Initial Antiretroviral Therapy

EACS European AIDS Clinical Society

Manuel Battegay

Infectious Diseases & Hospital Epidemiology
University Hospital Basel

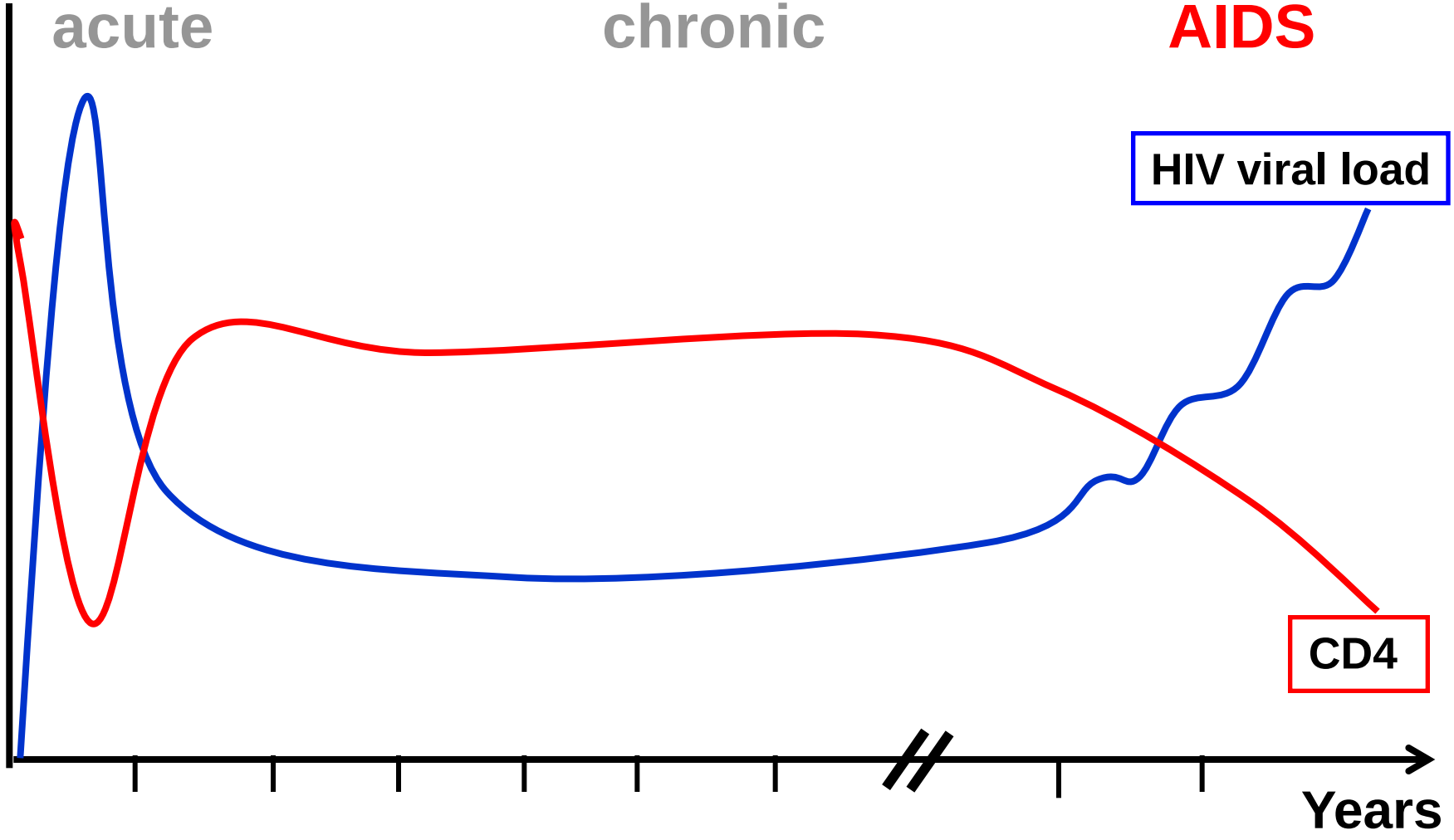
University Hospital Basel

Special thank to Luigia Elzi for helping preparing this lecture

Outline

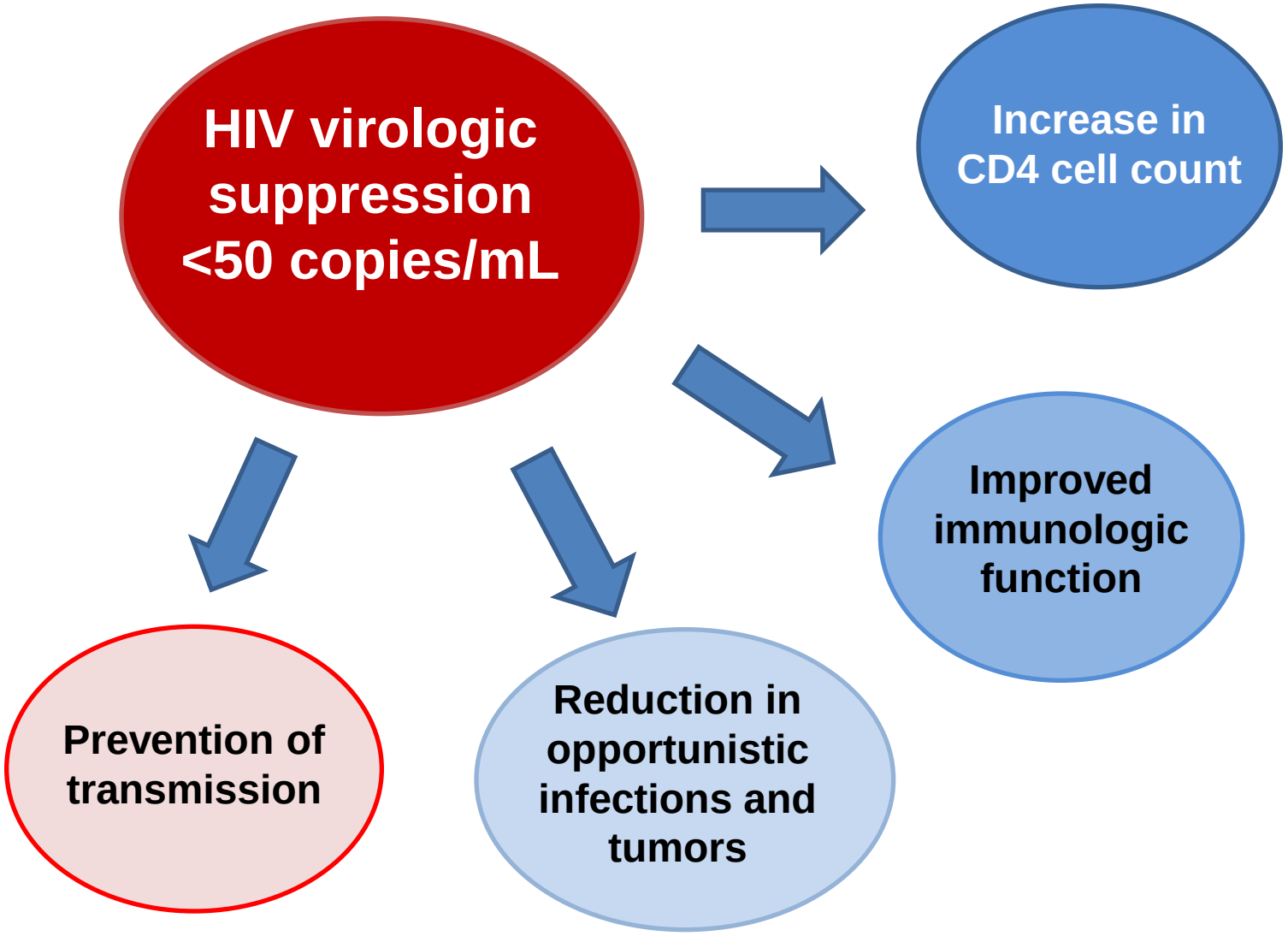
- Natural history of HIV
- Aims of antiretroviral therapy (cART)
- When to start
- What to start
- Monitoring
- When to change

Natural history of HIV

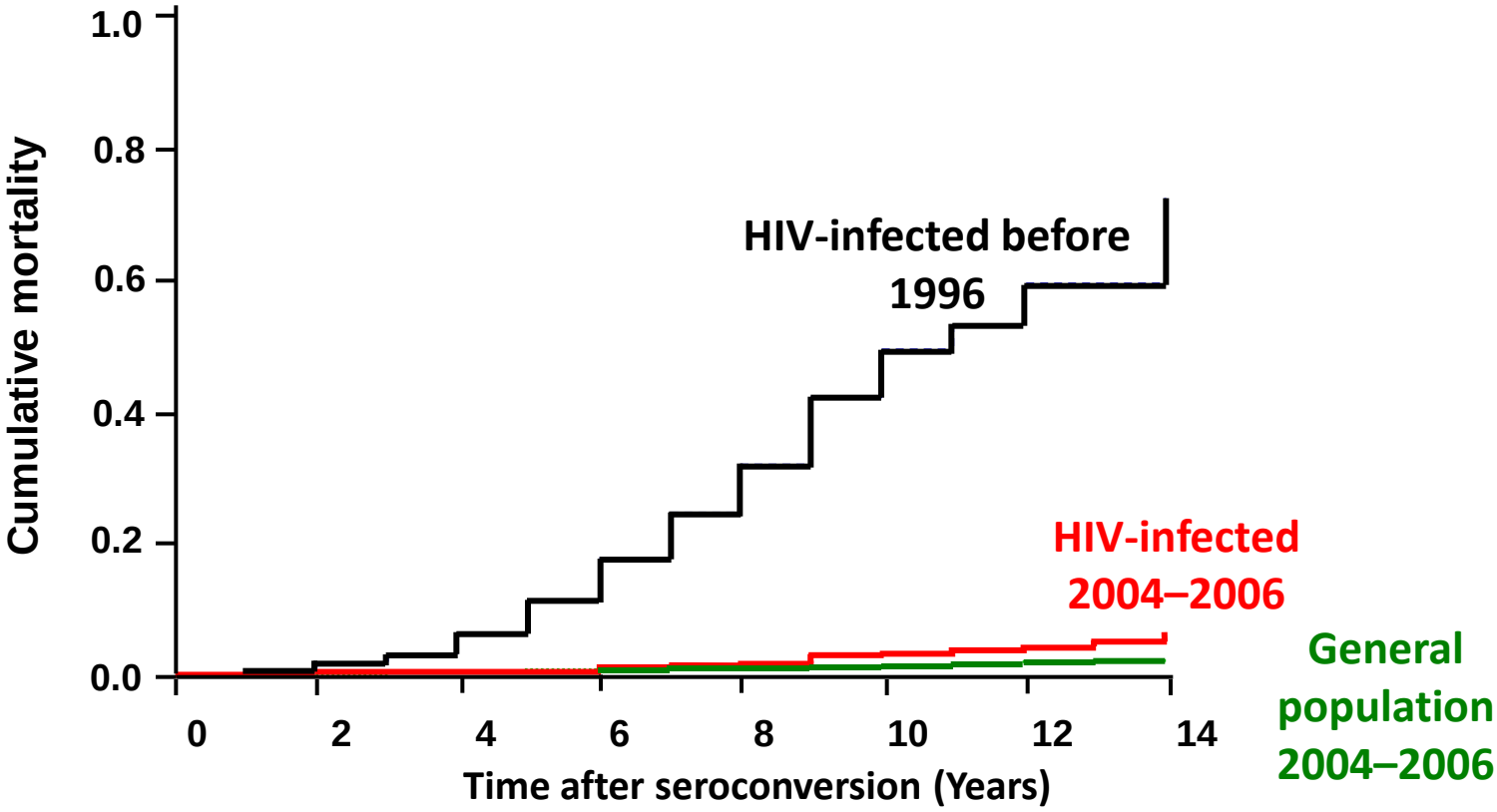


Saag MS et al, Nat Medicine; Mellors J et al, Science, 1996

Goals of ART


HIV virologic suppression <50 copies/mL
Increase in CD4 cell count
Improved immunologic function
Reduction in opportunistic infections and tumors
Prevention of transmission

ART improves life expectancy



Assumptions: Start ART if CD4 cell count <350 cells/µL
90% virologic suppression <50 copies/mL

Hammer SM et al, ACTG 320, N Engl J Med, 2007; Egger et al, SHCS, BMJ 2007; Bhaskaran K et al, CASCADE, JAMA 2008; Hogg et al The ART-CC, Lancet 2008; Elzi L et al, Arch Int Med 2010

No difference in mortality HIV vs non-HIV

- 80’642 and 3’280 HIV-infected persons
- No significant difference in mortality in comparison to ‘general population’, if
  - ART
  - Well controlled virus
  - No illicit drug use
  - No prior AIDS

Implications for care, work, life

C Lewden et al., Int J Epidemiol 2012, Rotger AJ, AIDS, 2013

Transmission reduction with ART

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

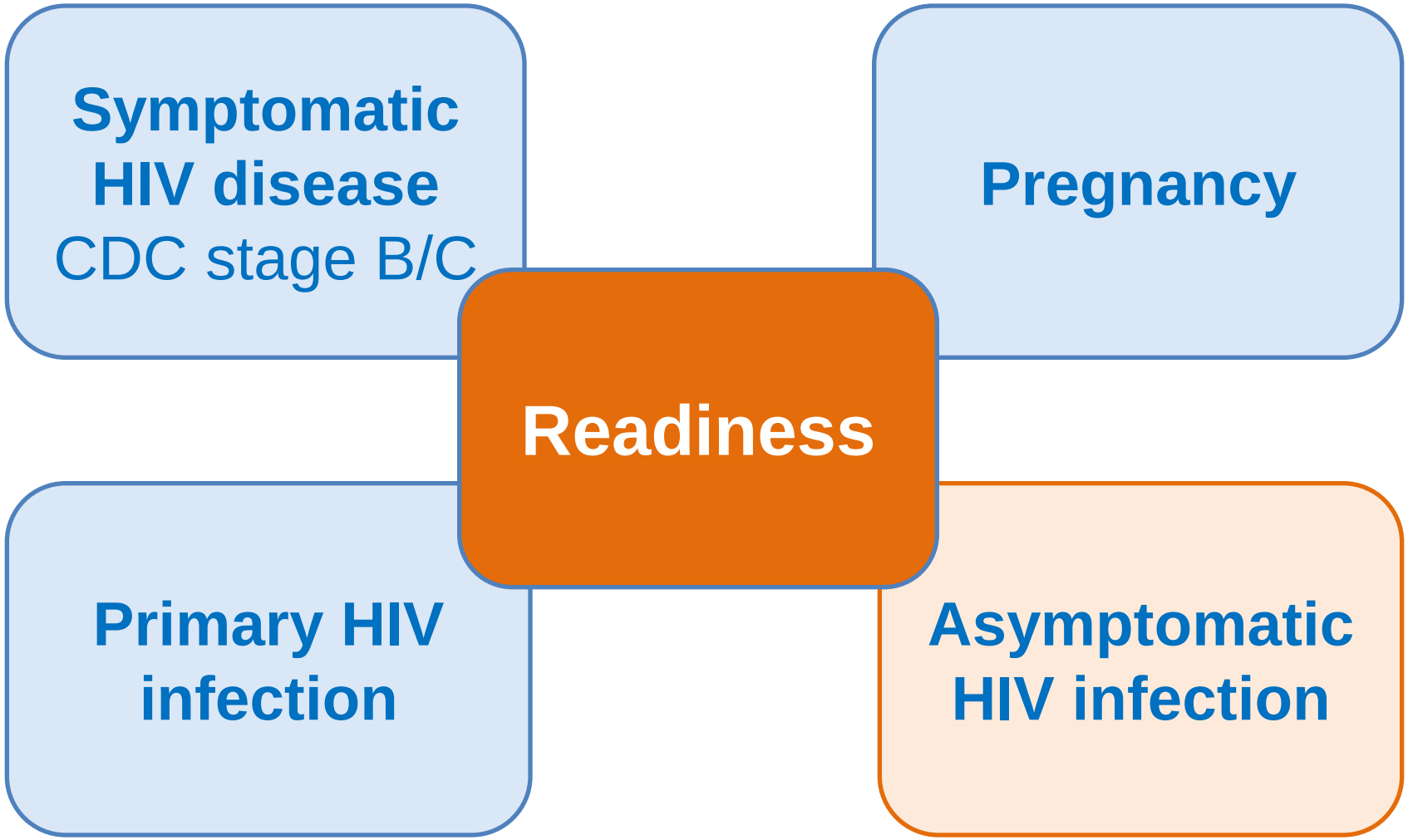
Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe

- 1763 discordant couples (HIV+/HIV-)
- Reduction, if early ART **96% !**
  - 1 Transmission early ART
  - 27 Transmissions Standard ART

Chronic Diseases Clinic Ifakara

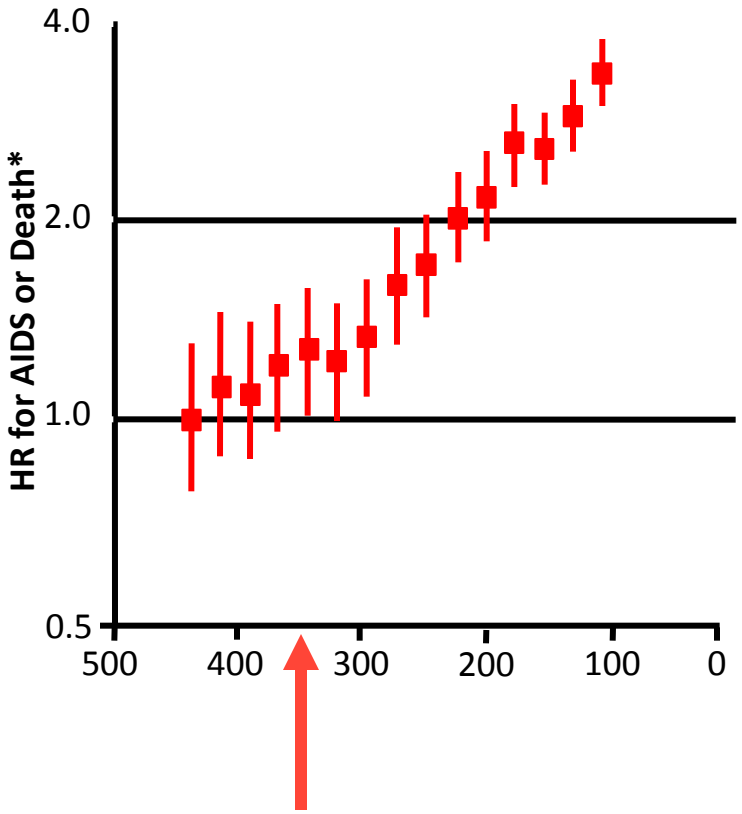
IHI, Swiss TPH, USB

When to start



ART-CC: Supports Initiating ART at CD4 threshold of 350 cells/mm^3

N=24,444 (15 cohorts from US and Europe)



Comparison	HR* (95% CI)
1-100 vs 101-200	3.35 (2.99-3.75)
101-200 vs 201-300	2.21 (1.91-2.56)
201-300 vs 301-400	1.34 (1.12-1.61)
251-350 vs 351-450	1.28 (1.04-1.57)
351-450 vs 451-550	0.99 (0.76-1.29)

*Adjusted for lead-time and unobserved events

Sterne et al. Lancet 2009

HIV Causal Collaboration
ART-naive, CD4>500, no AIDS, N= 20,970

SCRIPT ONLY

Table 2. Hazard Ratios of All-Cause Mortality or the Combined End Point of AIDS-Defining Illness or Death, for cART Initiation at CD4 Cell Count Thresholds Ranging From 0.200 to 0.500 × 10^9 cells/L

Outcome and CD4 Threshold	Persons, *n**	Outcomes, *n**	Median CD4 Cell Count at cART Initiation, × 10^9 cells/L†	Hazard Ratio (95% CI)	
				0.500 Threshold as Reference	0.350 Threshold as Reference
All-cause mortality					
0.500 × 10^9 cells/L	8392	65	0.392	1.00 (reference)	0.99 (0.71–1.36)
0.450 × 10^9 cells/L	8281	81	0.358	1.03 (0.92–1.14)	1.01 (0.82–1.26)
0.400 × 10^9 cells/L	8201	89	0.314	1.05 (0.86–1.27)	1.03 (0.91–1.17)
0.350 × 10^9 cells/L	8144	94	0.290	1.01 (0.84–1.22)	1.00 (reference)
0.300 × 10^9 cells/L	8101	97	0.257	1.01 (0.85–1.19)	0.99 (0.78–1.26)
0.250 × 10^9 cells/L	8078	95	0.210	1.09 (0.92–1.29)	1.07 (0.86–1.34)
0.200 × 10^9 cells/L	8066	99	0.167	1.20 (0.97–1.48)	1.18 (0.95–1.46)
AIDS-defining illness or death					
0.500 × 10^9 cells/L	8392	158	0.391	1.00 (reference)	0.72 (0.59–0.88)
0.450 × 10^9 cells/L	8281	209	0.358	1.14 (1.07–1.22)	0.83 (0.72–0.95)
0.400 × 10^9 cells/L	8201	256	0.316	1.29 (1.15–1.46)	0.94 (0.86–1.01)
0.350 × 10^9 cells/L	8144	296	0.291	1.38 (1.23–1.56)	1.00 (reference)
0.300 × 10^9 cells/L	8101	317	0.257	1.48 (1.33–1.64)	1.07 (0.92–1.24)
0.250 × 10^9 cells/L	8078	329	0.210	1.67 (1.50–1.85)	1.20 (1.05–1.38)
0.200 × 10^9 cells/L	8066	330	0.168	1.90 (1.67–2.15)	1.37 (1.20–1.57)

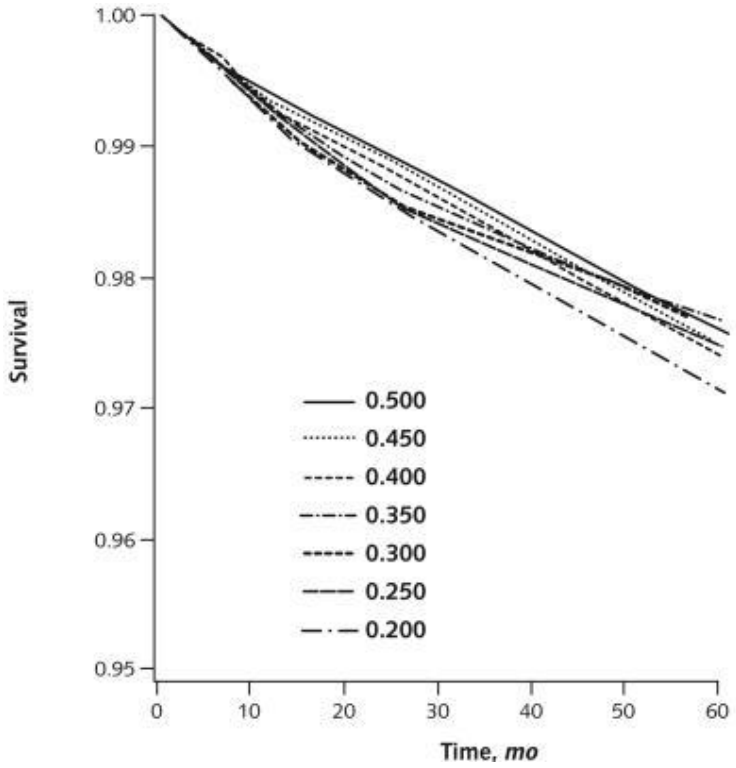
cART = combined antiretroviral therapy.
* Each person's data may be consistent with several CD4 thresholds.
† Among persons who initiate cART without being censored.

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

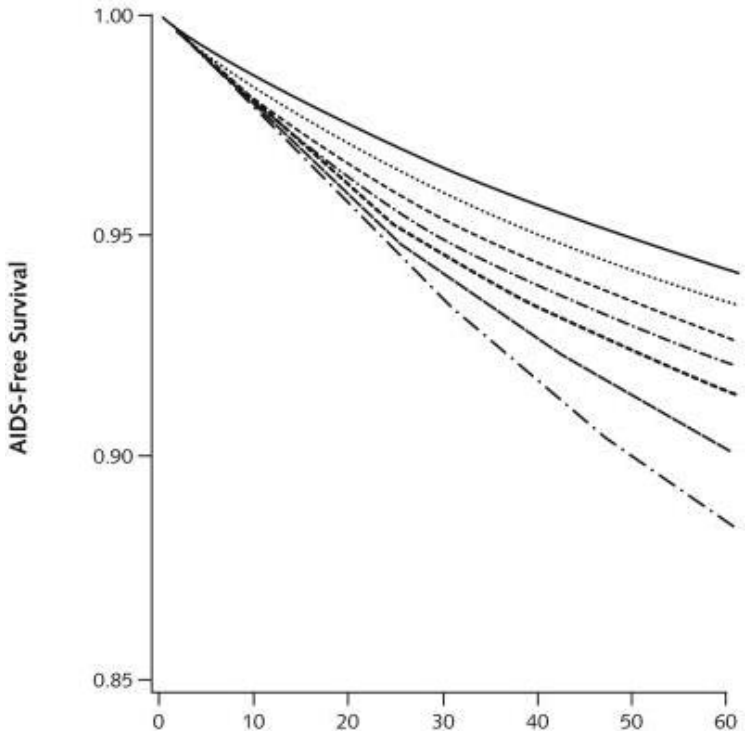
Cain et al., Ann Intern Med, 2011:154:509-115

5-year outcome by CD4 at starting ART

All-cause mortality



AIDS events



Delaying ART initiation until CD4<350 is estimated to result in a 38% increase of AIDS-events or death compared with starting ART at CD4 of 500, i.e. **48 pts need to initiate ART at CD4 500 to prevent 1 AIDS/death**

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

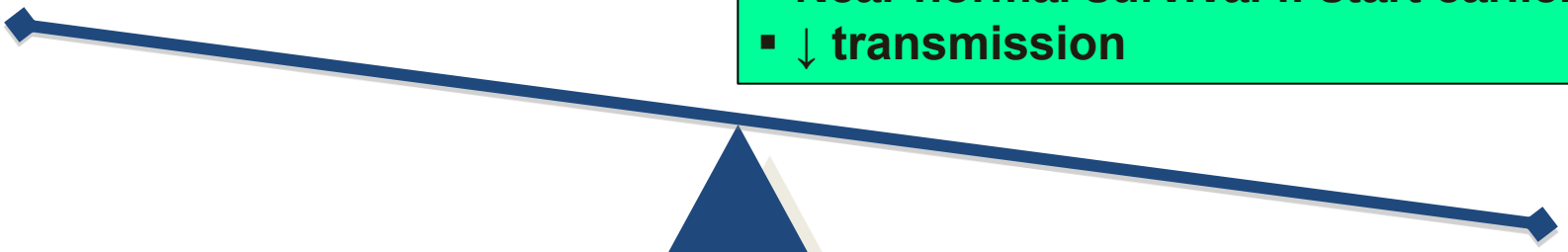
EACS Guidelines

Condition	Current CD4+ lymphocyte count [ii,iii]	
	350-500	> 500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease – otherwise unexplained	C	C
High risk for CVD (> 20 % estimated 10-yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [iv]	D
HCV for which anti-HCV treatment is being considered or given	R [v]	D [vi]
HCV for which anti-HCV treatment not feasible	R	C

When to Start Therapy: Balance Now Favors Earlier Antiretroviral Therapy

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia
- Near normal survival if start earlier
- ↓ transmission

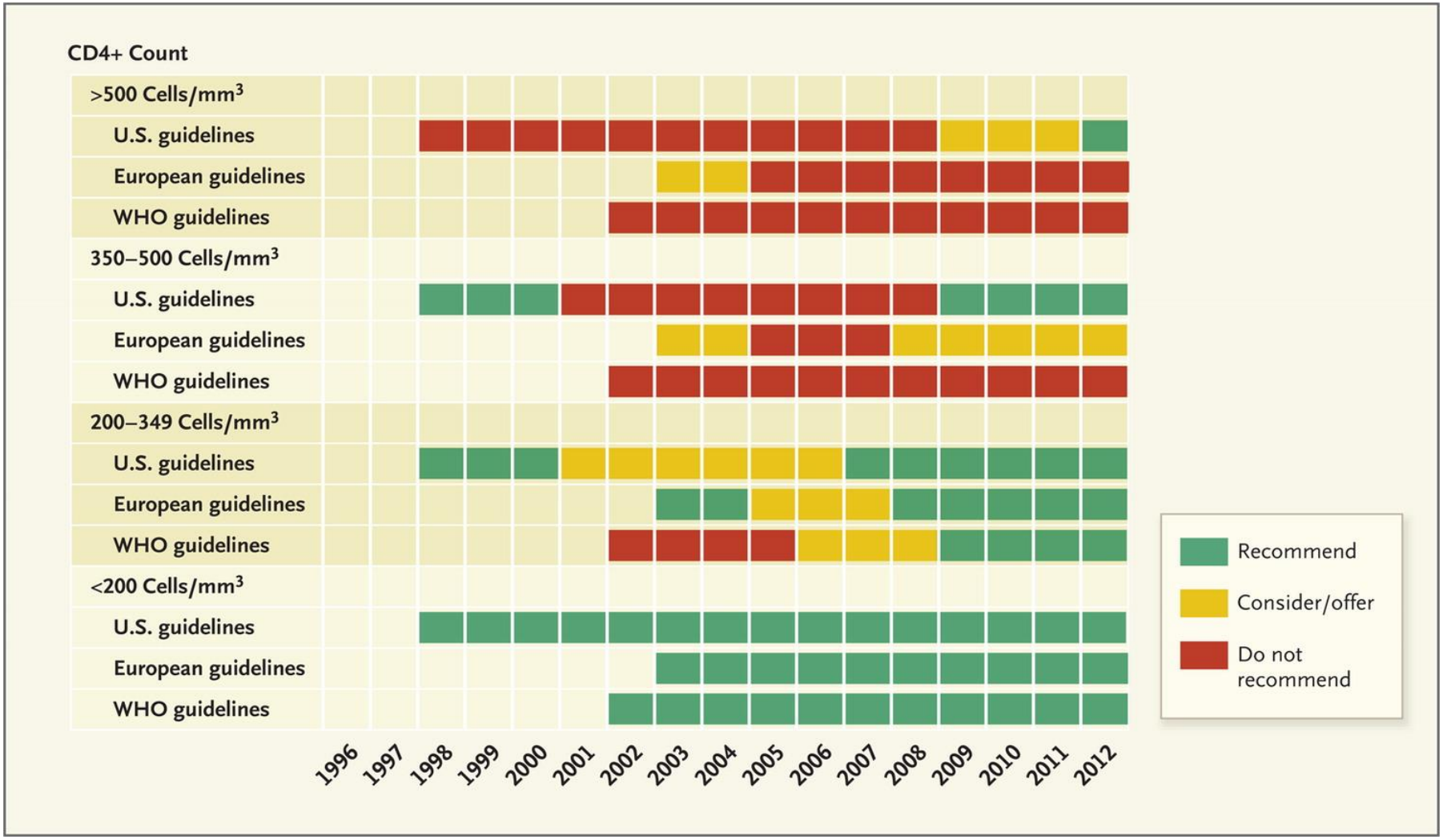


Delayed ART

Early ART

Slide from Joel E. Gallant, MD, MPH

ART Guidelines



De Cock K, N Engl J Med, 2013

HIV TREATMENT

WHO-2013: Changes in Recommendations When to Start in Adults

TARGET POPULATION *(ARV-NAIVE)*	2010 ART GUIDELINES	2013 ART GUIDELINES	STRENGTH OF RECOMMENDATION & QUALITY OF EVIDENCE
HIV+ ASYMPTOMATIC	CD4 ≤350 cells/mm^3	**CD4 ≤500 cells/mm^3 (CD4 ≤ 350 cells/mm^3 as a priority)**	***Strong, moderate-quality evidence*** NEW
HIV+ SYMPTOMATIC	WHO clinical stage 3 or 4 regardless of CD4 cell count	No change	***Strong, moderate-quality evidence***
PREGNANT AND BREASTFEEDING WOMEN WITH HIV	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, moderate-quality evidence*** NEW
HIV/TB CO-INFECTION	Presence of active TB disease, regardless of CD4 cell count	No change	***Strong, low-quality evidence***
HIV/HBV CO-INFECTION	Evidence of chronic active HBV disease, regardless of CD4 cell count	**Evidence of severe chronic HBV liver disease, regardless of CD4 cell count**	***Strong, low-quality evidence*** NEW
HIV+ PARTNERS IN SD COUPLE	No recommendation established	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, high-quality evidence*** NEW

WHO-2013: Recommendations: CD4 Independent Conditions

INITIATE ART REGARDLESS OF CD4 COUNT OR CLINICAL STAGE		RECOMMENDATION
ADULTS WITH HIV…	…and active TB disease	*Strong, low-quality evidence*
	…and HBV co-infection with severe liver disease	*Strong, low-quality evidence* NEW
	…who are pregnant or breastfeeding	*Strong, moderate-quality of evidence* NEW
	…in a HIV serodiscordant partnership	*Strong, high-quality evidence* NEW
CHILDREN < 5 YEARS OLD WITH HIV	Infants diagnosed in the first year of life	*Strong, moderate-quality of evidence*
	Children infected with HIV between one and below five years of age	*Conditional, very-low quality evidence* NEW

Is the patient ready for ART ?

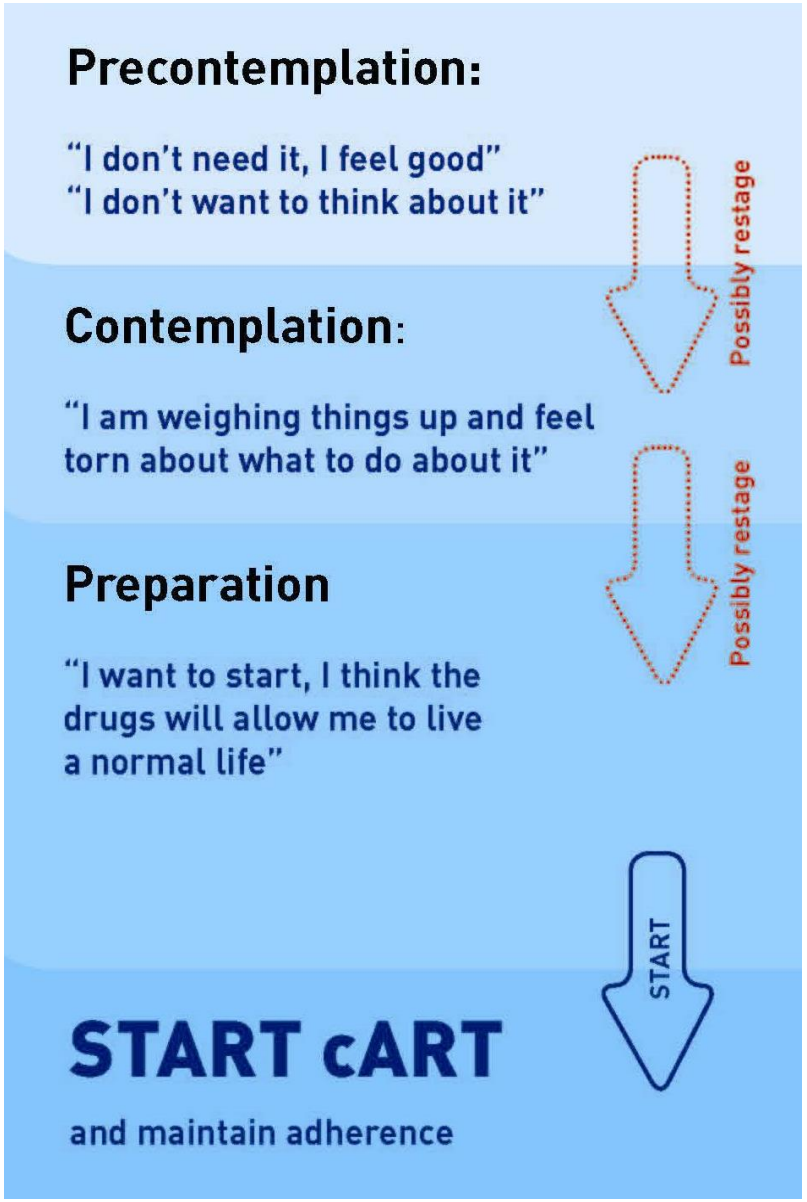
«I would like to talk about HIV medication»

Please wait …

«What do you think about it?»

Patient factors: Depression
Drug, alcohol addiction
Cognitive problems
Low health literacy

System factors: Health insurance
Continuity of drug supply
Low social support



SCRIPT ONLY

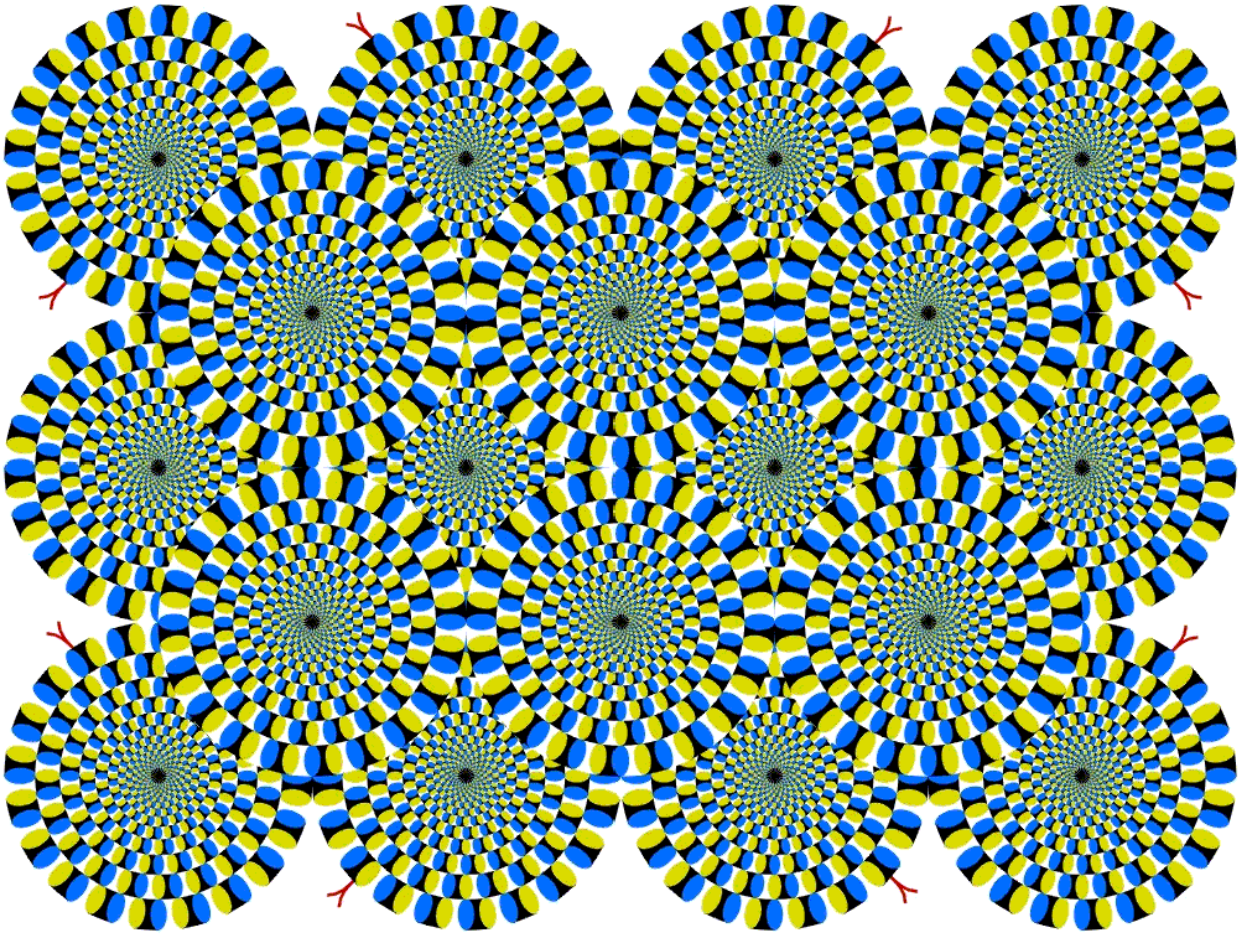
Assessing HIV-positive Persons´ Readiness to Start and Maintain ART

Goal: to help patients start and/or maintain ART	
Successful ART requires a person´s readiness to start and adhere to the regimen over time. The trajectory from problem awareness to maintenance on ART can be divided into five stages. Knowing a person´s stage, health care providers use appropriate techniques to assist them to start and maintain ART.	Identify the person to start's stage of readiness using WEMS[i] techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medication." <wait> "What do you think about it?" Based on the person´s response, identify his/her stage of readiness and intervene accordingly[ii]

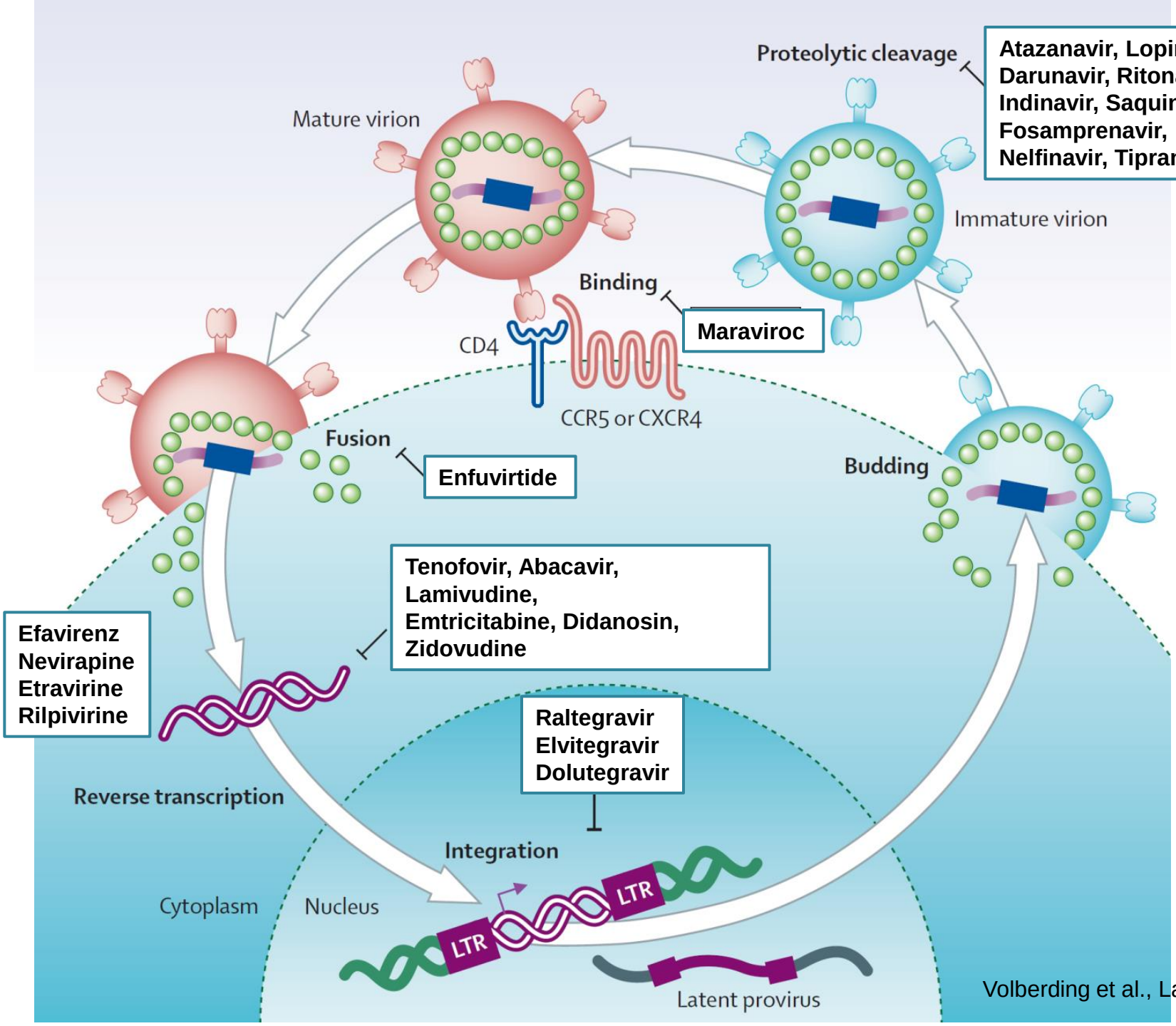
Stages of readiness to start ART	
Precontemplation: *"I don't need it, I feel good."* *"I don't want to think about it."*	Support: Show respect for the person´s attitude. / Try to understand the patient's health and therapy beliefs. / Establish trust. / Provide concise, individualized information. / Schedule next appointment.
Contemplation: *"I am weighing things up and feel torn about what to do about it."*	Support: Allow ambivalence. / Support the person in weighing pros and cons. / Assess the patient's information needs and support his/her information seeking. / Schedule the next appointment.
Preparation: *"I want to start, I think the drugs will allow me to live a normal life."*	Support: Reinforce the person´s decision. / Decide with the person which is the most convenient regimen. / Educate the person on adherence, resistance, side effects. / Discuss integration into daily life. / Respect the person´s self assessment. Ask: How confident are you that you can take your medication as we discussed (specify) once you have started? Use VAS 1-10[iii] Consider skills training: • Medication-taking training, possibly MEMS • Directly observed therapy with educational support • Use aids: mobile phone alarm, pillboxes • Involve supportive tools/persons where appropriate
START ART ↓	
Action: *"I will start now."*	**'Final check':** With a treatment plan established, is the patient capable of taking ART?
Maintenance: *"I will continue" or "I have difficulties continuing over the long run"* Caveat: A patient can relapse to an earlier stage, even from "maintenance" to "precontemplation" ↑	Assess: Adherence every 3-6 months[iv] Evaluate adherence: For persons with good adherence: show respect for their success. Assess: The person´s own perception of ability to adhere to, and continue, treatment. Ask: In the next 3-6 months, how confident are you that you can take your medication? Use VAS 1-10[iii] For a person without sufficient adherence: use mirroring techniques[v] on problems, ask open questions to identify dysfunctional beliefs. Assess: Stage of readiness and provide stage-based support Assess: Barriers and facilitators[vi] Schedule next appointment and repeat support

EACS Guidelines

Perception v Reality



Slide courtesy Mark Nelson, London



Volberding et al., Lancet 2010

What to start in 2013

6 drug classes

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

New Classes

Fusion Inhibitors

- Enfuvirtide

R5 Inhibitors

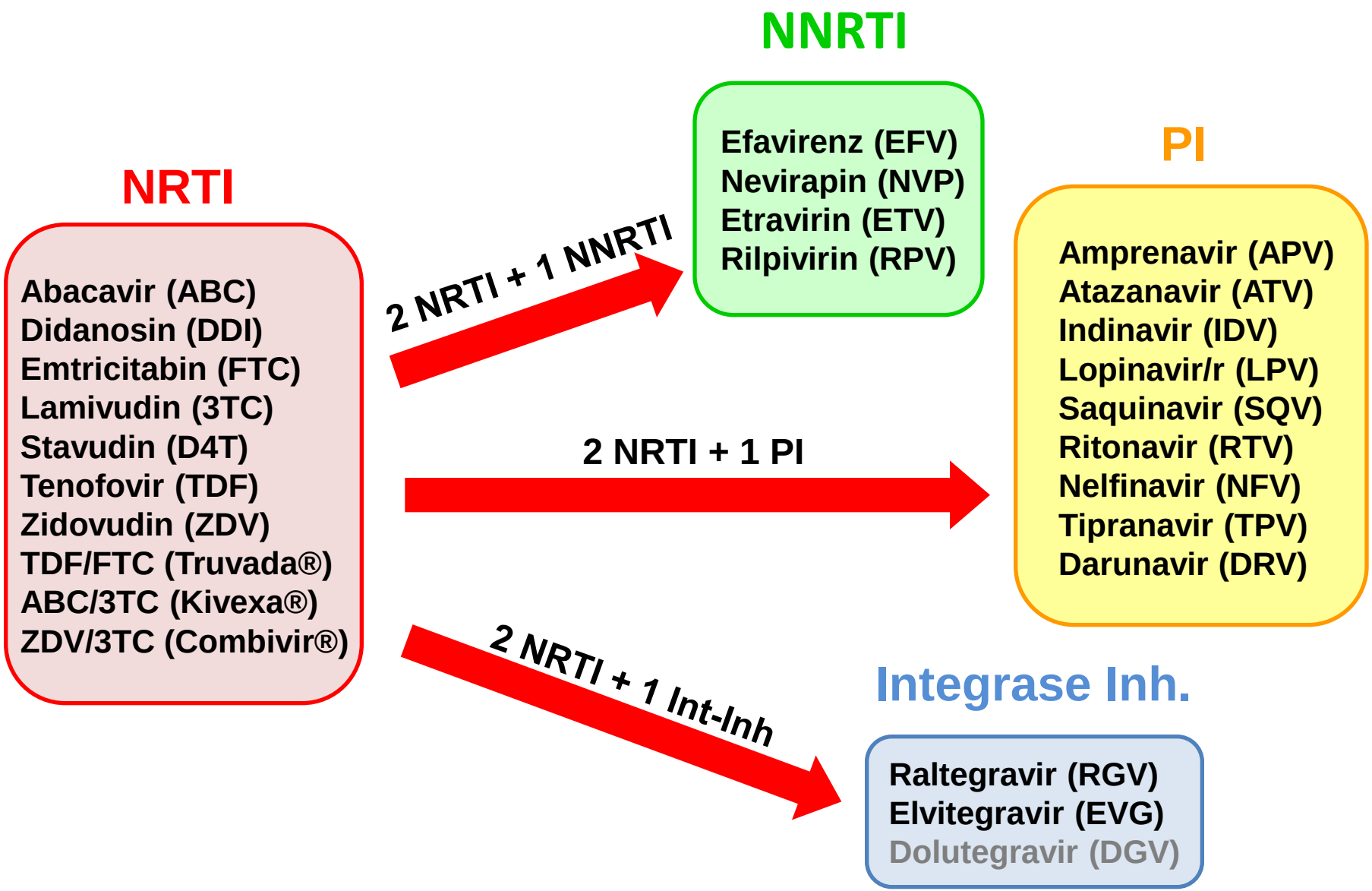
- Maraviroc

Integrase Inhibitors

- Raltegravir
- Elvitegravir

Slide courtesy Mark Nelson, London

How to start


NNRTI
Efavirenz (EFV)
Nevirapin (NVP)
Etravirin (ETV)
Rilpivirin (RPV)
PI
Amprenavir (APV)
Atazanavir (ATV)
Indinavir (IDV)
Lopinavir/r (LPV)
Saquinavir (SQV)
Ritonavir (RTV)
Nelfinavir (NFV)
Tipranavir (TPV)
Darunavir (DRV)
NRTI
Abacavir (ABC)
Didanosin (DDI)
Emtricitabin (FTC)
Lamivudin (3TC)
Stavudin (D4T)
Tenofovir (TDF)
Zidovudin (ZDV)
TDF/FTC (Truvada®)
ABC/3TC (Kivexa®)
ZDV/3TC (Combivir®)
2 NRTI + 1 NNRTI
2 NRTI + 1 PI
2 NRTI + 1 Int-Inh
Integrase Inh.
Raltegravir (RGV)
Elvitegravir (EVG)
Dolutegravir (DGV)

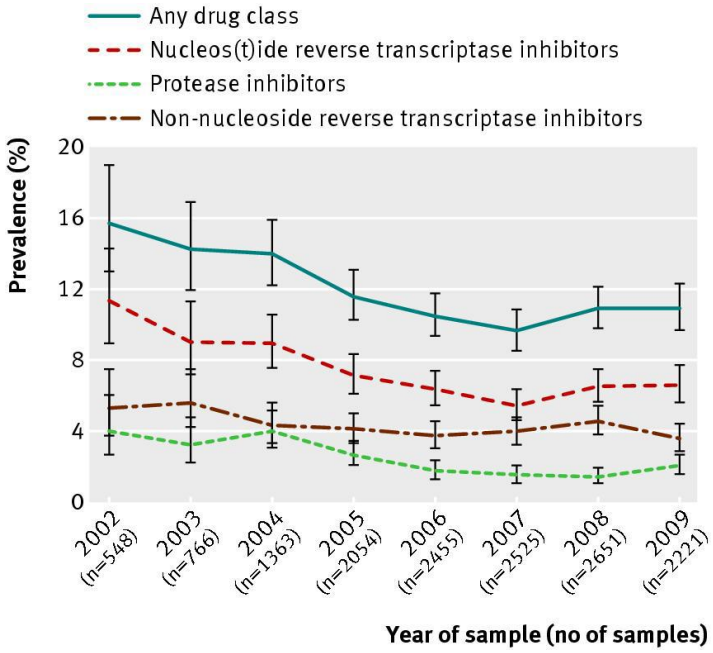
Considerations When Selecting First-line Antiretroviral Therapy

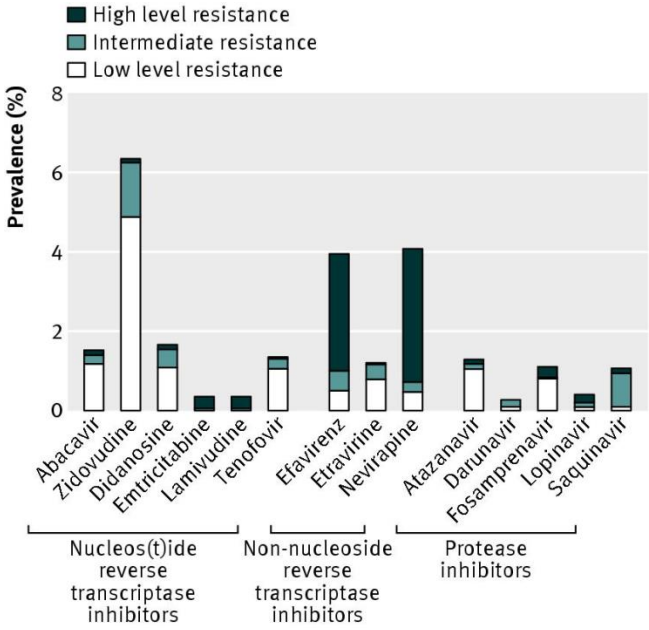
Patient Factors	Antiretroviral Drug Factors
▪ Baseline CD4+ cell count/ HIV-1 RNA	▪ Efficacy
▪ Age	▪ Baseline drug susceptibility/resistance
▪ Sex	▪ Tolerability
▪ Occupation (eg, work schedule)	▪ Long-term toxicity, metabolic effects
▪ Comorbid conditions (eg, CV risk)	▪ Drug interactions
▪ Plans for pregnancy	▪ Dosing frequency
▪ Access to care	▪ Pill burden
▪ Concurrent medications	▪ Pharmacokinetics
▪ Adherence to other medications	▪ Cost
▪ Genetics: HLA-B*5701, CV risk	▪ Tropism

Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

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 13.6 single
Spain, 2007-10 1’864	3.9	3.9	2.3	n.a.	8.6
UK, 2007-09 14’584	6.6	3.6	2.1	n.a.	10.9 10.3 single

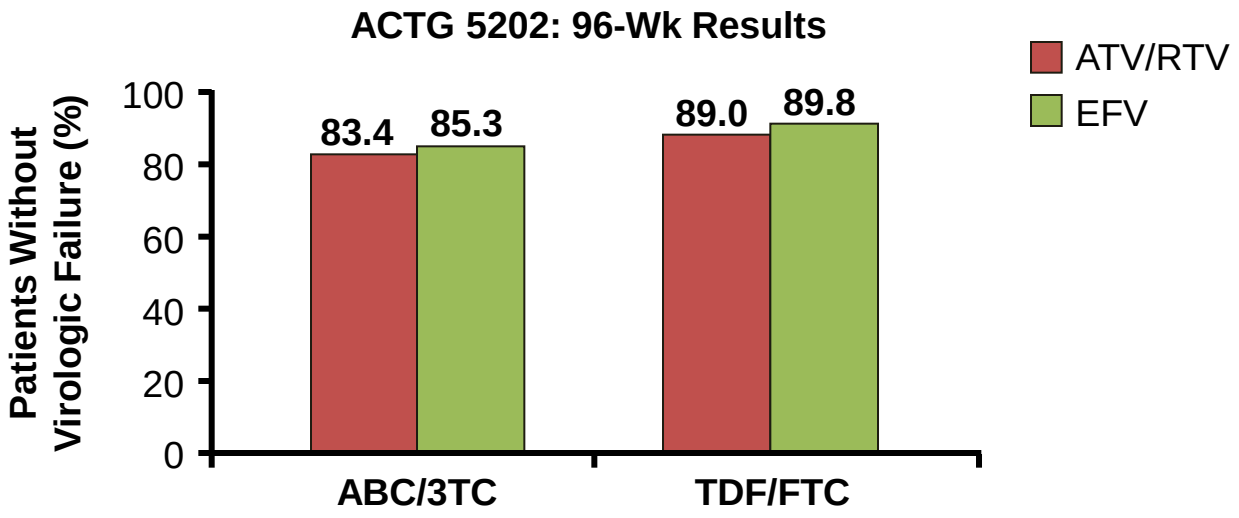




Kim D, et al, CROI, 2013; Monge S, et al, CMI, 2012, UK Collaborative Group on HIV Drug Resistance, BMJ, 2012;

Trade-Offs: Efavirenz-Based ART

Advantages	Disadvantages
▪ Long history of use; much clinical trial data ▪ Current gold standard for first-line therapy ▪ As effective or more effective than other regimens in head-to-head comparisons ▪ 1 pill QD coformulation of EFV/TDF/FTC ▪ Long half-life ▪ Appropriate for pts receiving tx for TB	▪ Low genetic barrier to resistance—single mutation ▪ Higher risk of NRTI resistance with NNRTI failure (compared with boosted PIs) ▪ CNS adverse effects ▪ Teratogenicity (?) ▪ Potential drug interactions (CYP450)



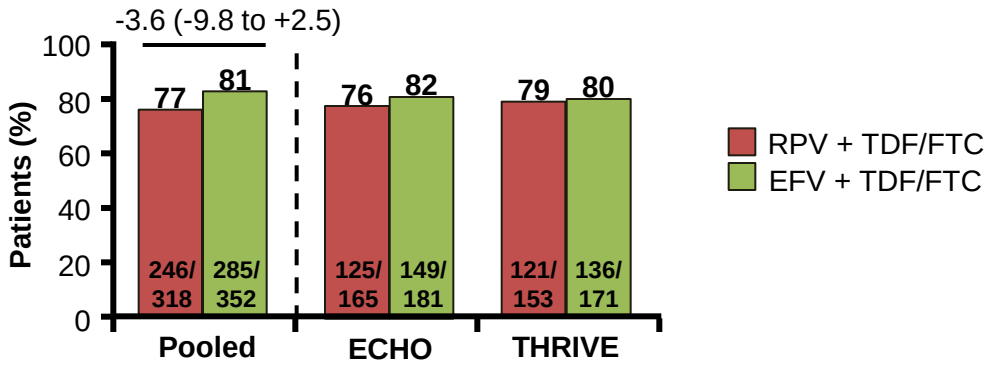
Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

SCRIPT ONLY

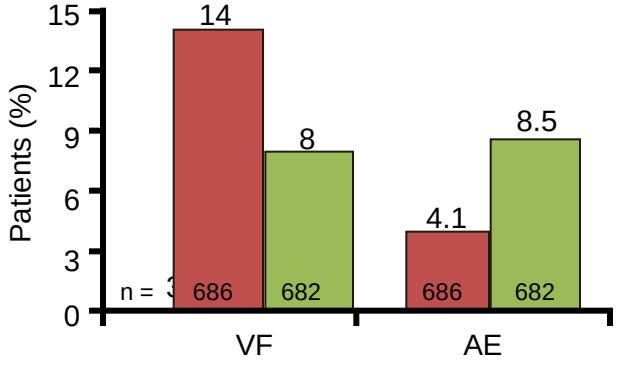
Trade-Offs: Rilpivirine

Advantages	Disadvantages
▪ Better tolerated than EFV (fewer CNS effects, rash) ▪ Fewer lipid effects than EFV ▪ Coformulation with TDF/FTC As switch agent ▪ PK data suggest switch from EFV possible if made *after* virologic suppression ▪ RPV/TDF/FTC coformulated so switch can be from one single-tablet regimen to another	▪ May be less effective at high VL ▪ Less forgiving of nonadherence ▪ More resistance (NNRTI and NRTI) than EFV at failure, including ETR cross-resistance ▪ Must be taken with 500-cal food ▪ Cannot use with PPI, caution with H2 blockers As switch agent ▪ To date, only supported by small, noncomparative study

HIV-1 RNA < 50 copies/mL at Wk 48 Among Pts With BL HIV-1 RNA > 100,000 c/mL

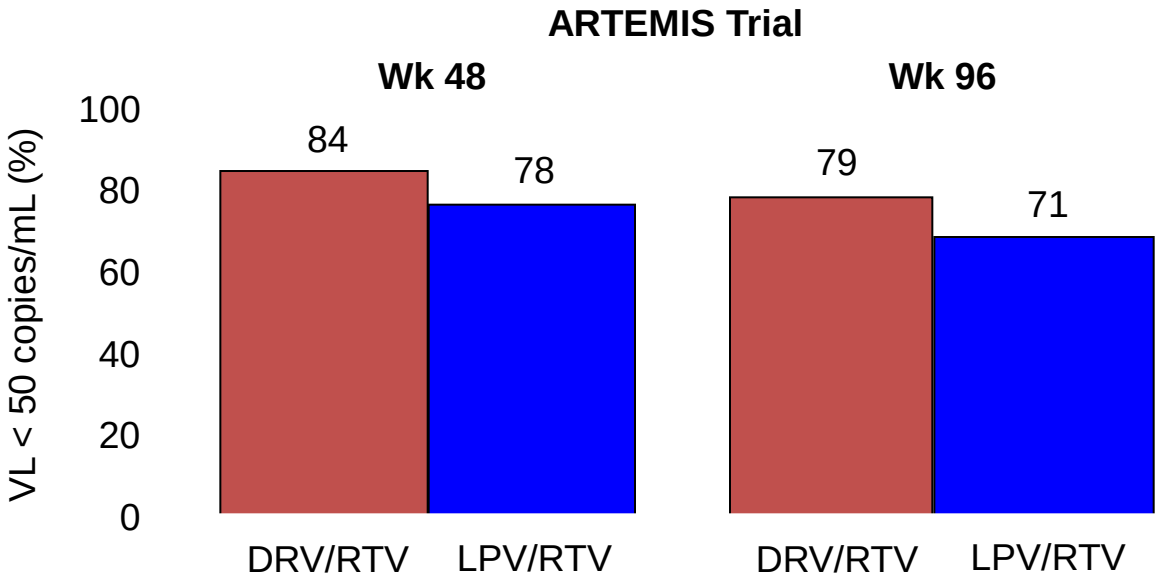


Tx Failure in ECHO and THRIVE



Trade-Offs: Darunavir/Ritonavir

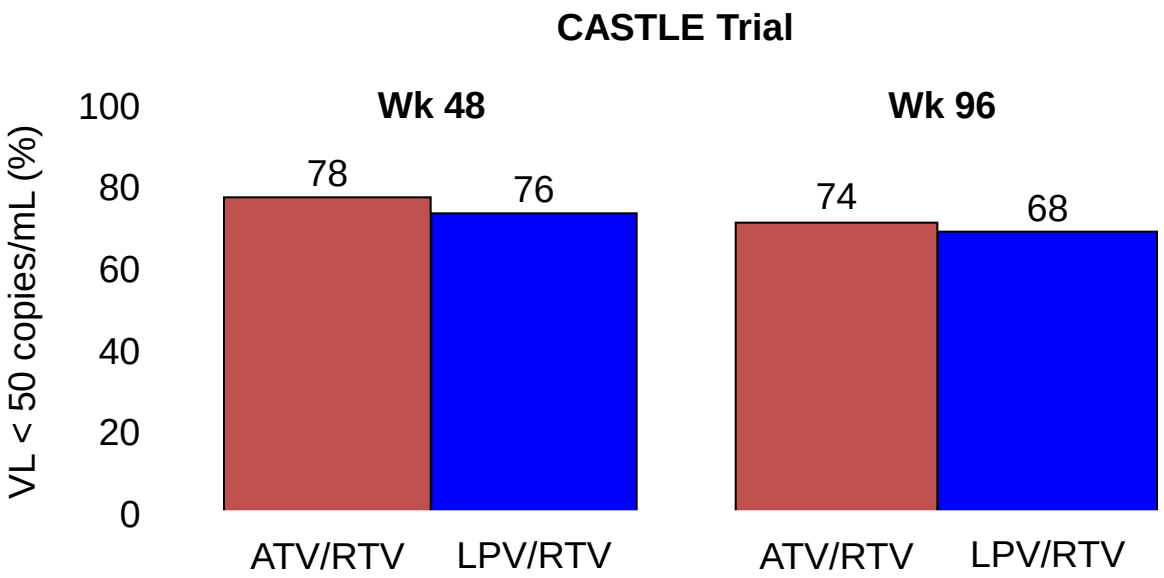
Advantages	Disadvantages
▪ Favorable lipid profile ▪ Low risk of resistance at failure ▪ Relatively low pill burden ▪ Daily dose requires only RTV 100 mg/day	▪ Rash in ~ 6% of pts; use with caution in pts with sulfa allergy ▪ No coformulations with other classes ▪ Not compared head to head with any of the other recommended agents



Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

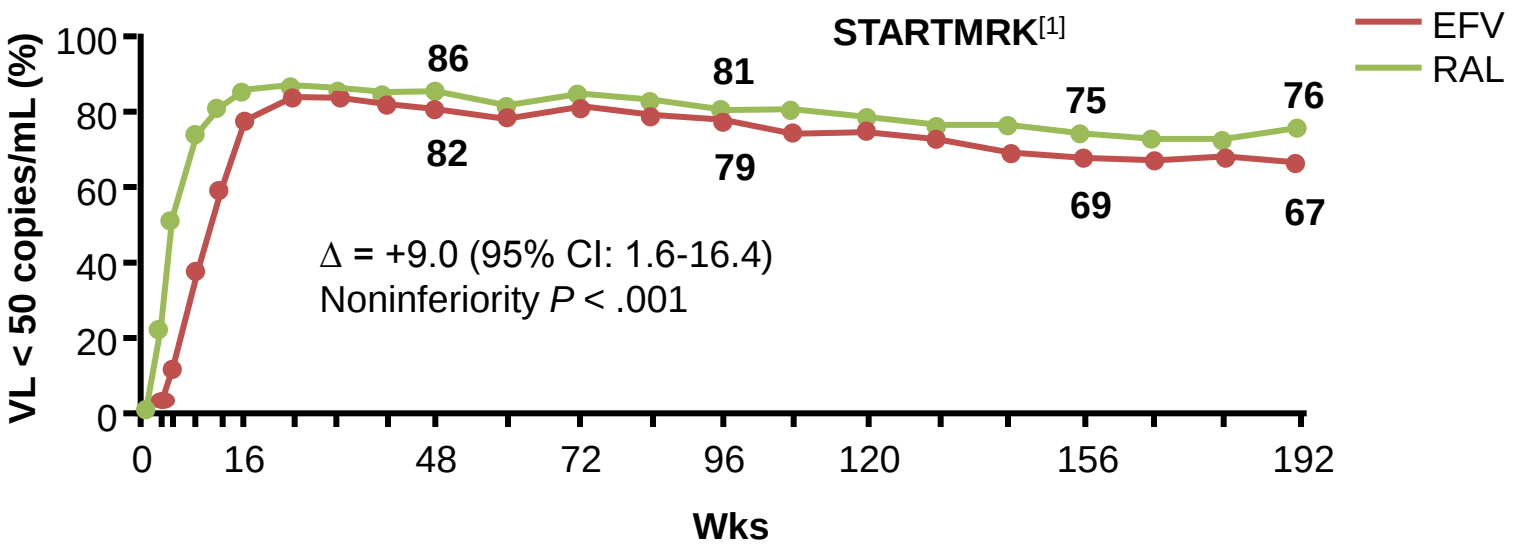
Trade-Offs: Atazanavir/Ritonavir

Advantages	Disadvantages
▪ Efficacy comparable to EFV at Wk 96 ▪ Favorable lipid profile ▪ Low risk of resistance at failure ▪ Low pill burden (2/day) ▪ Daily dose requires only RTV 100 mg/day	▪ Absorption impaired with acid-reducing agents ▪ Associated w/rise in unconjugated bilirubin and scleral icterus in 4% to 9% of pts ▪ Food requirement for dosing ▪ No coformulations with other classes



Trade-Offs: Raltegravir-Based ART

Advantages	Disadvantages
▪ 5-yr efficacy comparable to efavirenz regardless of baseline VL or CD4+ count ▪ Very Few adverse events ▪ Few drug-drug interactions ▪ Neutral effect on lipids ▪ Greater CD4+ increase than with EFV	▪ Twice-daily administration ▪ Low genetic barrier to resistance ▪ Risk of NRTI resistance with failure ▪ No coformulations with other classes ▪ Potential for skin reactions ▪ Little data with other NRTIs than TDF/FTC

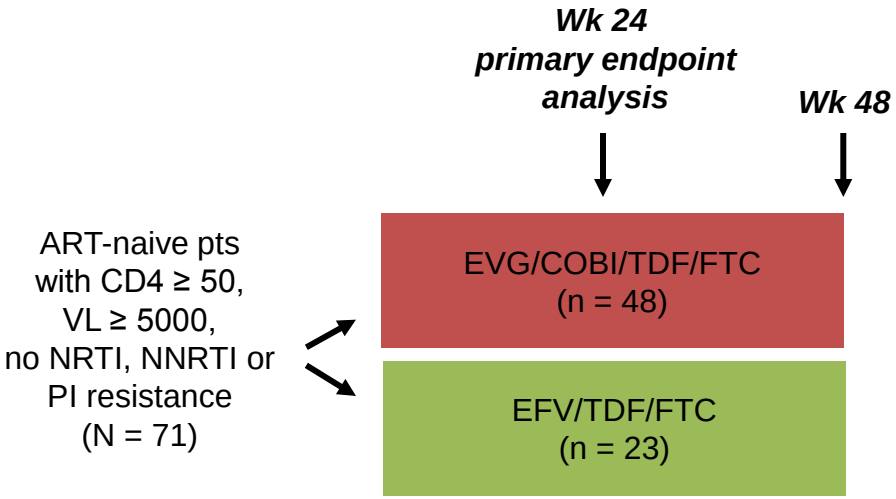


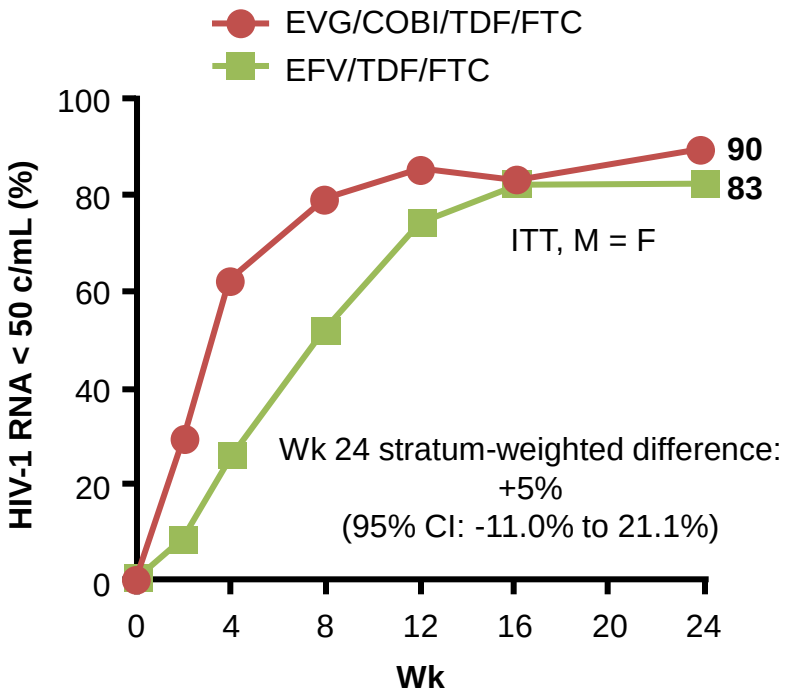
Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

SCRIPT ONLY

"Quad": Cobicistat-Boosted EVG + TDF/FTC vs EFV/TDF/FTC in Naive Pts

- Cobicistat (GS-9350, COBI): CYP3A inhibitor (boosting agent)
- Elvitegravir (EVG): integrase inhibitor



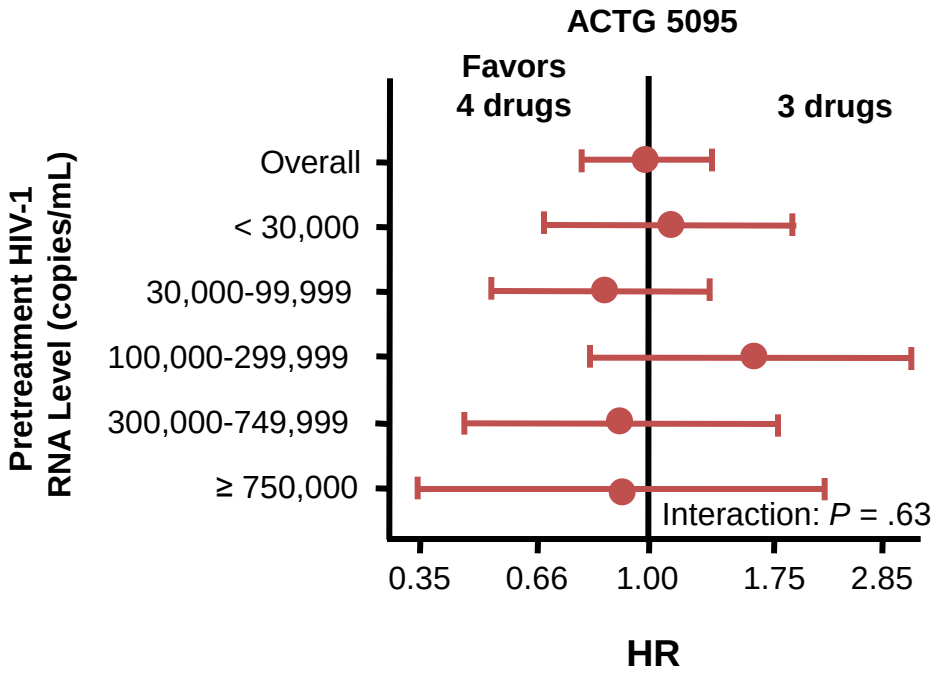


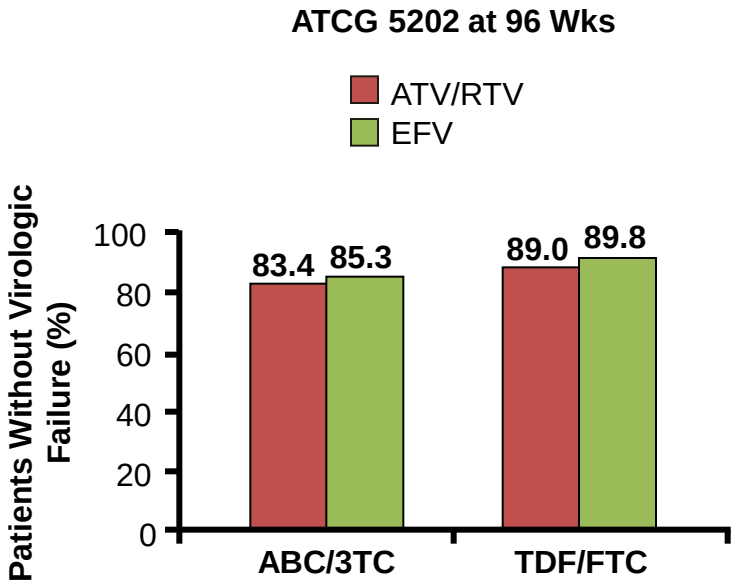
Cohen C, et al. AIDS. 2011;25:F7-12.

Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

Patients With High HIV-1 RNA

Regimen/Trial	Efficacy at HIV-1 RNA > 100,000 copies/mL
EFV + NRTIs	▪ ACTG 5095: EFV similarly effective at all HIV-1 RNA strata
ATV/RTV + TDF/FTC	▪ CASTLE: Similar to LPV/RTV at 48 and 96 wks ▪ ACTG 5202: Similar to EFV at 48 or 96 wks
DRV/RTV + TDF/FTC	▪ ARTEMIS: Superior to LPV/RTV at 48 and 96 wks
RAL + TDF/FTC	▪ STARTMRK: Similar to EFV through 192 wks





Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

ART and Effects on Lipids

- RAL appears to be neutral with respect to lipid changes[1]
- EFV associated with greater lipid change than RAL in STARTMRK[1]
- EFV associated with greater cholesterol changes than ATV/RTV in ACTG 5202[2]
- Both ATV/RTV and DRV/RTV associated with lesser lipid change than LPV/RTV[3,4]

1. Lennox J, et al. Lancet. 2009;374:796-806 2. Daar ES, et al. Ann Intern Med. 2011;154:445-456.
3. Molina JM, et al. Lancet. 2008;372:646-655. 4. Ortiz R, et al. AIDS. 2008;22:1389-1397.

ART and Renal Function

- TDF may be associated with declining renal function over time in some patients[1]
- Some studies suggest greater decline in renal function with TDF + boosted PIs vs TDF + NNRTIs[2,3]
- Cumulative exposure to ATV/RTV associated with increased risk of chronic kidney disease in cohort study; risk reversed upon stopping[4]
- In clinical studies of RAL, no clinically important PK differences have been observed between subjects with severe renal impairment and healthy subjects[5]

1. Tenofovir [package insert]. September 2011. 2. Morlat P, et al. IAS 2011. Abstract WEPDB0104.
3. Gallant JE, et al. AIDS. 2009;23:1971-1975. 4. Mocroft A, et al. AIDS. 2010;24:1667-1678.
5. Raltegravir [package insert]. November 2011.

Comorbidities

• **Cardiovascular disease**	**Avoid** abacavir (?), lopinavir/r, fos-Amp
• **Hepatitis B**	**Prefer** TDF-FTC, 3TC
• **Renal disease**	**Avoid** tenofovir, PI
• **Tuberculosis**	**Prefer** efavirenz, raltegravir
• **Gastroesofageal reflux**	**Avoid** atazanavir, rilpivirin
• **Depression**	**Avoid** efavirenz
• **Drug addiction**	**Avoid** NNRTI

Dosing Comparisons

Regimen/Trial	Dosing	Food requirements
EFV/TDF/FTC	▪ 1 pill once daily	▪ Empty stomach (recommended dosing at bedtime)
ATV/RTV + TDF/FTC	▪ 3 pills once daily	▪ Must be taken with food
DRV/RTV + TDF/FTC	▪ 4 pills once daily	▪ Must be taken with food
RAL + TDF/FTC	▪ 3 pills divided across 2 daily doses	▪ With or without food

Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

SCRIPT ONLY

Convenience

- **Once-daily versus twice-daily**
- **One pill:** TDF-FTC-EFV (Atripla®);

  TDF-FTC-RPV (Eviplera®, Complera®);

  TDF-FTC-EVG-COB (Stribild®)
- **To take with food:** rilpivirin, elvitegravir, atazanavir, darunavir, saquinavir
- **To take before sleeping:** efavirenz
- **Sirup or soluble tablets available**

Which Patient for Which Regimen?

Regimen	More Favorable for Patients With:	Less Favorable for Patients With:
NNRTI based	▪ Wants maximum simplicity (1 pill per day) ▪ Concerns about renal function	▪ Concerns about adherence ▪ A job that requires concentration (EFV) ▪ Planning pregnancy or early pregnancy (EVF) ▪ Taking other drugs metabolized by CYP 3A6
PI based	▪ Concerns about irregular adherence ▪ Prefers not to deal with CNS adverse effects ▪ Might become pregnant ▪ Prefers once-daily dosing	▪ Hyperlipidemia at BL ▪ Concerns about renal function ▪ Taking other drugs metabolized by CYP system ▪ Might have an issue with potential for jaundice or scleral icterus (ATV) ▪ Diabetes
II based	▪ Prefers not to deal with adverse effects associated with other regimens ▪ Needs concomitant drugs with interactions with other ARVs ▪ Concerns about CV risk ▪ Doesn't mind twice daily dosing (RAL) ▪ Wants maximum simplicity (1 pill per day) ▪ (Elvitegravir)	▪ Concerns about second daily dose (RAL) ▪ Concerns about adherence ▪ Concerns about cost of medicines

Adapted from slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

SCRIPT ONLY

Which Patient for Which Regimen?

Agent	More Favorable for Patients With:	Less Favorable for Patients With:
ABC/3TC	▪ Concerns about renal function ▪ Baseline VL < 100,000 copies/mL	▪ Higher baseline VL ▪ Moderate or higher CV risk ▪ Contraindicated in pts with positive HLA B5701
RPV	▪ Doesn't want to deal with CNS adverse effects ▪ Concerns about lipids ▪ Baseline VL < 100,000 copies/mL	▪ Concerns about irregular adherence ▪ GI issues ▪ Higher baseline VL
MVC	▪ Concerns about CV risk ▪ Concerns about irregular adherence ▪ Effective in pts with high BL VL	▪ Concerns about second daily dose ▪ Cannot afford tropism testing ▪ Takes many other drugs
LPV/RTV	▪ Might become pregnant ▪ Effective in pts with high BL VL	▪ CV risk or hyperlipidemia ▪ Decreased renal function ▪ GI tolerability issues (nausea and diarrhea)
NVP	▪ Might become pregnant ▪ Needs very tolerable agent ▪ Effective in pts with high BL VL	▪ High baselineCD4+ cell count ▪ HBV or HBV coinfection

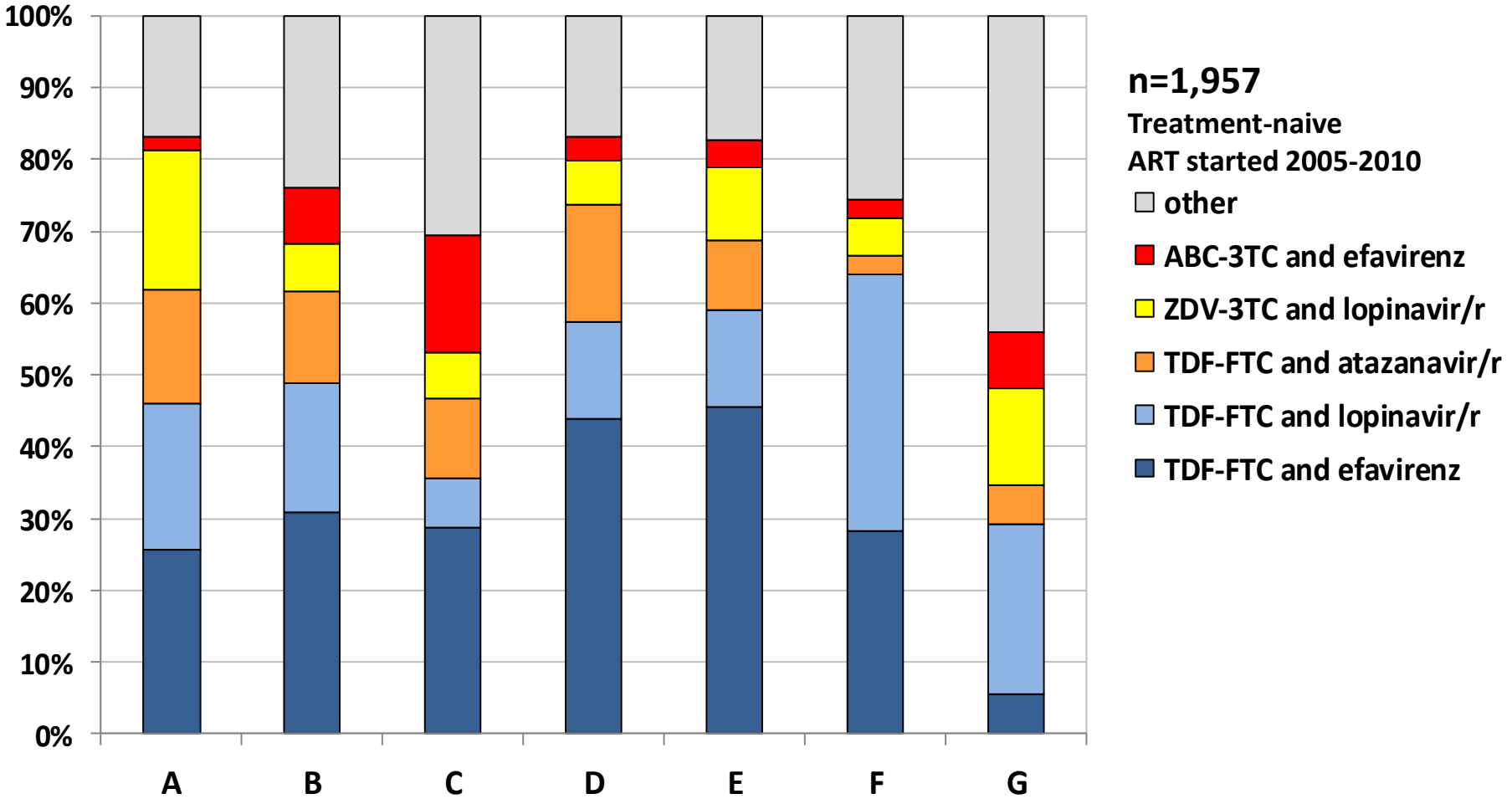
Slide, CCO, Jose R. Arribas, MD, and Anton L. Pozniak, MD

EACS Guidelines

EACS 2012

A	B
NNRTI	**NRTI**
• EFV [(i)] • RPV [(ii)]	ABC/3TC [(vii)] or TDF/FTC
• NVP [(iii)]	TDF/FTC
Ritonavir-boosted PI	
• ATV/r [(iv)] • DRV/r [(iv)] • LPV/r [(v)]	ABC/3TC [(vii)] or TDF/FTC
ITI	
• RAL	TDF/FTC

ART according to study sites



SHCS sites

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

Different treatment 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

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

Drug specific toxicity

Class	Substance	Name	Toxicity
NRTI	Abacavir	Ziagen, (Kivexa)	Hypersensitivity
	Lamivudine	3TC (Combivir, Kivexa)	Nausea, headache
	Didanosin	Videx	Pancreatitis, diarrhea
	Stavudine	Zerit	Polyneuropathy, lipodystrophy
	Zidovudin	Retrovir, (Combivir)	Nausea, anemia
	Tenofovir	Viread, (Truvada)	Tubular damage
	Emtricitabin	Emtriva, (Truvada)	Nausea, headache
NNRTI	Efavirenz	Stocrin	CNS, rash
	Etravirine	Intelence	Rash
	Nevirapine	Viramune	Hypersensitivity, hepatitis
PI	Atazanavir	Reyataz	Bilirubinemia (indirect)
	Lopinavir/r	Kaletra	Diarrhea, hyperlipidemia
	Darunavir	Prezista	Hepatitis, hyperlipidemia
II	Raltegravir	Isentress	Nausea, headache

SCRIPT ONLY

Safety and tolerability of current antiretroviral regimens in RCTs

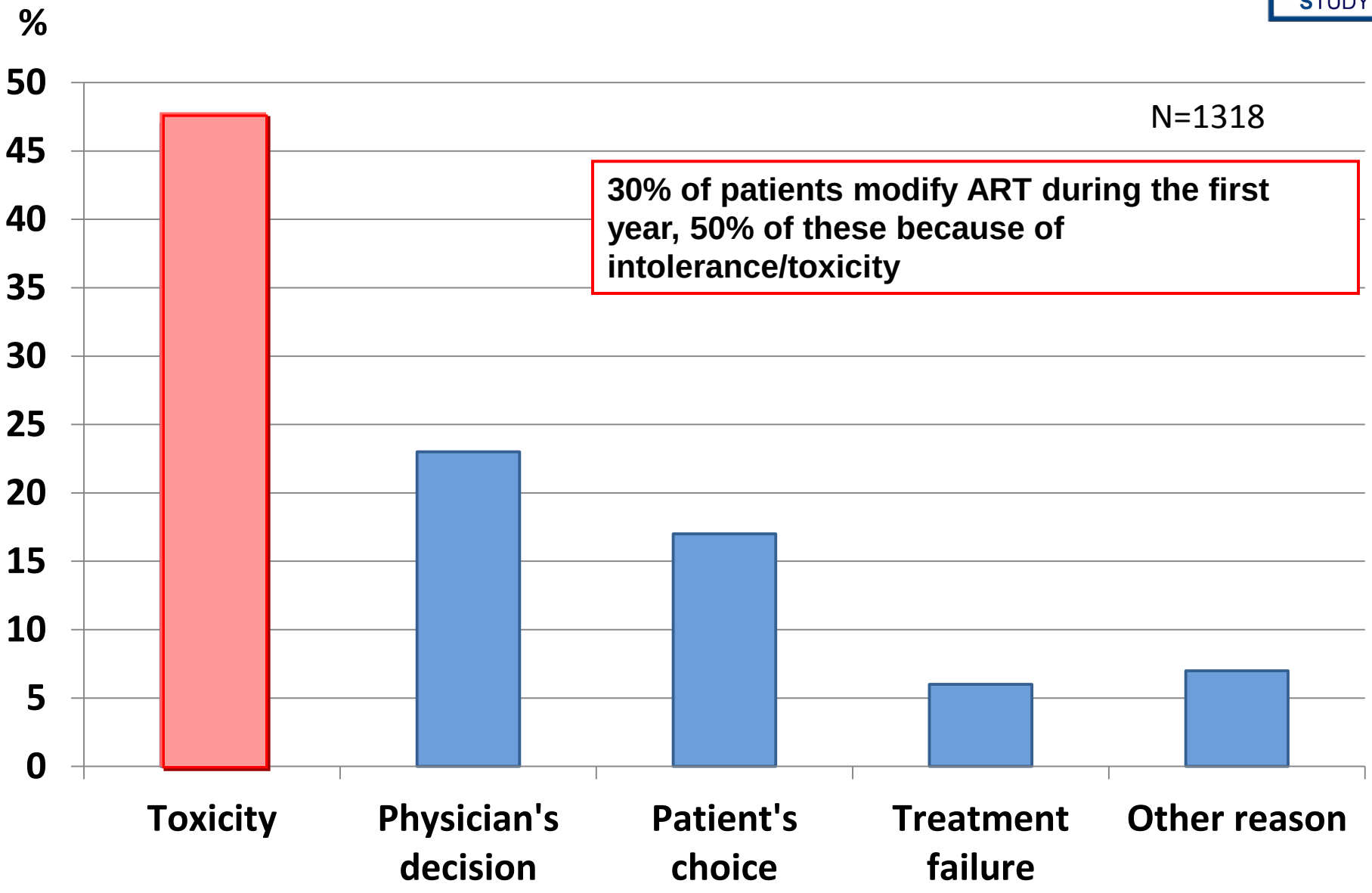
Study	Length	Drug regimen	Discontinuations Due to AEs,* %
AI424-089[1]	96 weeks	ATV + d4T + 3TC	3
		ATV/RTV + d4T + 3TC	8
GS934[2]	48 weeks	EFV + TDF + FTC	5
		EFV + ZDV/3TC	11
KLEAN[3]	48 weeks	FPV/RTV + ABC/3TC	12
		LPV/RTV + ABC/3TC	10
ARTEMIS[4]	48 weeks	DRV/RTV + TDF/FTC	3
		LPV/RTV + TDF/FTC	7
CASTLE[5]	48 weeks	ATV/RTV + TDF/FTC	2
		LPV/RTV + TDF/FTC	3
HEAT[6]	48 weeks	ABC/3TC + LPV/RTV	4
		TDF/FTC + LPV/RTV	6
GEMINI[7]	48 weeks	SQV/RTV + TDF/FTC	4
		LPV/RTV + TDF/FTC	7

1. Malan N et al IAS 2007. Abstract WEPEB024. 2. Arribas JR et al IAS 2007. Abstract WEPEB029. 3. Eron J Jr et al Lancet. 2006;368:476-482. 4. Ortiz R et al, AIDS, 2008. 5. Molina JM, et al, Lancet 2008. 6. Smith K, et al CROI 2008. Abstract 774. 7. Walmsley SL, et al EACS 2007. Abstract PS1.4.

Monitoring

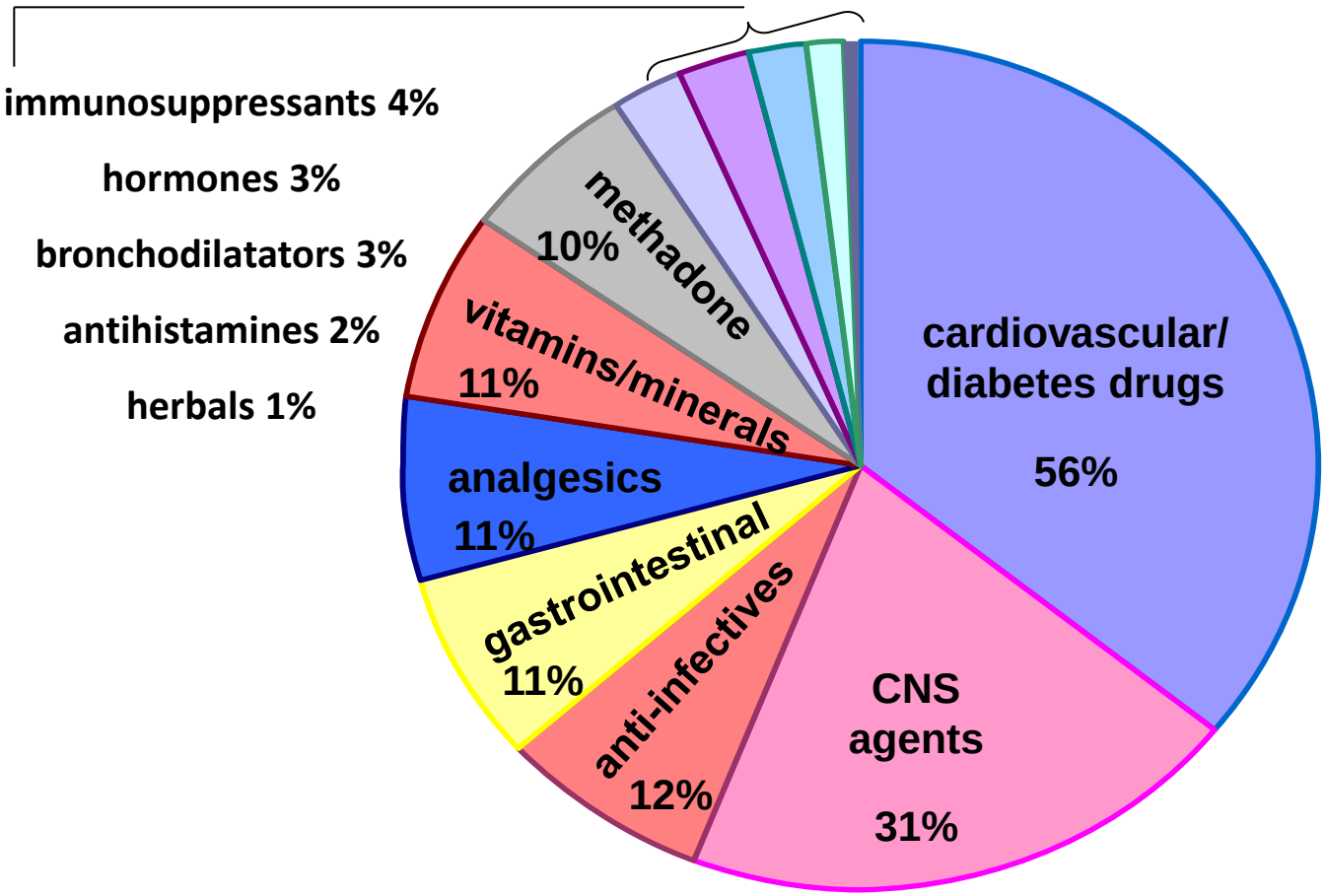
- Side effects
  - Tolerability
  - Toxicity
- Viral load after 1 month, 3 and 6 months
- CD4 measuring frequency depending on starting point: more frequently if below 200, otherwise same as for VL
- VL failure: <50 copies/mL after 6 months on ART

Main reason for ART modification



Elzi et al., Arch Intern Med, 2010

Co-medication in the SHCS



Interactions more frequent >50 y

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

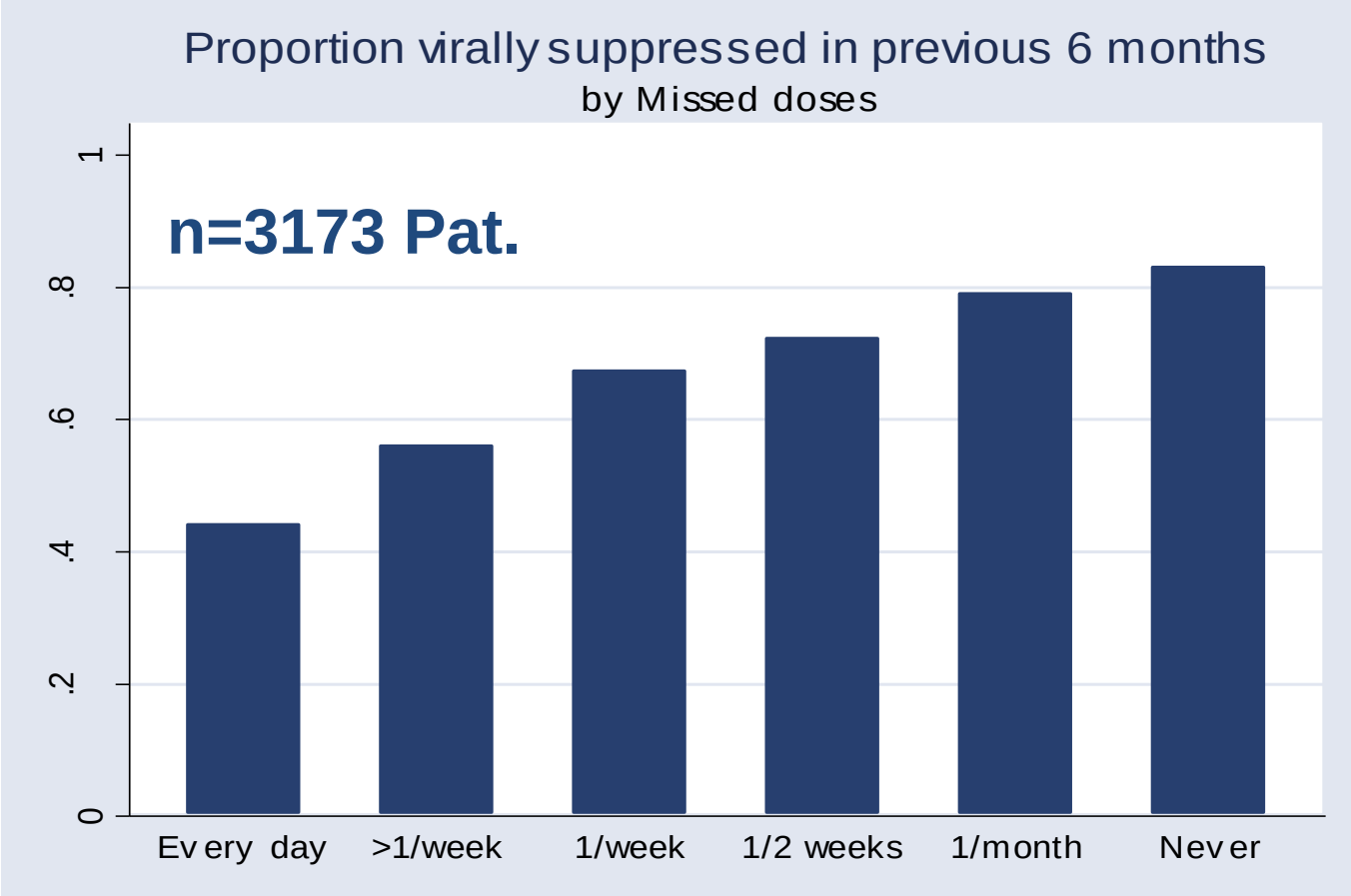
Marzolini & Battegay et al., Antiviral Therapy, 2010, Marzolini C et al. J Antimicrob Chemother 2011

Drug-drug interactions

www.hiv-druginteractions.org

Adherence

SWISS HIV COHORT STUDY



Suboptimal adherence leads to virologic failure and HIV progression

TR Glass et al., J Acquir Immune Defic Syndr. 2010

When to change

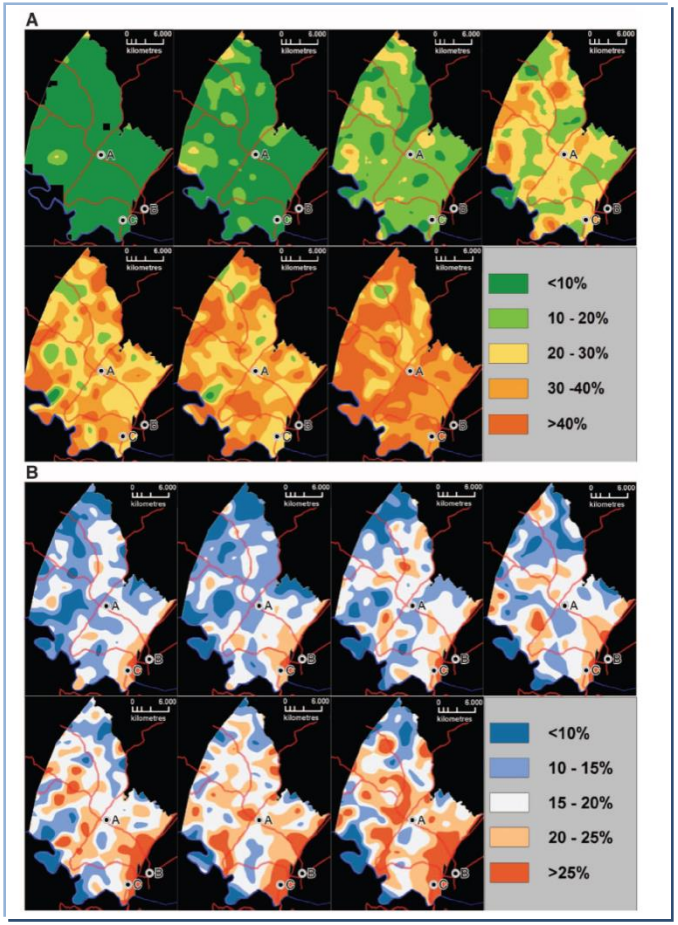
- **Virologic failure**
  - Non adherence
  - Drug-drug interactions
  - Intercurrent infections
- **Intolerance, toxicity**
- **Convenience** (simplification)


CCM

Aubert V, Barth J, Battegay M, Bernasconi E, Böni J, Brazzola P, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Cheseaux JJ, Drack G, Duppenthaler A, Egger M, Elzi L, Fehr J, Fellay J, Flepp M, Francini K, Francioli P (President of the SHCS), Furrer H, Fux CA, Gorgievski M, Grawe C, Günthard H, Gyr T, Haerry D, Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Posfay-Barbe K, Rauch A, Regenass S, Rickenbach M, Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Scheibner K, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Wyler CA, Yerly S.

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%)

Retention in ART programmes