HIV - Therapy Principles

Manuel Battegay and Christine Katlama

Basel, Switzerland and Paris, France

EACS European AIDS Clinical Society

Disclosure

- MB has received honoraria for advisory board participation from Gilead, MSD, Pfizer, ViiV Healthcare.

- His institution has received support from AbbVie, BMS, Boehringer-Ingelheim, Gilead, Janssen, MSD, Pfizer, and ViiV Healthcare.

- CK has has received consulting fees or honoraria; her institution has received support from BMS, Gilead and ViiV Healthcare.

Outline

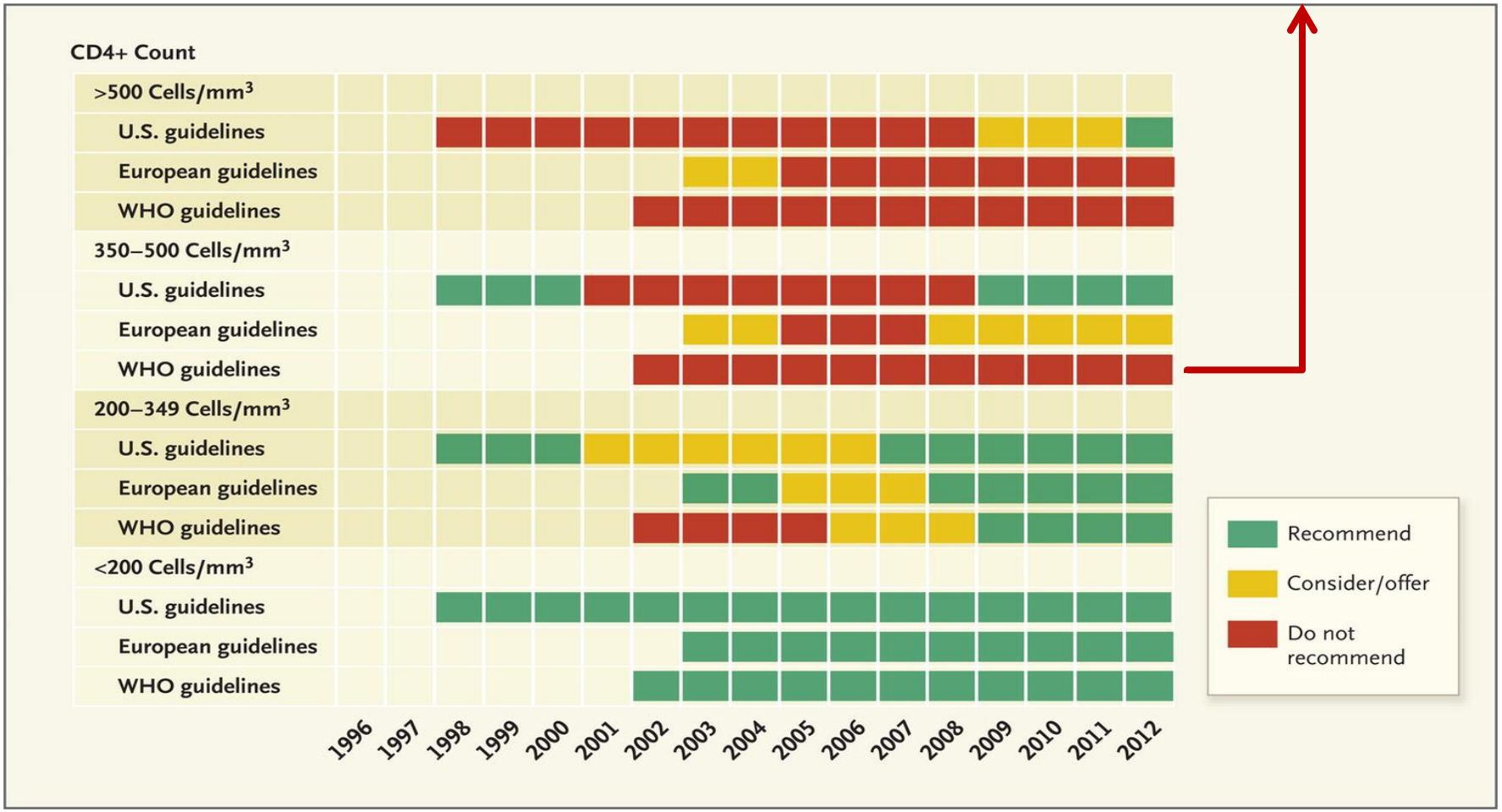
- **When to start** - Guidelines
  - Individualization
- **What to start** - Guidelines
  - Individualization
- **Real world**
- **Future perspectives**

Outline

- **When to start** - Guidelines
  - Individualization
- **What to start** - Guidelines
  - Individualization
- **Real world**
- **Future perspectives**

ART is started earlier

2013 ART GUIDELINES	STRENGTH OF RECOMMENDATION
CD4 ≤500 cells/mm^3 (CD4 ≤ 350 cells/mm^3 as a priority)	Moderate-quality evidence



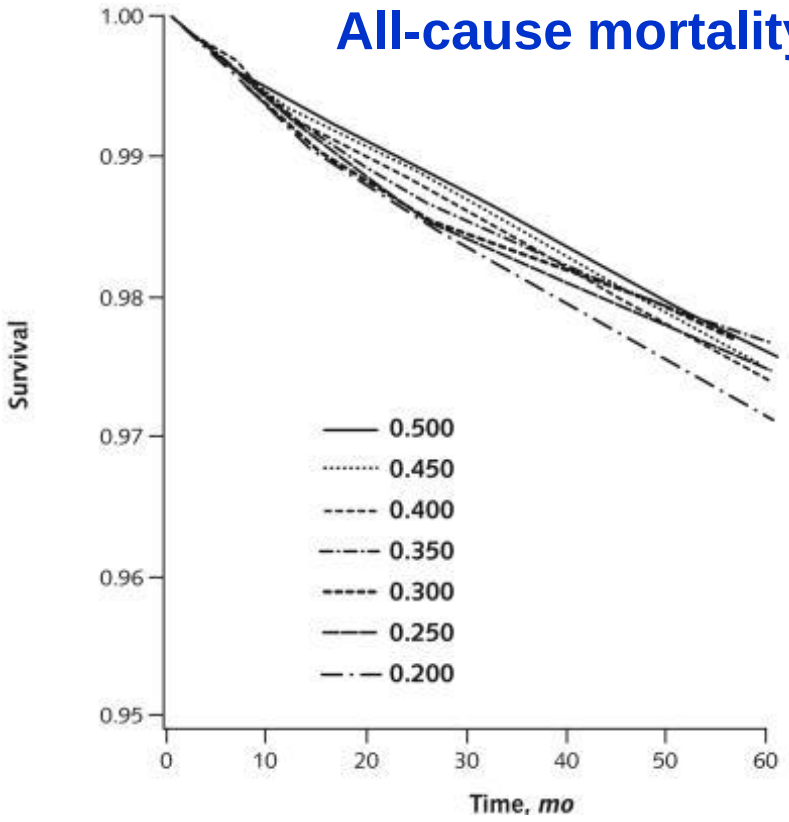
De Cock K, N Engl J Med, 2013

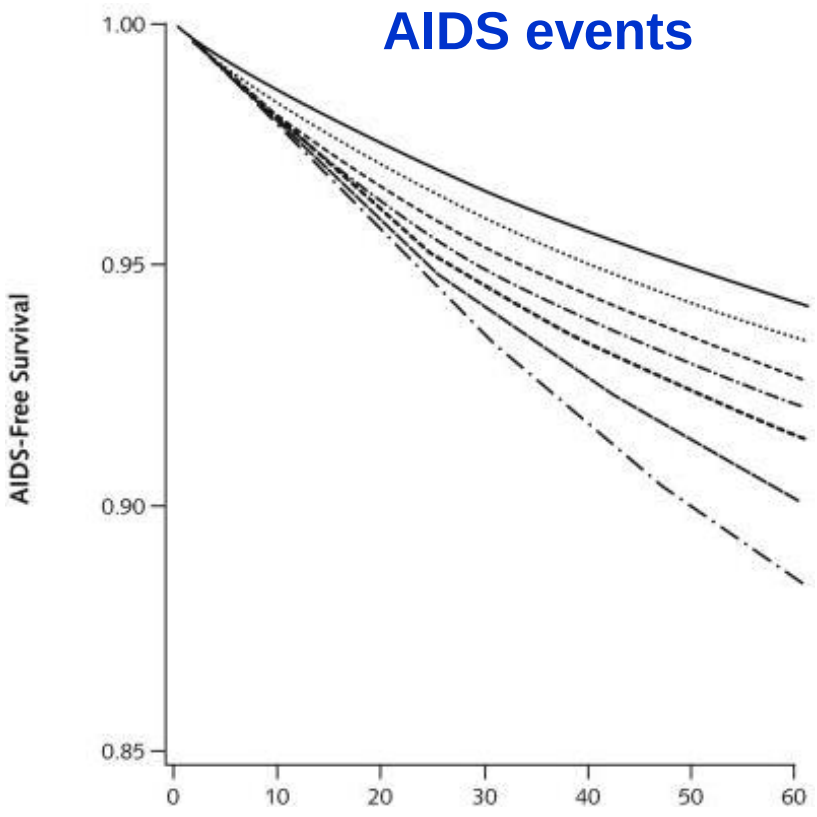
International Guidelines 2014 when to start

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.

5-year outcome by CD4 at starting ART

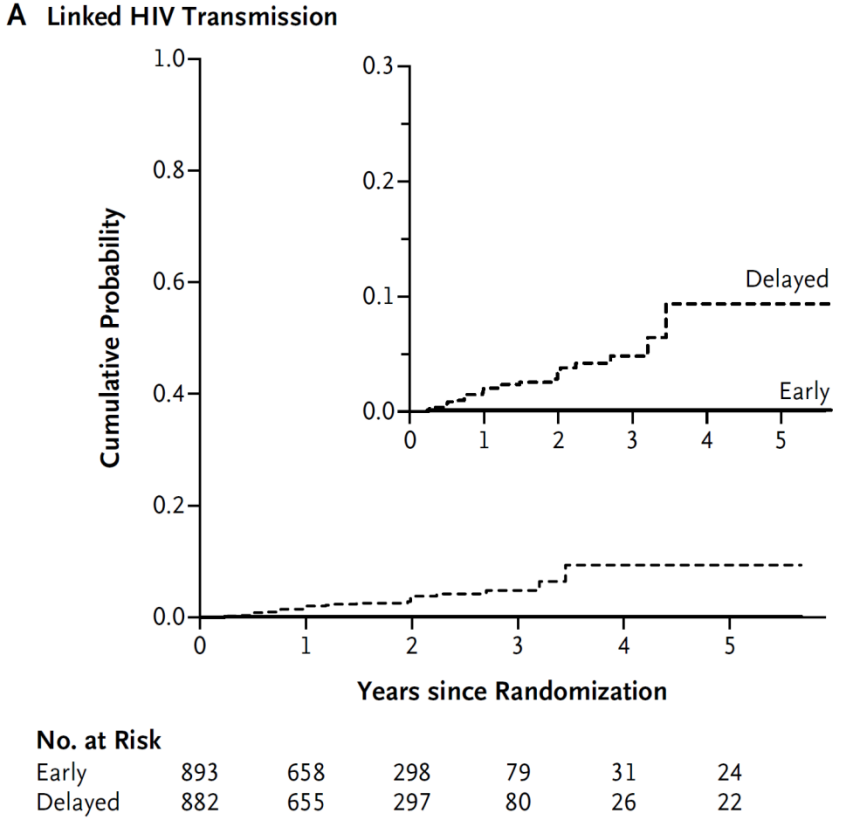


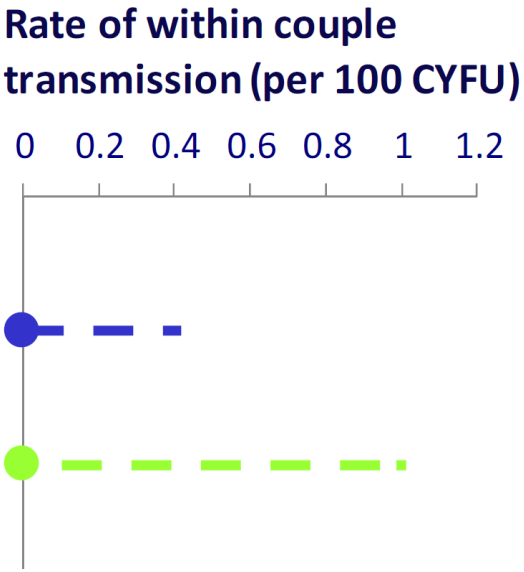


No changes in mortality but in AIDS-defining events with starting ART at increasing CD4 (>450 cells/µl)

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

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)

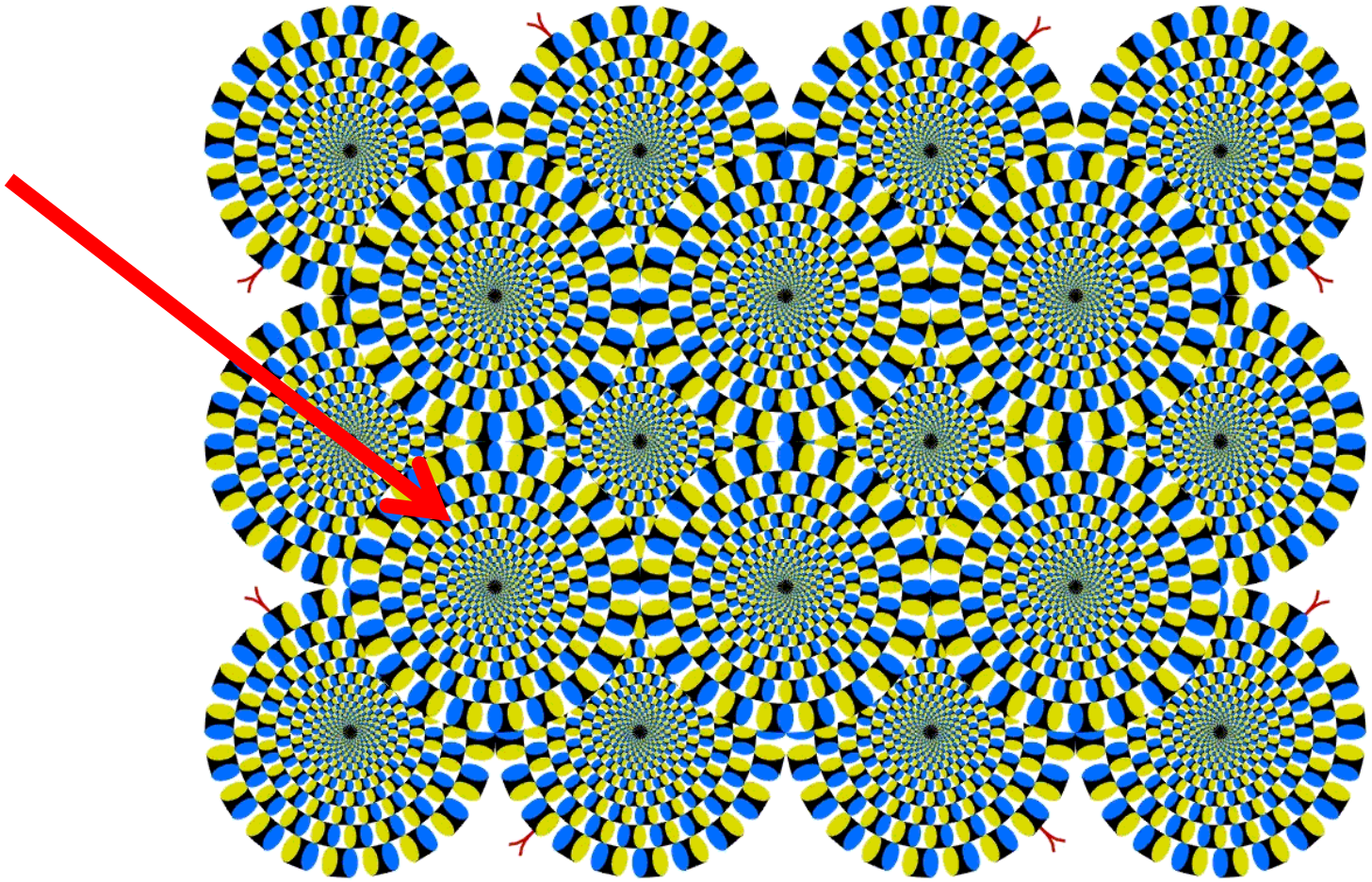
→ Interim results after 984 elegible serodiscordant couple-years of FUP: HIV transmission rate of zero through condomless sex with HIV-RNA <200 c/mL on ART

Rodger et al., CROI 2014

Individual counselling in clinics should be differentiated

- Discuss: Individual prognosis
  Transmission prevention
  Treatment as prevention
- Lack of data for very early start
  START trial ongoing
- ‘Only’ pathophysiological data for primary HIV
- Strong evidence of prevention of transmission
  Individual perspective
  Public health perspective

Perception versus Reality



Slide courtesy Mark Nelson, London

Is the patient ready for ART ?

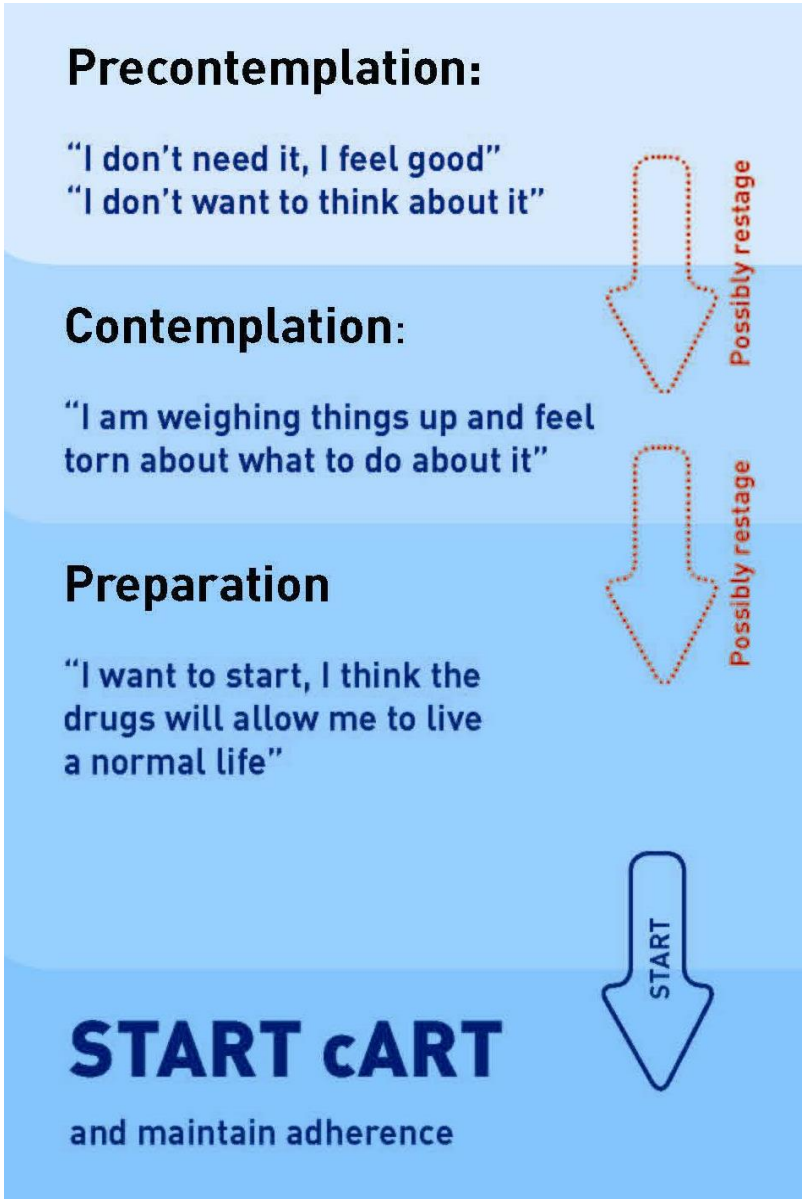
«I would like to talk about HIV medication»

… 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

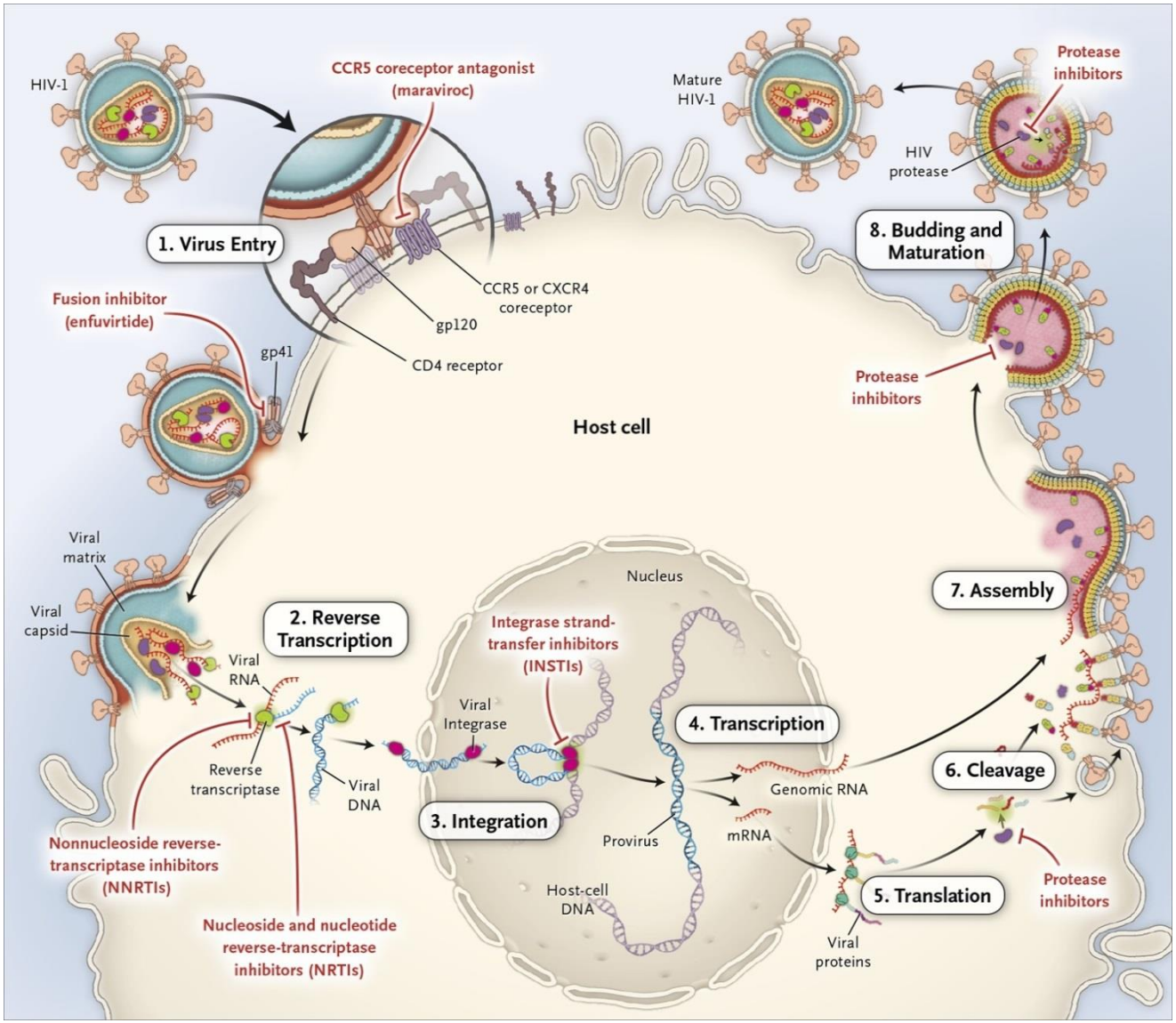


Fehr et al. Infection 2005, EACS Guidelines: www.eacsociety.org

Outline

- **When to start** - Guidelines
  - Individualization
- **What to start** - Guidelines
  - Individualization
- **Real world**
- **Future perspectives**

HIV-1 Cycle and Sites of Action ART



Gandhi M, Gandhi RT. N Engl J Med 2014

What to start

NRTI

Abacavir (ABC)
Didanosine (DDI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudin (D4T)
Tenofovir (TDF)
Zidovudine (ZDV)

2 NRTI + 1 NNRTI

NNRTI

Efavirenz (EFV)
Nevirapine (NVP)
Etravirine (ETV)
Rilpivirine (RPV)

2 NRTI + 1 PI

PI

Amprenavir (APV)
Atazanavir/r (ATV)
Indinavir (IDV)
Lopinavir/r (LPV)
Saquinavir/r (SQV)
Ritonavir (RTV)
Nelfinavir (NFV)
Tipranavir (TPV)
Darunavir/r (DRV)

2 NRTI + 1 Int-Inh

Integrase Inh.

Raltegravir (RGV)
Elvitegravir (EVG)
Dolutegravir (DGV)

EACS Guidelines 2014

A drug from column A should be combined with the drugs listed in column B(**)

A	B	Remarks
NNRTI	**NRTI**	
EFV(i) RPV(ii)	ABC/3TC(vii) or TDF/FTC	ABC/3TC co-formulated TDF/FTC co-formulated EFV/TDF/FTC co-formulated RPV/TDF/FTC co-formulated
PI/r		
ATV/r(iv) DRV/r(iv)	ABC/3TC(vii) or TDF/FTC	ATV/r: 300/100 mg qd DRV/r: 800/100 mg qd
INSTI		
EVG + COBI	FTC/TDF	EVG/COBI/FTC/TDF co-formulated (ix)
RAL	TDF/FTC or ABC/3TC	RAL: 400 mg bd

ii RPV: only if HIV-VL < 100,000 copies/mL; PPI contraindicated, H2 antagonists to be taken 12h before or 4h after RPV.

vii ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk and/or persons with a VL > than 100,000 copies/mL.

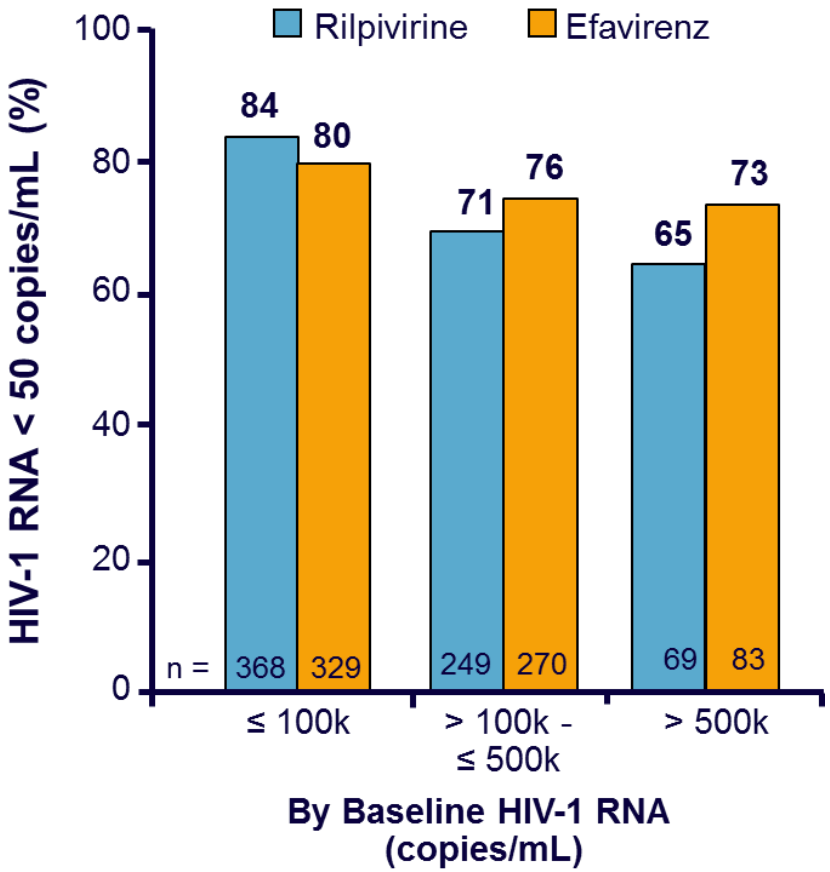
DHHS Guidelines: October 2013 Update on Integrase Inhibitors

Class	Preferred Regimens
NNRTI	EFV/TDF/FTC
Boosted PI	ATV/r + TDF/FTC DRV/r + TDF/FTC
INSTI	RAL + TDF/FTC EVG/COB/TDF/FTC DTG + ABC/3TC DTG + TDF/FTC

All 3 integrase inhibitors are now part of preferred first-line regimens

DHHS. Guidelines. February 2013. DHHS. Recommendation on INSTIs. October 2013.

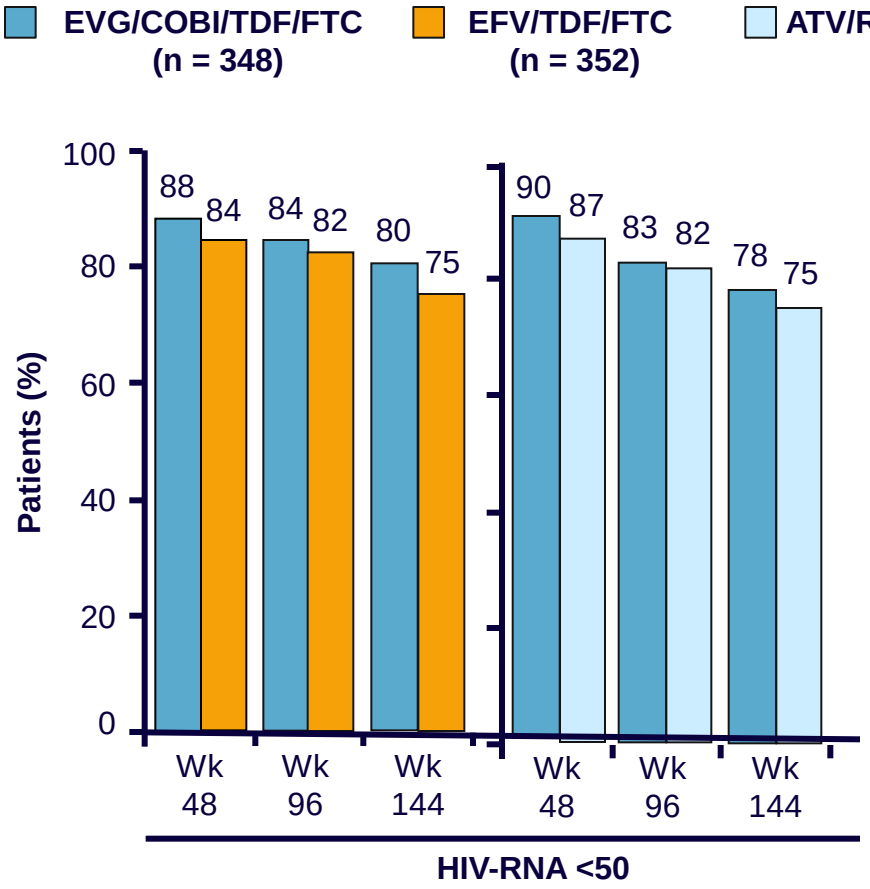
New drugs: Rilpivirine



- **Noninferior to Efavirenz** at week 96 (Echo-Thrive Study)
- More virologic failures if baseline HIV-RNA >10^5 copies/ml
- Cross-resistance with Etravirin (E138K)
- Fewer drug discontinuations due to AEs (rash, CNS)
- Better lipid profile

Cohen CJ, AIDS 2013; 27:939-950

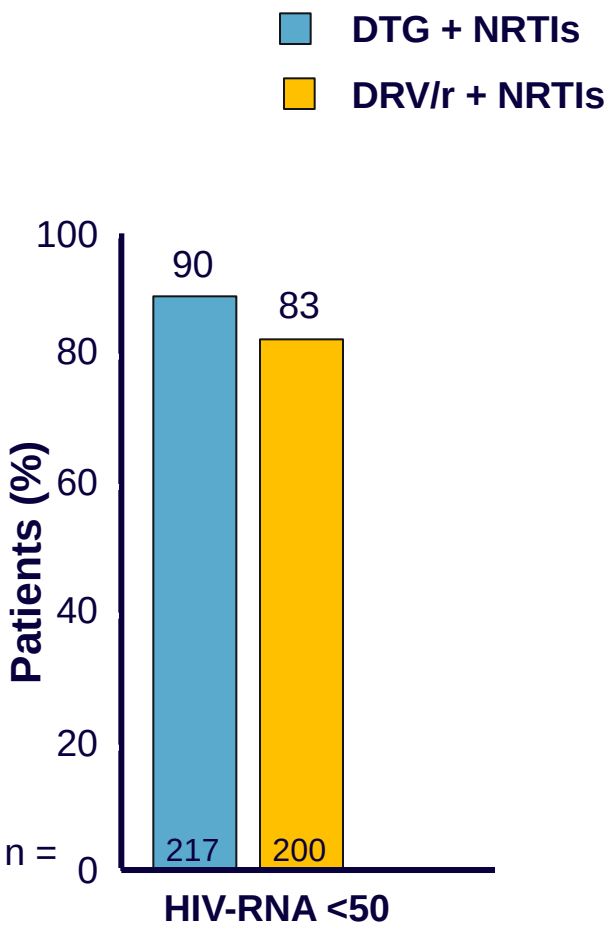
Elvitegravir/Cobicistat



- **Noninferior to EFV/TDF/FTC and ATV/RTV + TDF/FTC at week 144**
- 2% failed with resistance, usually to both NRTIs and EVG
- Less adverse events
- Small, rapid increase in serum creatinine (inhibition of tubular secretion)

Sax PE, et al. Lancet. 2012;379:2439-2448; Zolopa A, et al. JAIDS. 2013;63:96-100; Wohl D, et al. ICAAC 2013. Abstract H-672a; DeJesus E, et al. Lancet. 2012;379:2429-2438; Rockstroh J, et al. JAIDS; 2013; 62:483-486; Clumeck N, et al. EACS 2013. Abstract LBPS7/2.

Dolutegravir



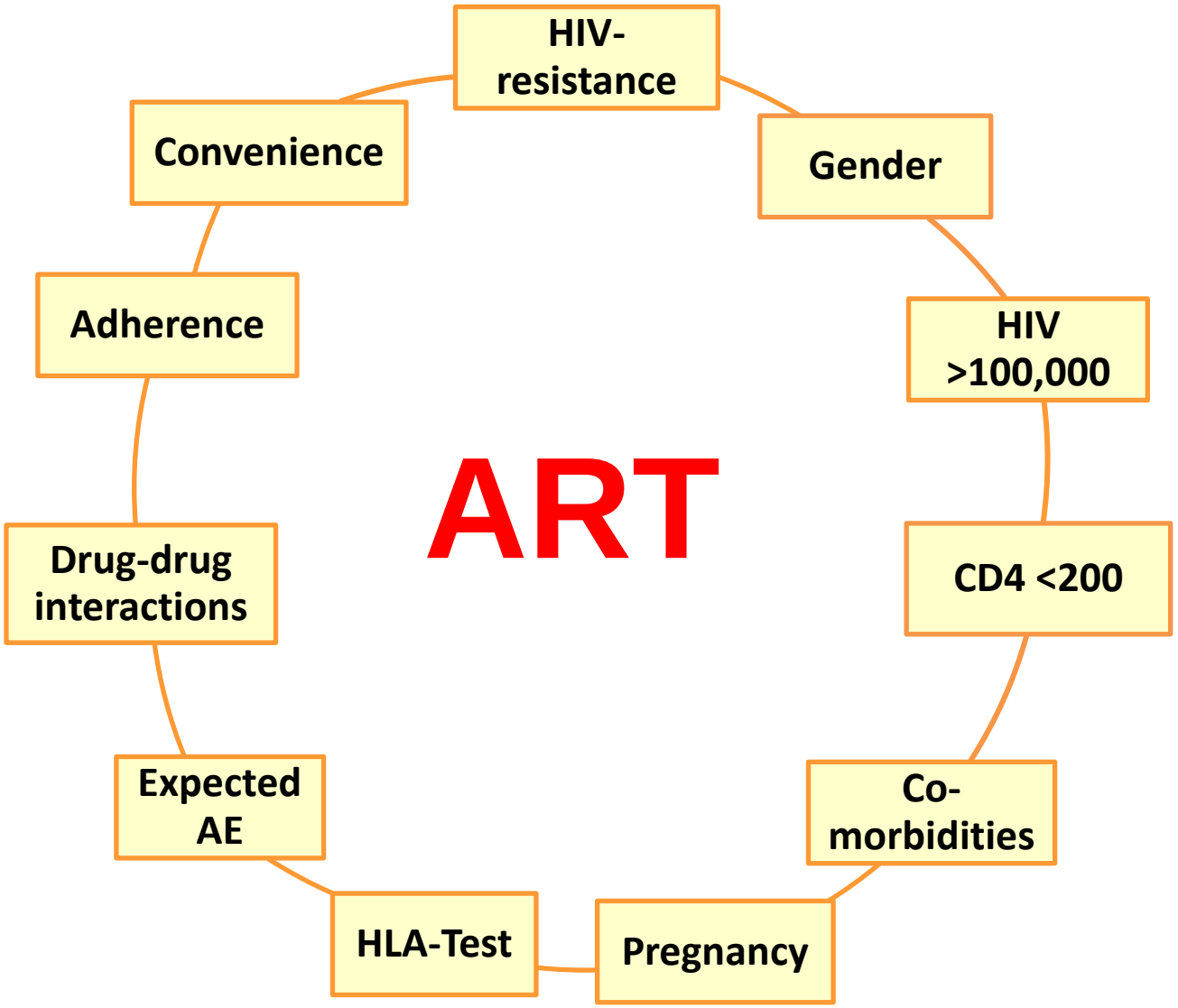
- DTG + NRTIs **noninferior to RAL** + NRTIs (SPRING-2 study) through wk 96;
- DTG + ABC/3TC **superior to EFV/TDF/FTC** through wk 96 (SINGLE study)
- DTG + NRTIs **superior to DRV/r** + NRTIs through wk 48 (FLAMINGO study);
- No DTG resistance mutations as yet detected with virologic failure
- DTG well tolerated
  - Fewer CNS and rash events than EFV
  - Less diarrhea than DRV/r
- Small rapid increase in serum creatinine (inhibition of tubular secretion of creatinine)

S. Walmsley et al, NEJM, 2013; S. Walmsley, CROI 2014, abstract 543; Raffi F, et al. Lancet. 2013;381:735-743. Raffi F, et al. IAS 2013. Abstract TULBPE17; Feinberg J, et al. ICAAC 2013. Abstract H-1464a.

Potential Benefits of New Treatment Options for HIV

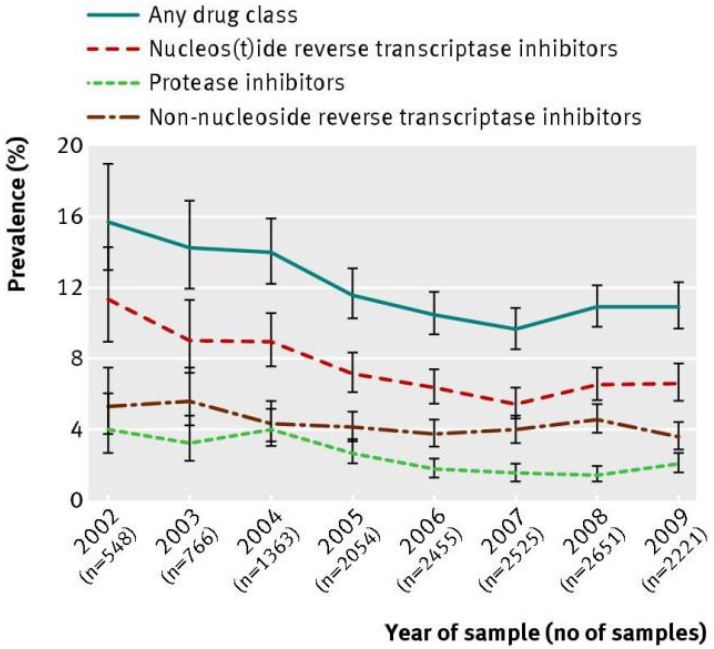
Rilpivirine	Elvitegravir/COB	Dolutegravir
Smallest single tablet	Single tablet regimen	Superior to EFV/TDF/FTC and DRV/r
Superior to EFV if HIV-RNA <100,000	Noninferior to EFV and ATV across HIV-RNA strata	Noninferior to EFV, RAL, DRV/r across HIV-RNA strata
Fewer CNS and rash than EFV	**Fewer CNS and rash than** EFV	**Fewer CNS and rash than** EFV
Better lipid profile than EFV	**Better lipid profile** than EFV, comparable to ATV/r	**Better lipid profile** than EFV
		No resistance detected with virologic failure
		Fewer drug-drug interactions than boosted PI, EVG/COB

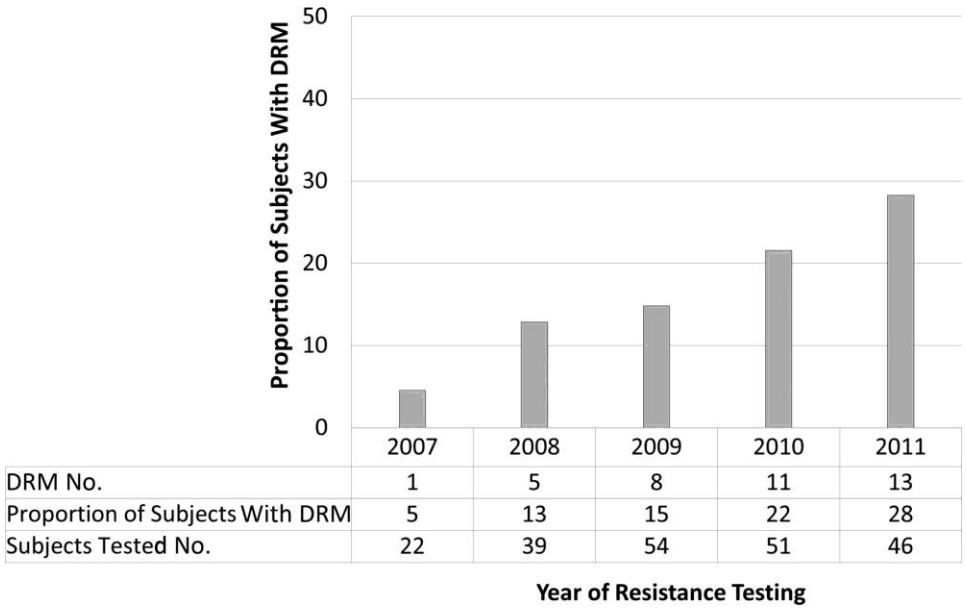
Considerations for ART choice



Transmission of HIV resistance %

	NRTI	NNRTI	PI	II	Total
US, 2007-10; N=18’144	6.7	8.1	4.5	n.a.	16.2
Spain, 2007-10; N=1’864	3.9	3.9	2.3	n.a.	8.6
UK, 2007-09; N=14’584	6.6	3.6	2.1	n.a.	10.9
US, 2007-2011; N=331	7	14	3	n.a.	18





	2007	2008	2009	2010	2011
DRM No.	1	5	8	11	13
Proportion of Subjects With DRM	5	13	15	22	28
Subjects Tested No.	22	39	54	51	46

Kim D et al, CROI, 2013; Monge S et al, CMI, 2012, UK Collaborative Group on HIV Drug Resistance, BMJ, 2012, Gagliardo C et al, Clin Inf Dis, 2014

ART and Effects on Lipids

- **Efavirenz**: Greater lipid change than RAL in STARTMRK
  Greater cholesterol changes than ATV/r in ACTG 5202
- **ATV/r and DRV/r**: Lesser lipid change than LPV/r
- **Raltregavir**: Neutral
- **Rilpivirine:** Better lipid profile than EFV
- **Dolutegravir**: Lipid profile better than EFV
- **Elvitegravir/COB**: Lipid profile similar to ATV/r, better than EFV

Lennox J, et al. Lancet. 2009;374:796-806 . Daar ES, et al. Ann Intern Med. 2011;154:445-456.
Molina JM, et al. Lancet. 2008;372:646-655. Ortiz R, et al. AIDS. 2008;22:1389-1397.

ART and Renal Function

- **Tenofovir**: decline of renal function over time in some patients, greater decline in renal function with TDF + boosted PIs vs TDF + NNRTIs
- **Atazanavir/r:** cumulative exposure associated with increased risk of chronic kidney disease in cohort study; risk reversed upon stopping
- **Raltegravir:** no clinically important PK differences between subjects with severe renal impairment and healthy subjects
- **Elvitegravir/COB and Dolutegravir**: small, rapid increase of serum creatinine (inhibition of tubular secretion of creatinine)

Morlat P, et al. IAS 2011. Gallant JE, et al. AIDS. 2009;23:1971-1975. Mocroft A, et al. AIDS. 2010;24:1667-1678.

Convenience

- **Once-daily versus twice-daily**
- **One pill:** TDF-FTC-EFV
  TDF-FTC-RPV
  TDF-FTC-EVG-COB
  ABC-3TC-DTG to come
- **Take with food:** Rilpivirine, Elvitegravir, Atazanavir, Darunavir
- **Take before sleeping:** Efavirenz
- **Sirup or soluble tablets available**

Individualized ART: new drugs

Drug	Considerations IN FAVOR	Considerations AGAINST
Efavirenz	- Co-formulation, 1 pill OD - Most experience	- Higher risk of resistance - AE: CNS, potential teratogeneous - Drug-drug interactions
Boosted PI	- Little risk of resistance - Preferred in pregnancy	- No coformulation with NRTI - Variable lipid effect, hyperbilirubinemia - Drug-drug interactions
Raltegravir	- Few AE - Few drug-drug interactions - Limited effect on lipids	- No coformulation with NRTI - Twice daily - Higher risk of resistance
Rilpivirine	- Co-formulation, 1 pill OD	- Less effective at high VL (>100,000) - Restricted use with PPI, H2-Blockers
Elvitegravir/ COB	- Co-formulation, 1 pill OD	- Cross-resistance with RAL - Drug-drug interactions - Concern of renal monitoring with COB
Dolutegravir	- Once-daily without boosting - Well-tolerated - Few drug-drug interactions	- n.a.

Individualized ART: Specific Circumstances

Circumstance	Agents
No genotype or low adherence	Boosted PI
High HIV-1 RNA (>100,000)	Caution with ABC, RPV, nuke sparing
Renal disease	Caution with TDF, ATV/r; monitoring may be complicated with EVG/COB
Dyslipidemia	RAL, DTG, RPV most lipid neutral
CV risk factors	Caution (?) with ABC, LPV/r No data for DRV/r, INSTIs, MVC
Pregnancy	Preferred: ZDV/3TC not anymore mandatory EFV can be used after first 5-6 wks
Chronic HBV infection	Preferred TDF + 3TC or FTC
Decreased BMD	Caution with TDF
Concerns about CNS effects	Caution with EFV for at least first month
Tuberculosis	Prefer EFV or RAL
Gastroesophageal reflux	Avoid ATV/r and RPV

Outline

- **When to start** - Guidelines
  - Individualization
- **What to start** - Guidelines
  - Individualization
- **Real world**
- **Future perspectives**

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**

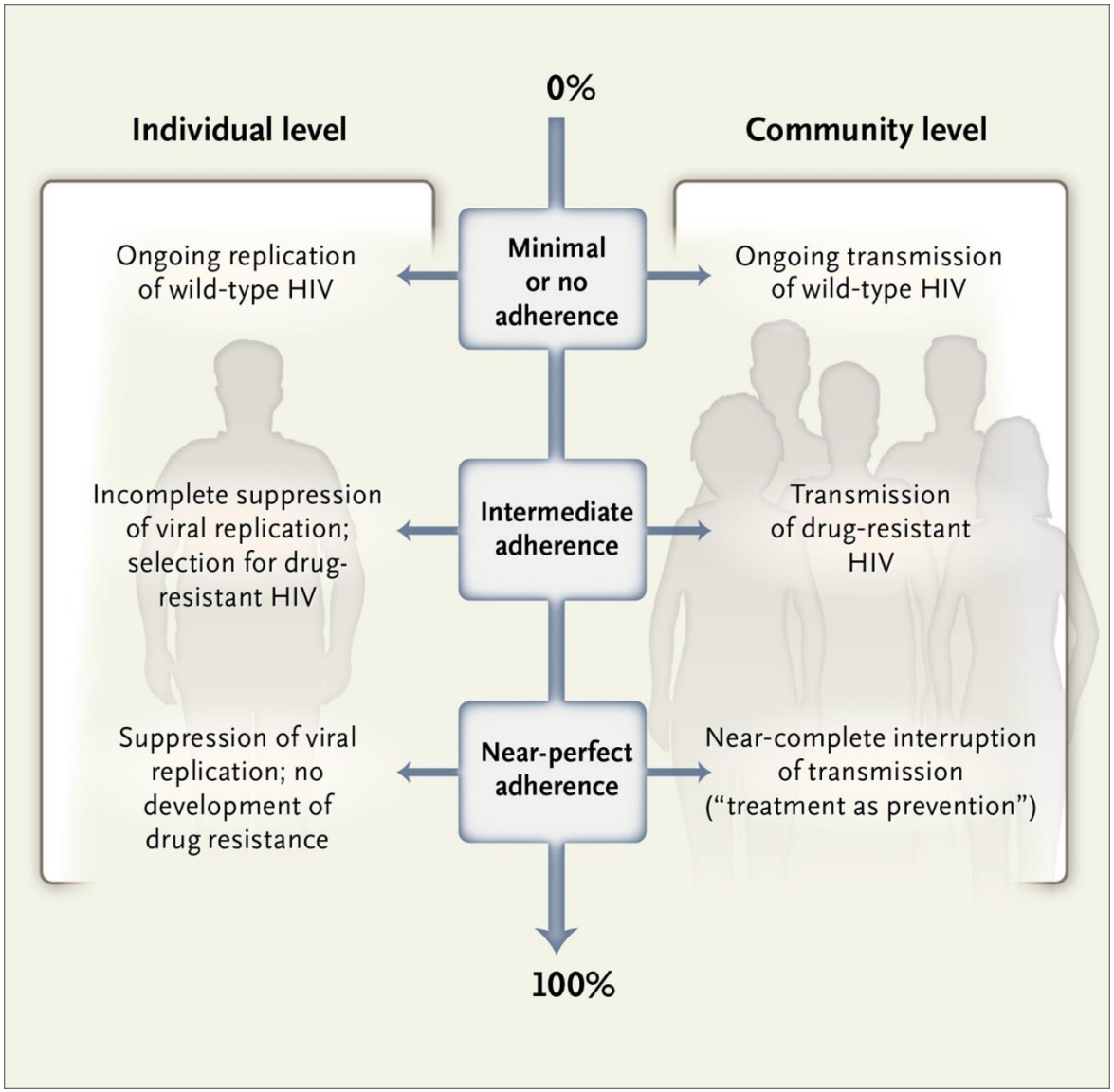
Individualisation

Gender, Drug use, Hepatitis, CVD, high VL

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

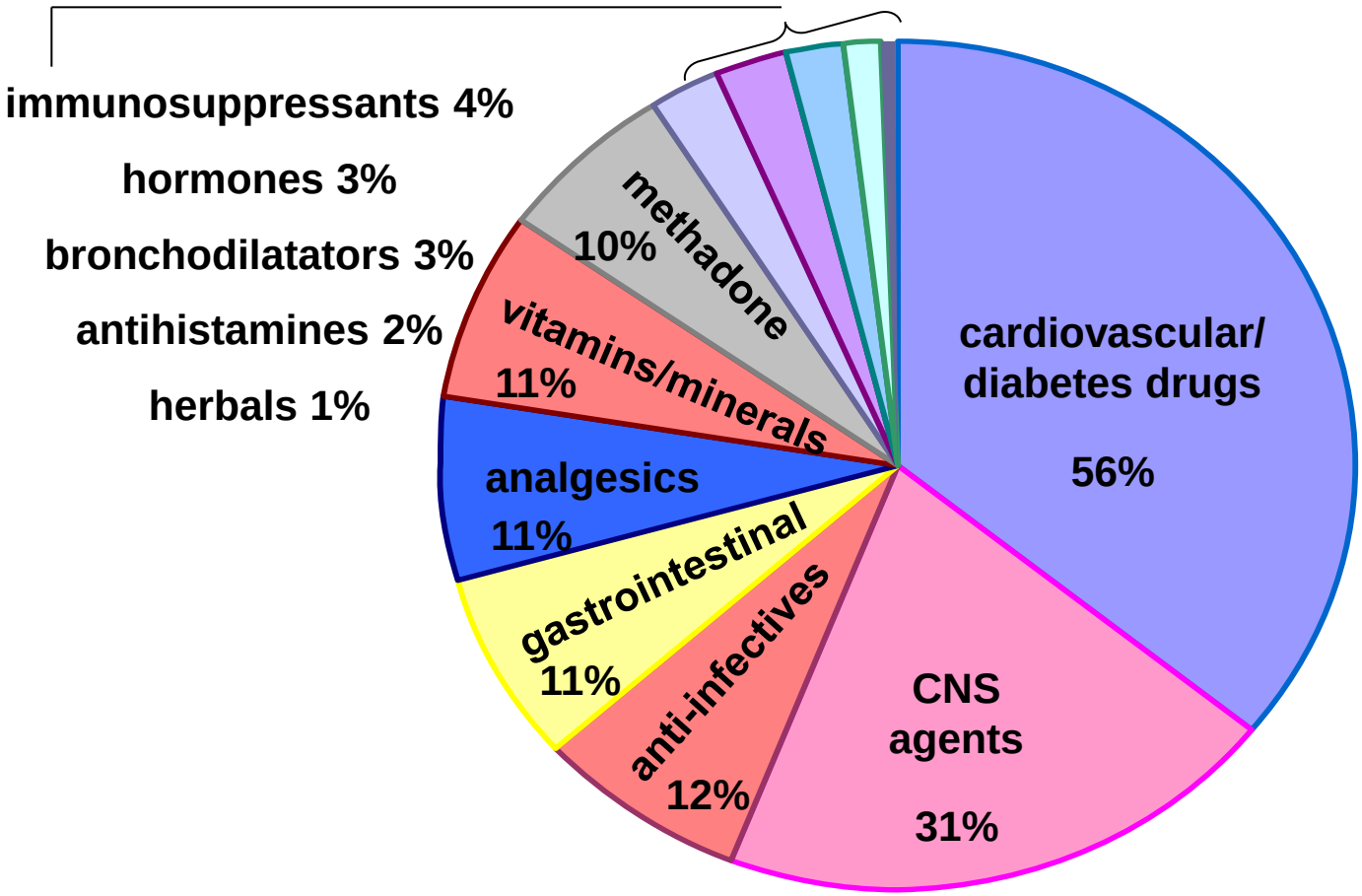
Elzi & Battegay et al., Arch Intern Med, 2012

Effects on the Individual and Community of Various Levels of Adherence



Gandhi M, Gandhi RT. N Engl J Med 2014

Co-medication in the SHCS



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

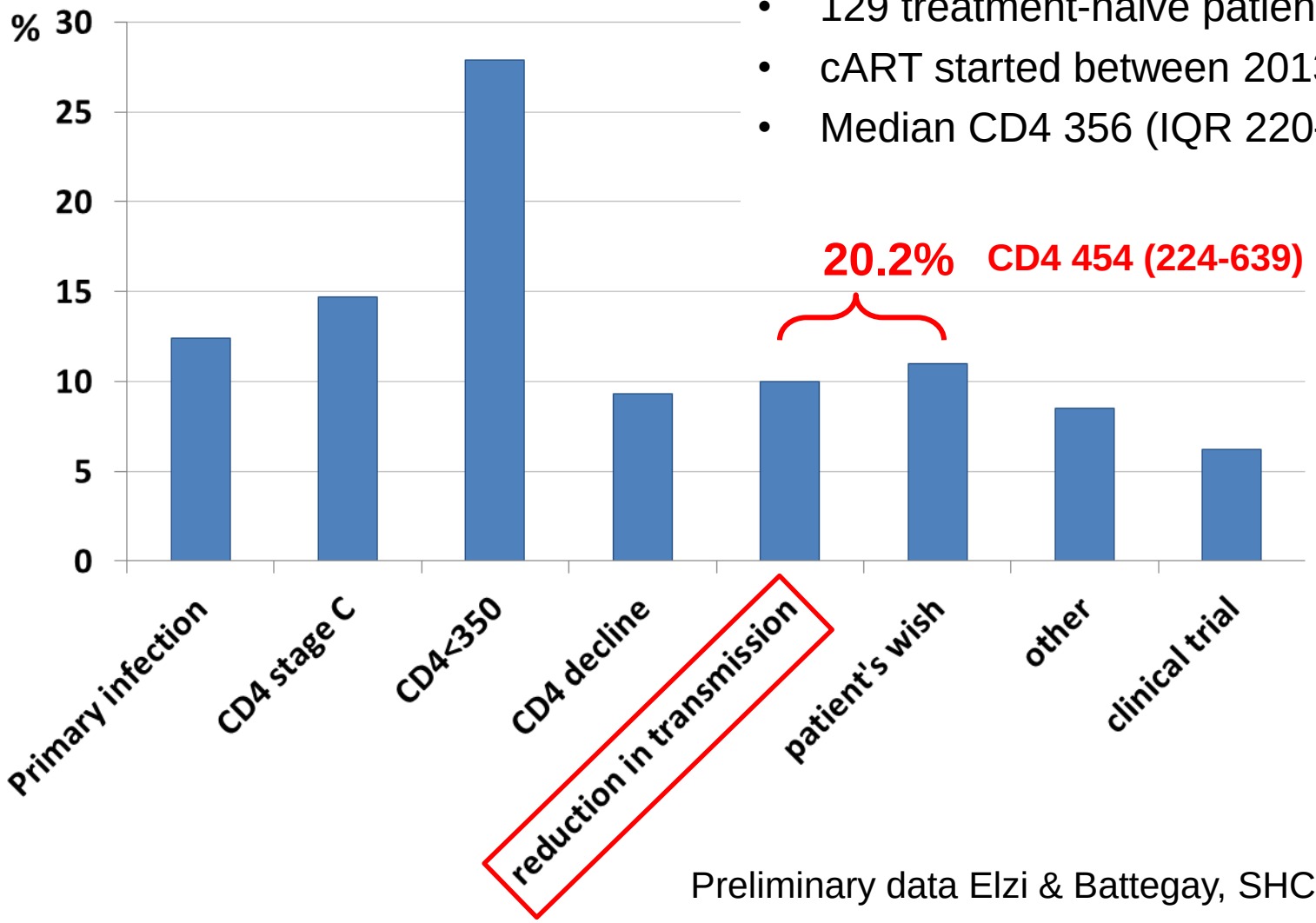
Drug-drug interactions

	non-ARV drugs	ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	RAL
Cardiovascular drugs	atorvastatin	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔
	fluvastatin	↔	↔	↔	↑	↑	↔	↔	↔	↔
	pravastatin	↔	↑81%	↔	↓44%	↓	↔	↔	↔	↔
	rosuvastatin	↑213%	↑48%	↑107%	↔	↑	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↓68%	↓	↓	↔	↔	↔
CNS drugs	diazepam	↑	↑	↑	↓	↑	↓	↔	↔	↔
	[illegible]								↔	↔
	[illegible]								↔	↔
	[illegible]								↔	↔
	mirtazapine	↑	↑	↑	↓	↓	↓	↔	↔	↔
	paroxetine	↑↓?	↓39%	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↓	↓49%	↓	↓39%	↓	↓	↔	[illegible]	↔
	bupropion	[illegible]								↔
	boceprevi	[illegible]								↔
anti-infectives	clarithromycin	[illegible]								↔
	fluconazole	↔	↔	↔	↔	E86%	E100%	E	[illegible]	↔
	itraconazole	↑E	↑E	↑E	↓	↓E	↓61%	E	E	↔
	rifabutin	↑	↑E50%	↑	↓	D37%	↑17%	D	*	↔
	rifampicin	D72%	D	D	D26%	D	D58%	D80%	D	D40%
	telaprevir	↓20%E17%	↓35%D40%	↓54%	↓26%D7%	↓16%	↓?	↓5%E	E	E31%
	antacids	D	↔	↔	↔	↔	↔	D	↔	D
	PPIs	D	↔	↔	↔	↔	↔	D	↔	E
	H2 blockers	D	↔	↔	↔	↔	↔	D	↔	E
	St John's wort	D	D	D	D	D	D	D	D	↔
	methadone	↓[ii, iii]	↓16%	↓53%[iii]	↓52%	↑6%	↓≈50%	↓16%	↔	↔

www.eacsociety.org/guidelines

www.hiv-druginteractions.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

The patient's perspective

- «I was involved in the choice of my ART regime together with my physician»

  → **89% agree/strongly agree**

- «I had a preference for a certain ART regime»

  → **39% agree/stronlgy agree**

Preliminary data Elzi & Battegay, SHCS #644

Outline

- **When to start** - Guidelines
  - Individualization
- **What to start** - Guidelines
  - Individualization
- **Real world**
- **Future perspectives**