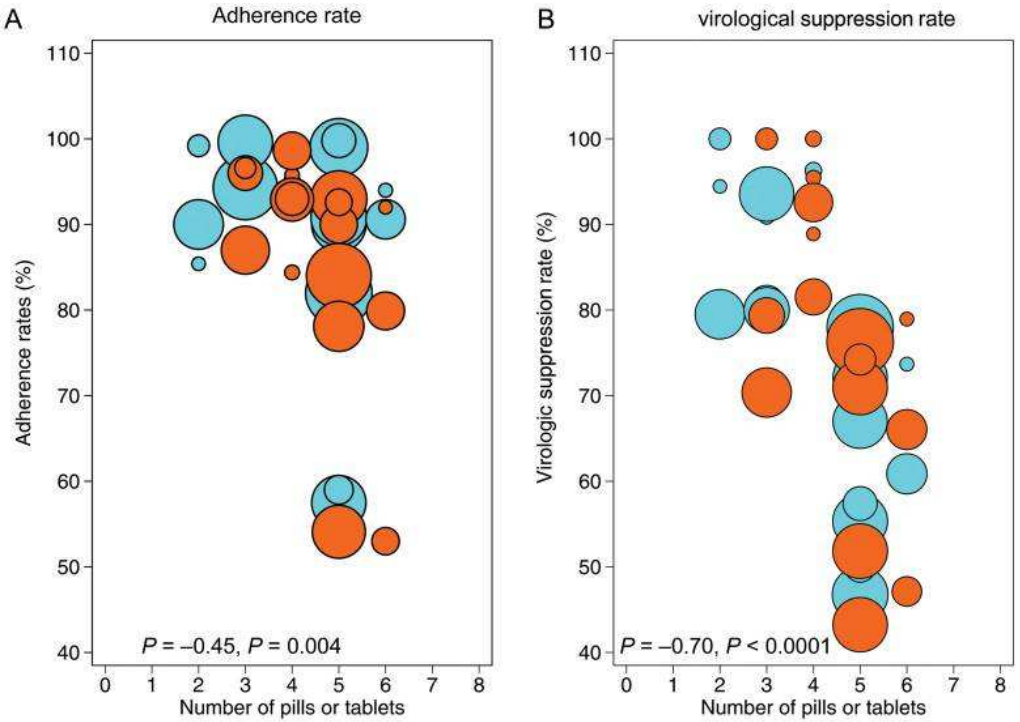
Adherence



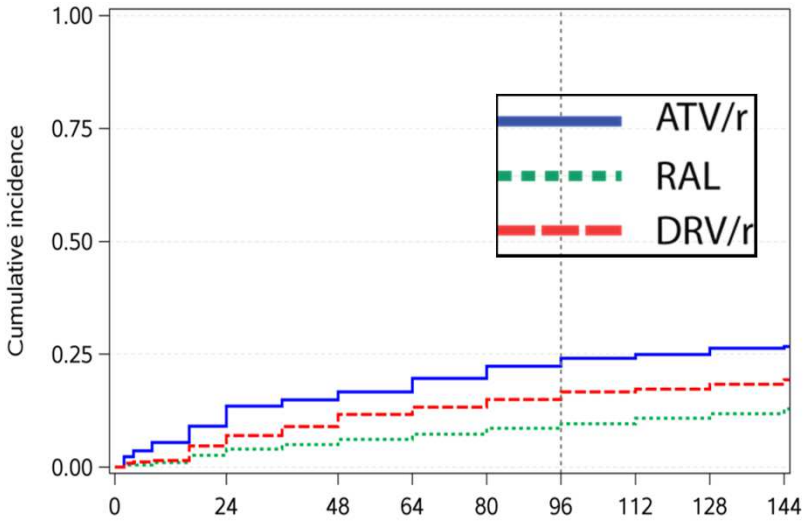
Adherence

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

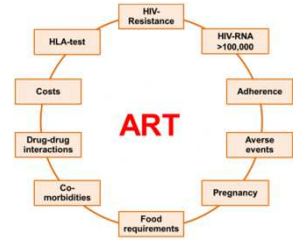
Nachega et al., Clin Infect Dis, 2014; Landovitz, Abstract CROI 2014

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.

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

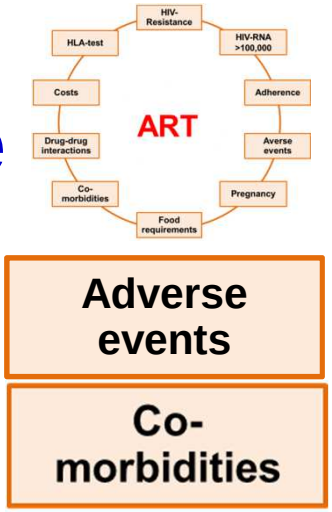
- **Raltegravir, EVG/COBI, Dolutegravir**

  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*

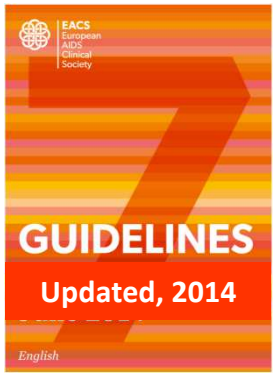
*inhibition of tubular secretion of creatinine, renal function not altered

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

Pregnancy

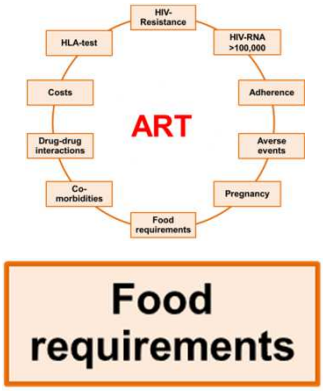
13,124 live births; 1994 and 2010, 42% (n=5,388) ART exposed in first trimester of pregnancy. Under EFV 4 neurological defects observed; significance depending on classification.



- Scenario on how to adapt ARV treatment in case of pregnancy or planned pregnancy
- Preferred drugs: LPV/r, SQV/r, ATV/r but EVF, DRV/r and RAL can be maintained if already used pre-pregnancy
- Consider adding RAL when ART started at a late stage of pregnancy

Sibuide J et al, PLoS Med, 2014, Brogly SB et al, Pediatr Infect Dis J. 2010

Food requirements



550 Kcal

- Rilpivirine

375 Kcal

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

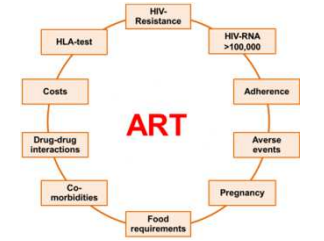
Fasting

- Efavirenz

Independent

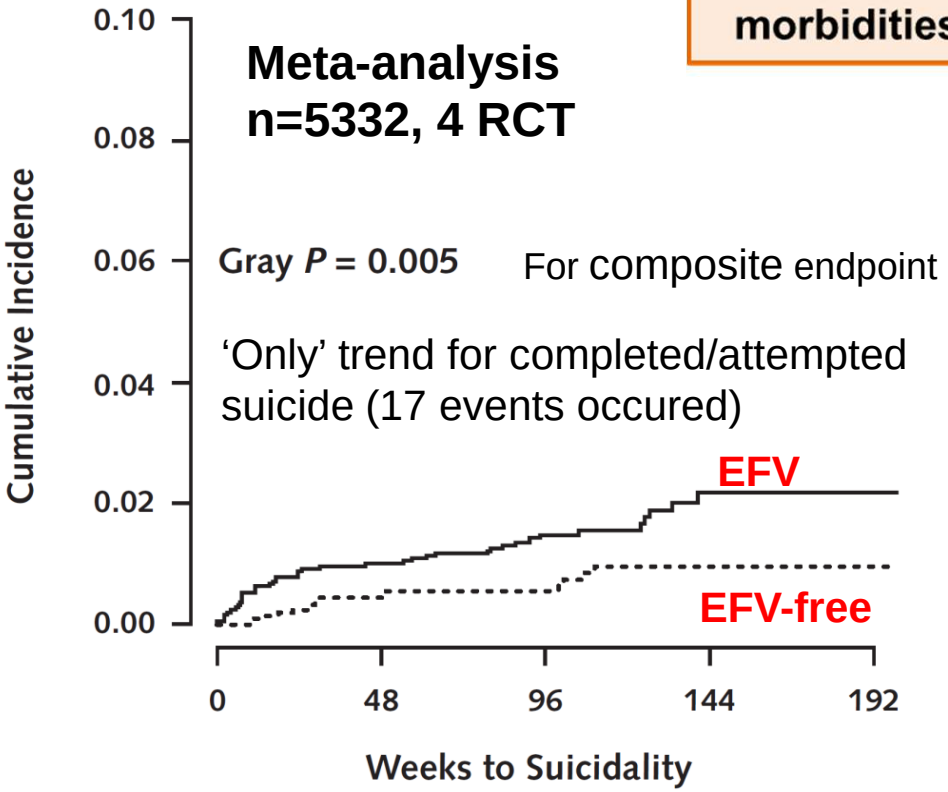
- Dolutegravir
- Raltegravir

Depression



Co-morbidities

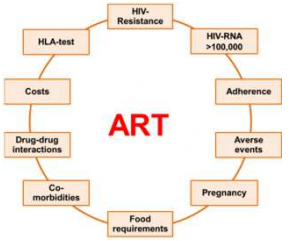
- **Efavirenz** (6%)
  2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)



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

Gastroesophageal reflux



Co-morbidities

Drug-drug interactions

- **Antacids:**

  → **caution** with:

  Rilpivirine, Atazanavir, all INSTIs

- **H_2 antagonists:**

  → **caution** with:

  Rilpivirine, Atazanavir

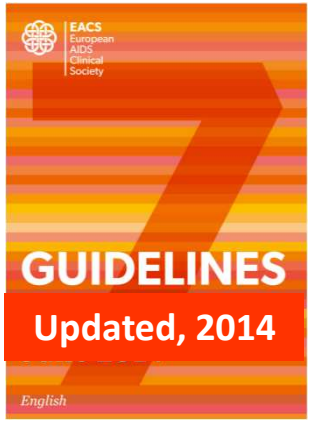
  AUC ↓ 76% **AUC ↓ 23-41%**

- **Proton pump inhibitors:**

  → **caution Rilpivirine, Atazanavir**

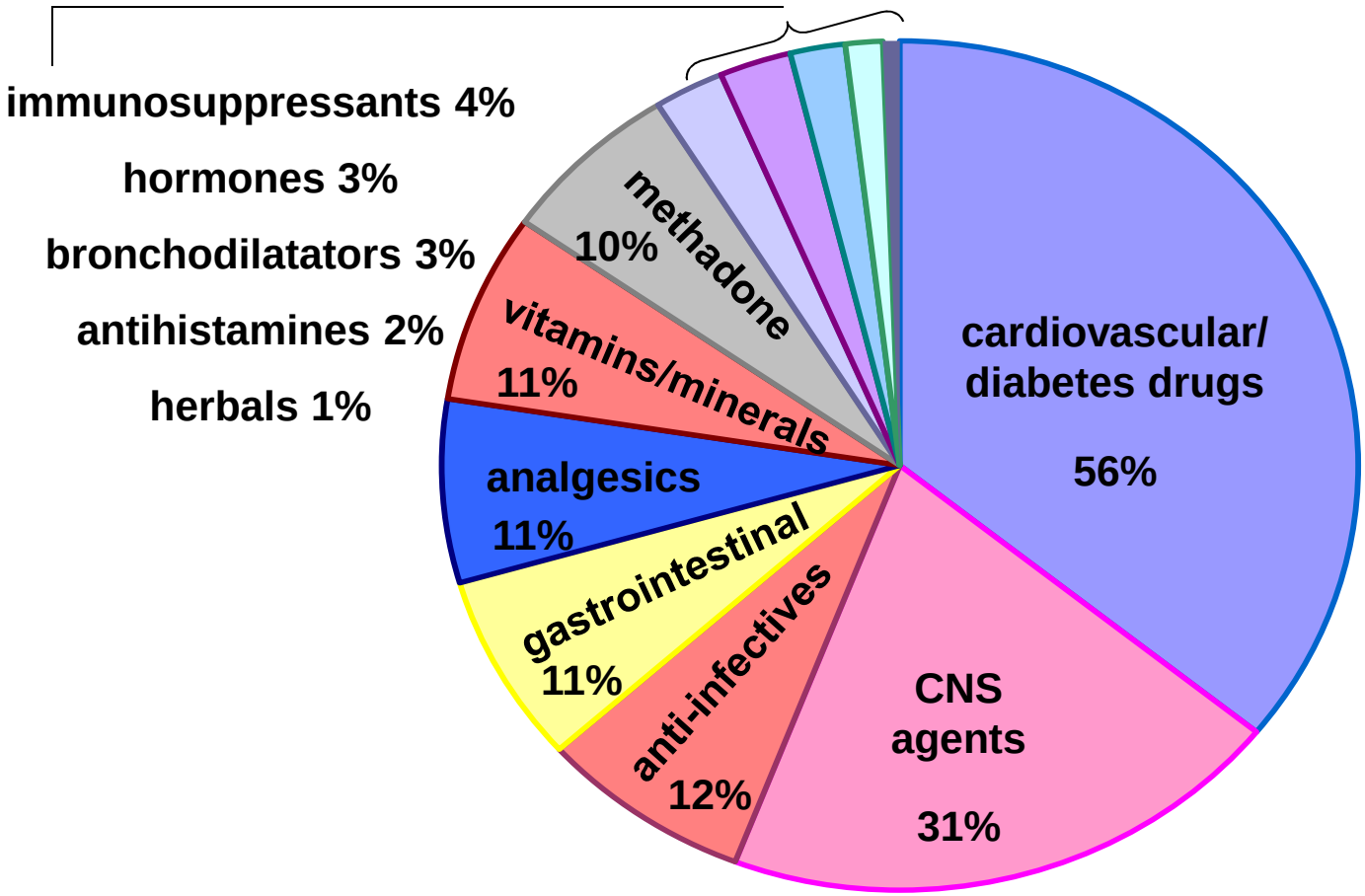
  Cmin ↓37% **Cmin ↓ 78-93%**

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.



Co-medication in the SHCS

SWISS HIV COHORT STUDY

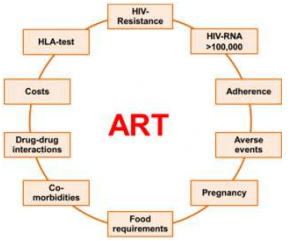


Interactions more frequent >50 y

- **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

Nuke free/sparing initial ART

PI

- Atazanavir/r
- Darunavir/r
- Lopinavir/r

1 PI + 1 NNRTI	**NNRTI**: Efavirenz
1 PI + 1 INSTI	**INSTI**: Raltegravir
1 PI + 1 NRTI	**NRTI**: Lamivudine
1 PI + 1 FI	**FI**: Maraviroc

Nuke free/sparing initial ART

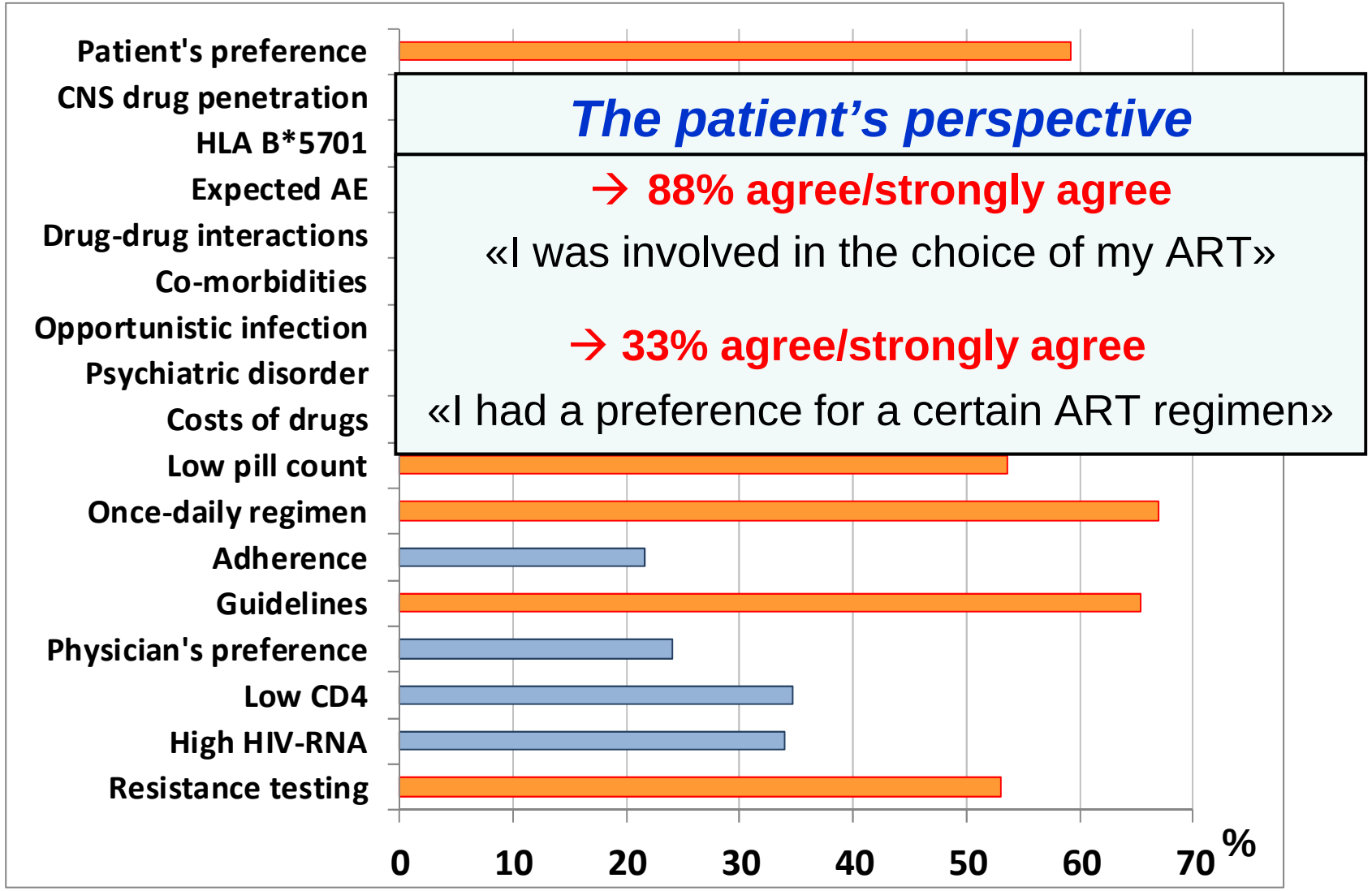
Study	Regimen	Comparison	Efficacy
SPARTAN	**ATV/r + RAL**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 24: 74.6% vs 63.3% → **non-inferior** (but high bilirubinemia and resistance to RAL)
A4001078	**ATV/r + MVC**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 48: 74.6% vs 83.6% → **non-inferior**
NEAT001/ ANRS143	**DRV/r + 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, abstract AIDS 2014

Reasons for a specific initial ART: *the physician's choice 2013-14*

SWISS HIV COHORT STUDY

n=184 treatment naive patients



The patient's perspective

→ 88% agree/strongly agree

«I was involved in the choice of my ART»

→ 33% agree/strongly agree

«I had a preference for a certain ART regimen»

Preliminary data Elzi et al., SHCS #644

Genetic Associations of ART Toxicity

Gene	Toxicity	Evidence
HLA B*5701	Abacavir hypersensitivity	Confirmed in large RCT
HLA DRB1*0101, HLA B*3505, HLA Cw8	Nevirapin rash +/- hepatitis Efavirenz rash	HLA association confirmed, different ethnicities
CYP 2B6*6, other	Higher serum EFV levels, higher CNS toxicity, virological success	Confirmed Not confirmed
UGT1A1, SLC01B1	Hyperbilirubinemia ATV, IDV, LPV	confirmed
mtDNA haplogroups T, L1c	d4T neuropathy	Not confirmed
CFTR / SPINK	Pancreatitis	Confirmed in HIV seroneg.
MDR1 3435	Hyperbilirubinemia, renal toxicity of TDF	Not confirmed
Resistin	Metabolic syndrome	Not confirmed
APOE4, Mannose binding lectin (MBL)-2	HIV associated cognitive disordes	Not confirmed

Slide courtesy Philip Tarr

Lubomirov JID 2011

Different treatments are very efficent in the 'real world'

Variable	TDF-FTC efavirenz	TDF-FTC lopinavir/r	TDF-FTC atazanavir/r	ZDV-3TC lopinavir/r	ABC-3TC efavirenz	Other	p-value
HIV-RNA <50 copies/ml	**92%**	85%	86%	83%	90%	85%	**0.003**
Increase in CD4 cells	158 (84-240)	177 (97-284)	168 (96-279)	**209** (107-326)	173 (96-257)	181 (83-270)	**<0.001**
Switch of cART	22%	40%	21%	50%	**20%**	36%	**<0.001**

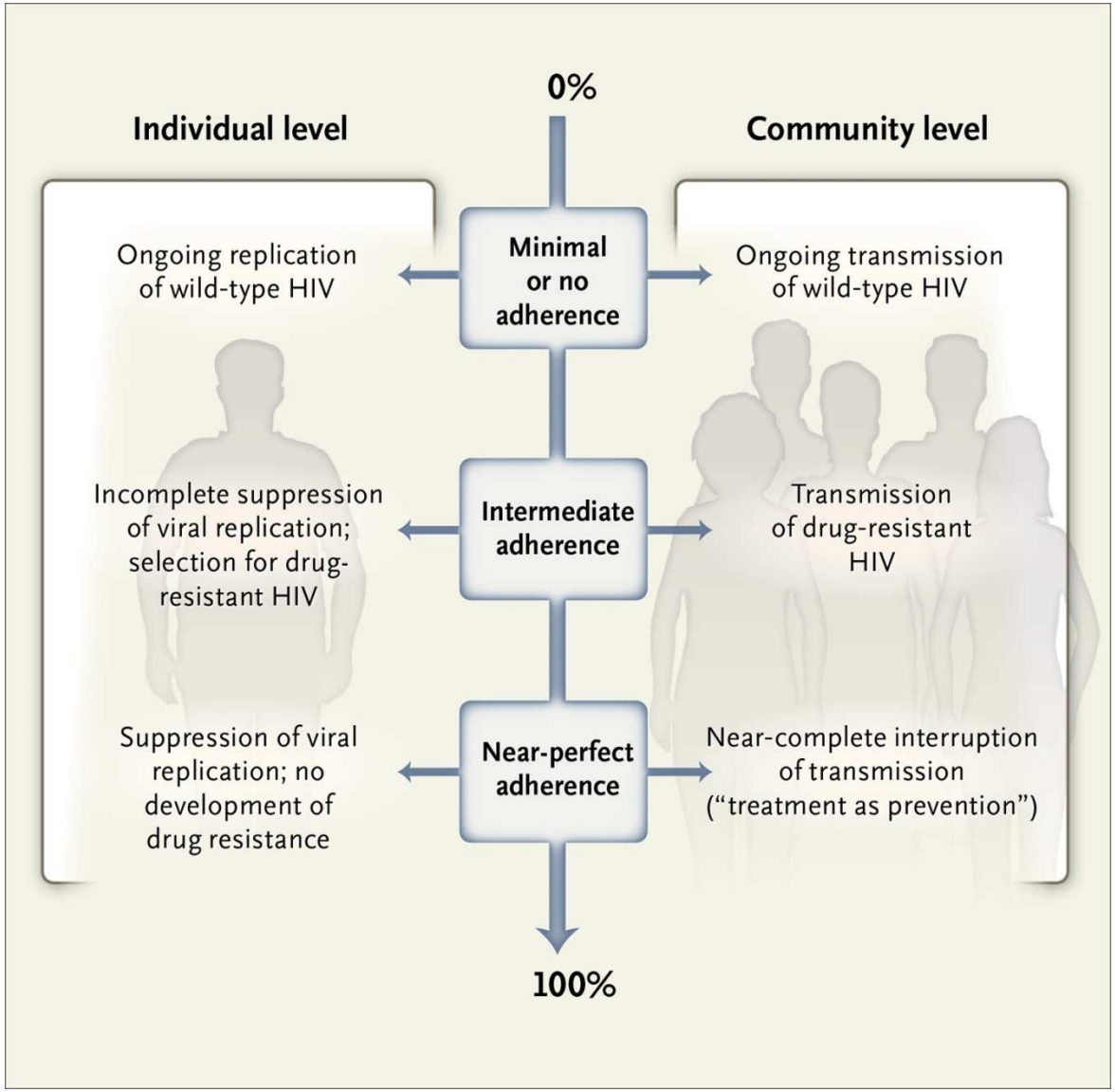
Individualisation

Gender, Drug use, Hepatitis, CVD, high VL

SHCS 2014 data on file: overall 92% of approx. 9000 patients <50 c/ml

Elzi & Battegay et al., Arch Intern Med, 2012

Effects on the Individual and Community of Various Levels of Adherence



Gandhi M, Gandhi RT. N Engl J Med 2014

HIV – when and what to start – ART principles 1

Drug	Considerations IN FAVOR	Considerations AGAINST
Efavirenz	• Co-formulation, 1 pill OD • Most experience	• Higher risk of resistance • AE: CNS • Drug-drug interactions
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
PI	• 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
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

HIV – when and what to start – antiretroviral therapy principles 2

- **Different recommended initial ART regimens demonstrate excellent potency and low but existing risk for adverse events.**
- **The choice of initial ART should take into consideration many individually presented factors such as resistance, comorbidities, drug drug interactions, adherence, convenience and others.**
- **Individualization of therapy should actively be discussed also taking the view of the patient into consideration.**
- **Newer drugs and drug regimens as well as alternative regimens add to the excellent possibilities of initial choice of therapy.**