HIV Treatment Guidelines Update

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HIV Treatment Guidelines

How are they made?

For whom?

According to which principles?

What do they say?

The First Eleven

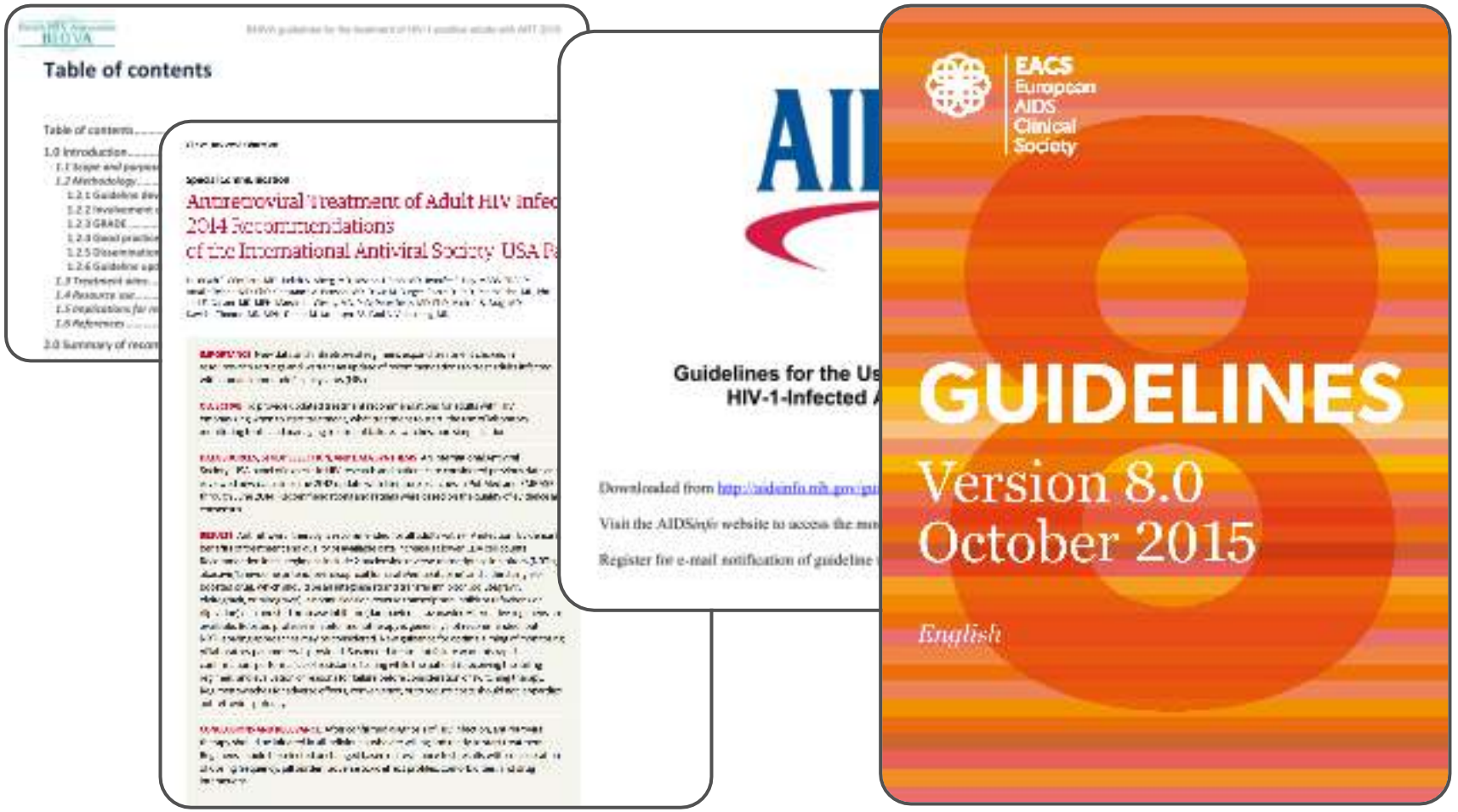


Table of contents
Antiretroviral Treatment of Adult HIV Infec
2014 Recommendations
of the International Antiviral Society USA
Guidelines for the Us
HIV-1-Infected
Downloaded from
Visit the AIDSinfo website to access the
Register for e-mail notification of guideline
EACS
European
AIDS
Clinical
Society
GUIDELINES
Version 8.0
October 2015
English

Treatment guidelines international

UK	NICE standards
USA	Experts & evidence levels
Europe	Experts
Germany	Elected experts
Netherlands	DHHS + comments by experts
…	

EU

WHO

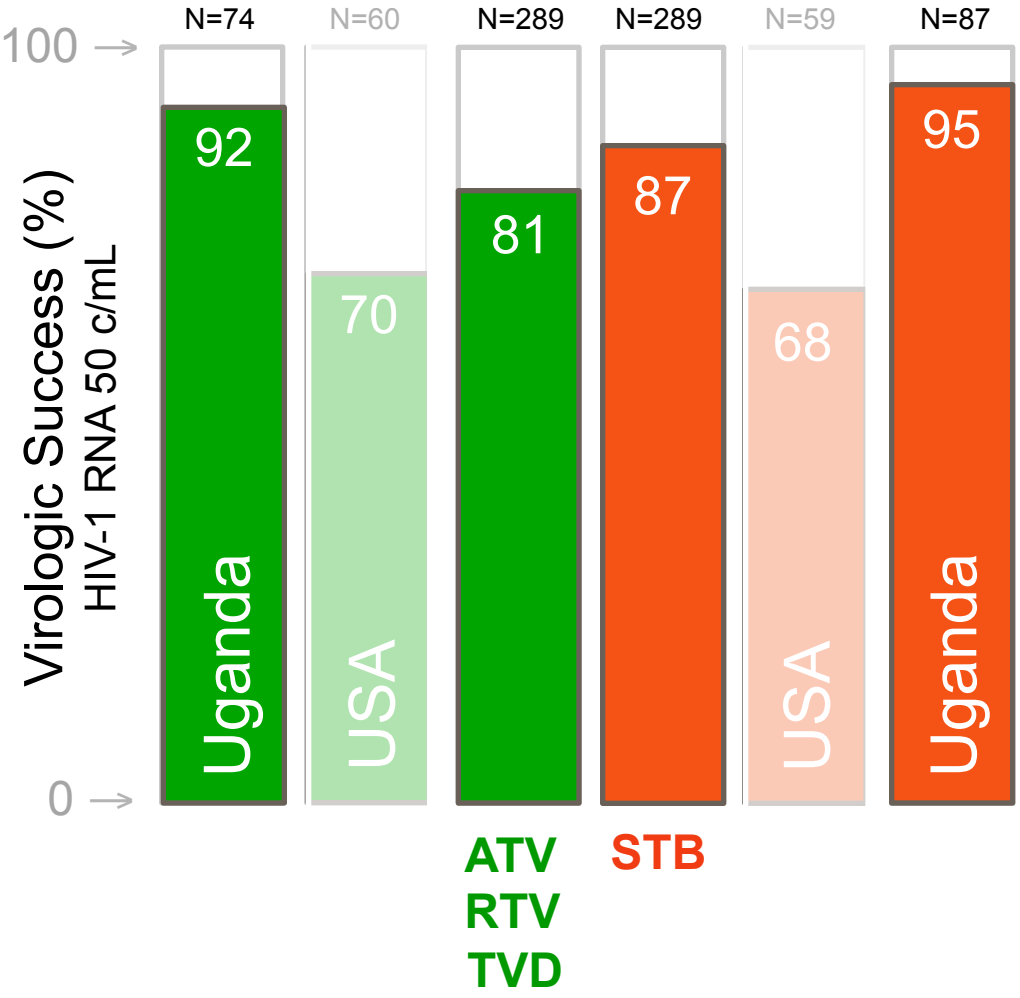
USA

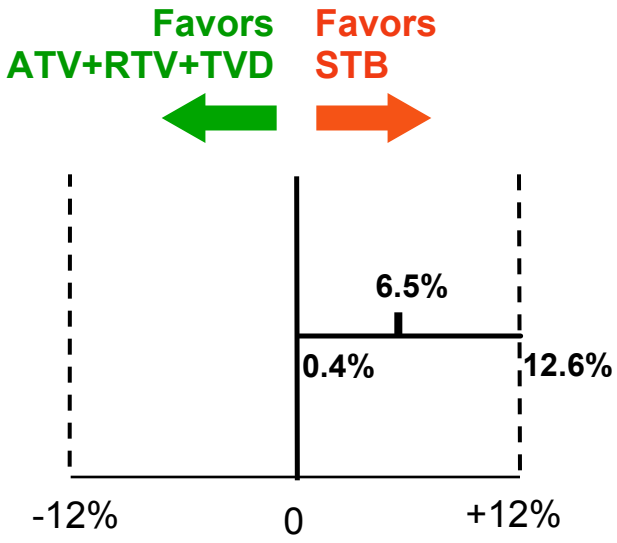
WHO ARV Guidelines Evolution 2002–2015

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

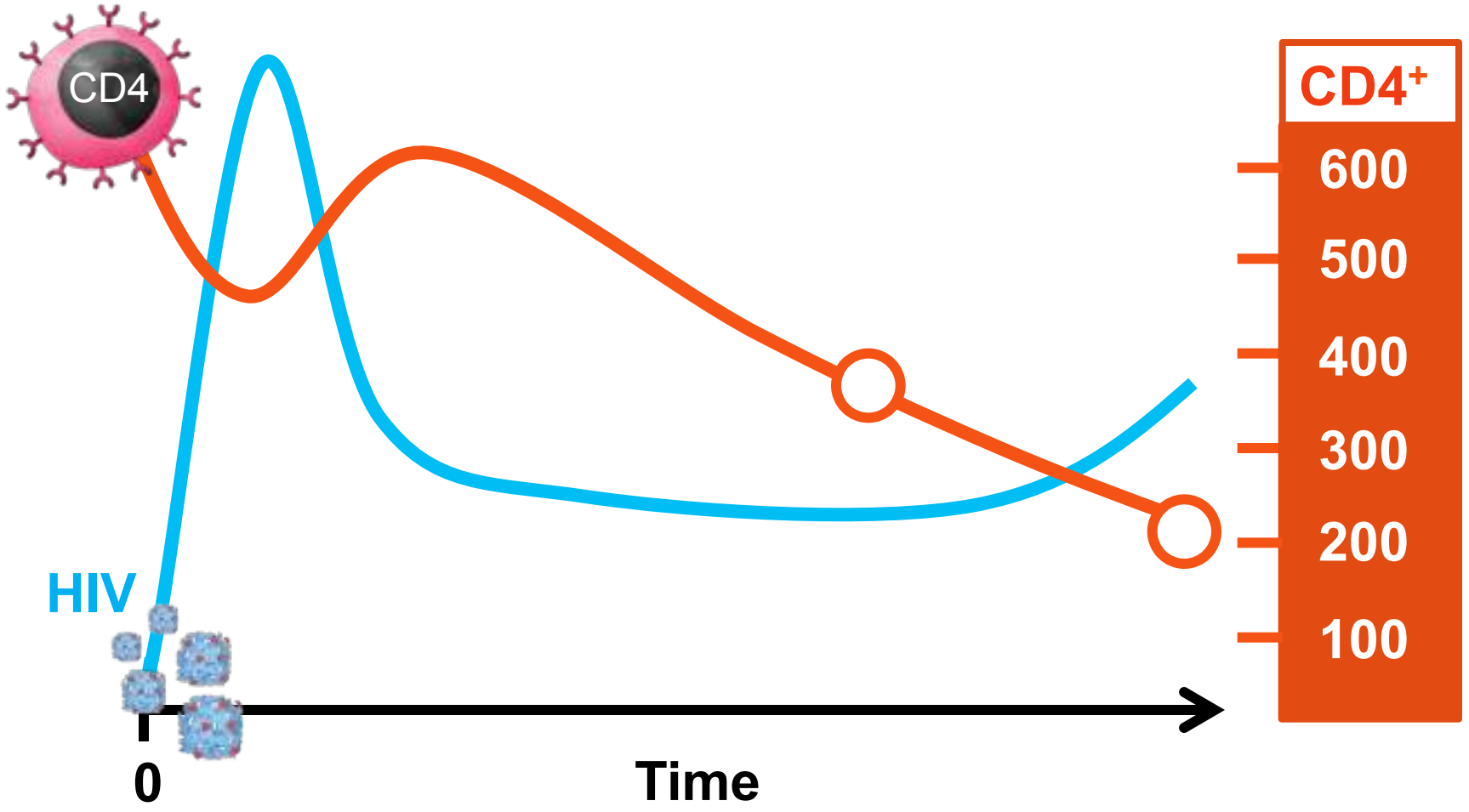
WAVES: **W**omen **A**ntiretro**V**iral **E**fficacy and **S**afety Study

Regional Differences in Efficacy at Week 48

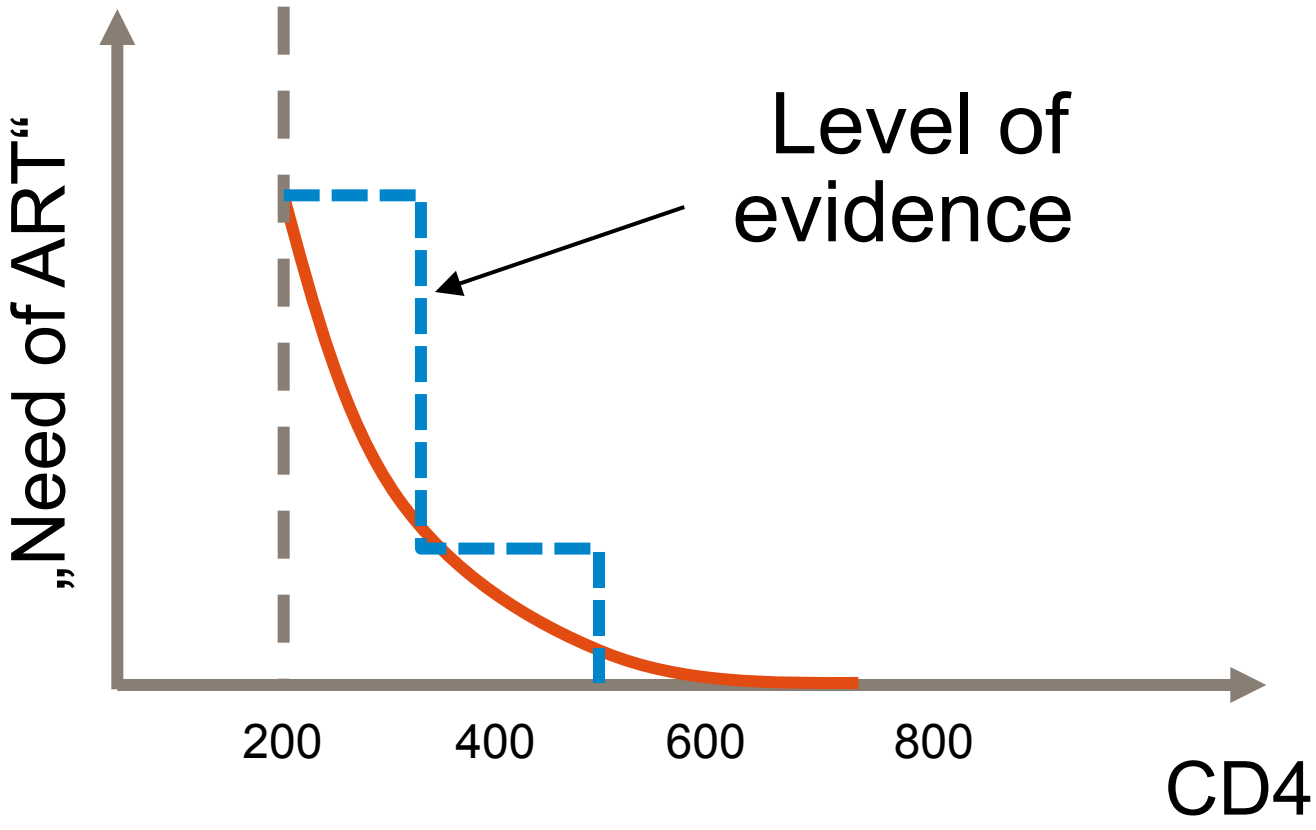




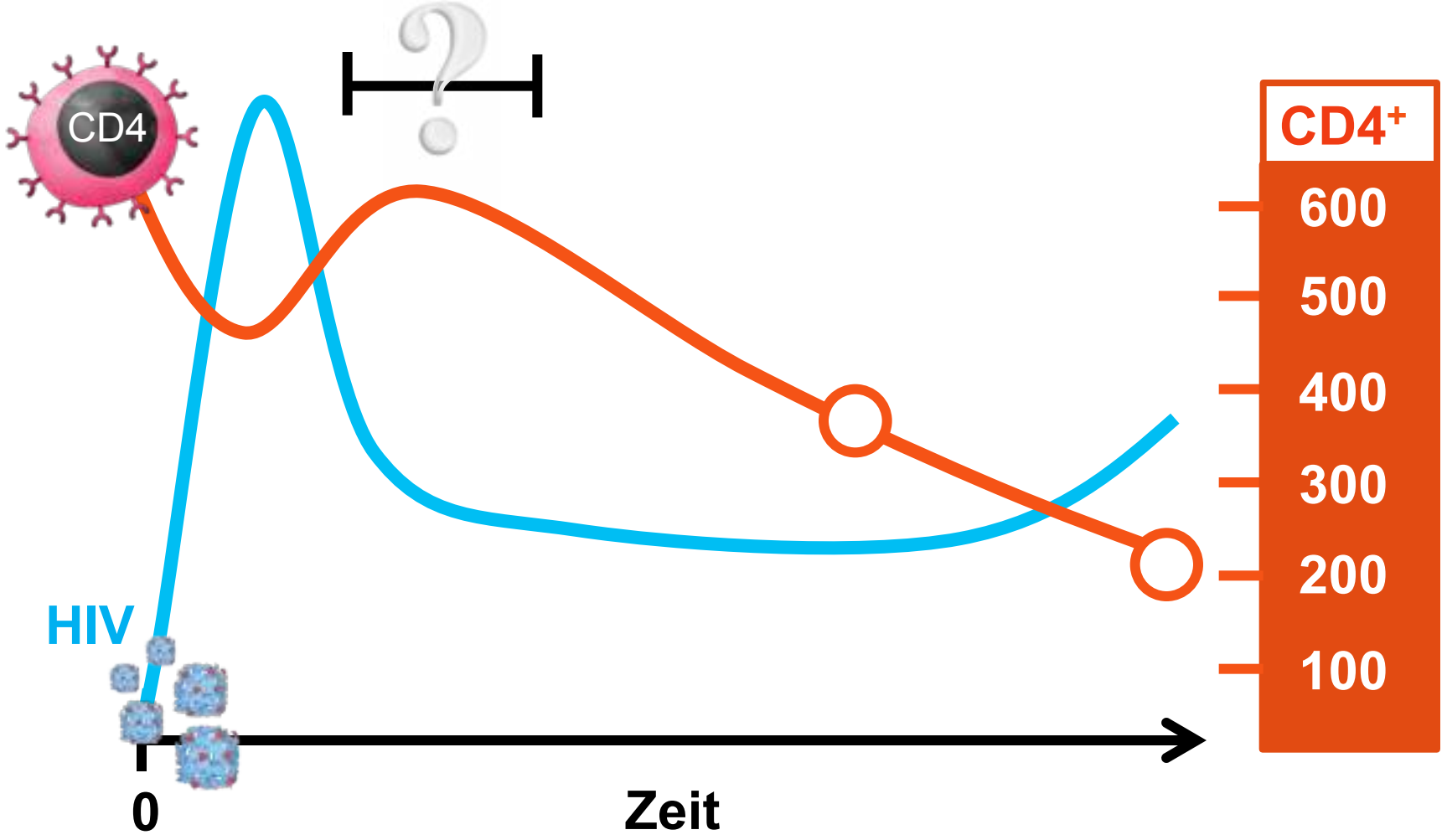
When to start ART?



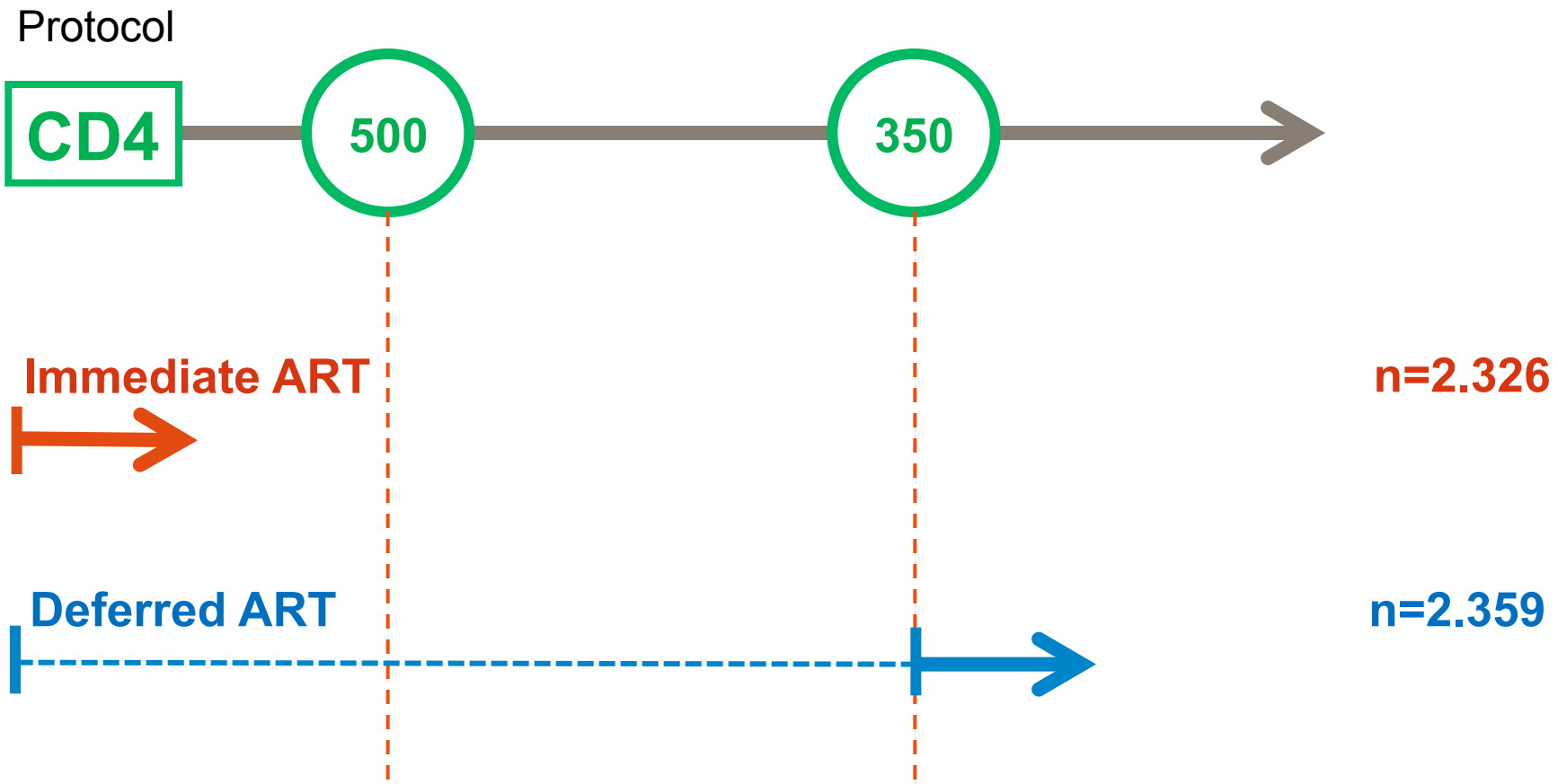
CD4 cell count and „need of ART“



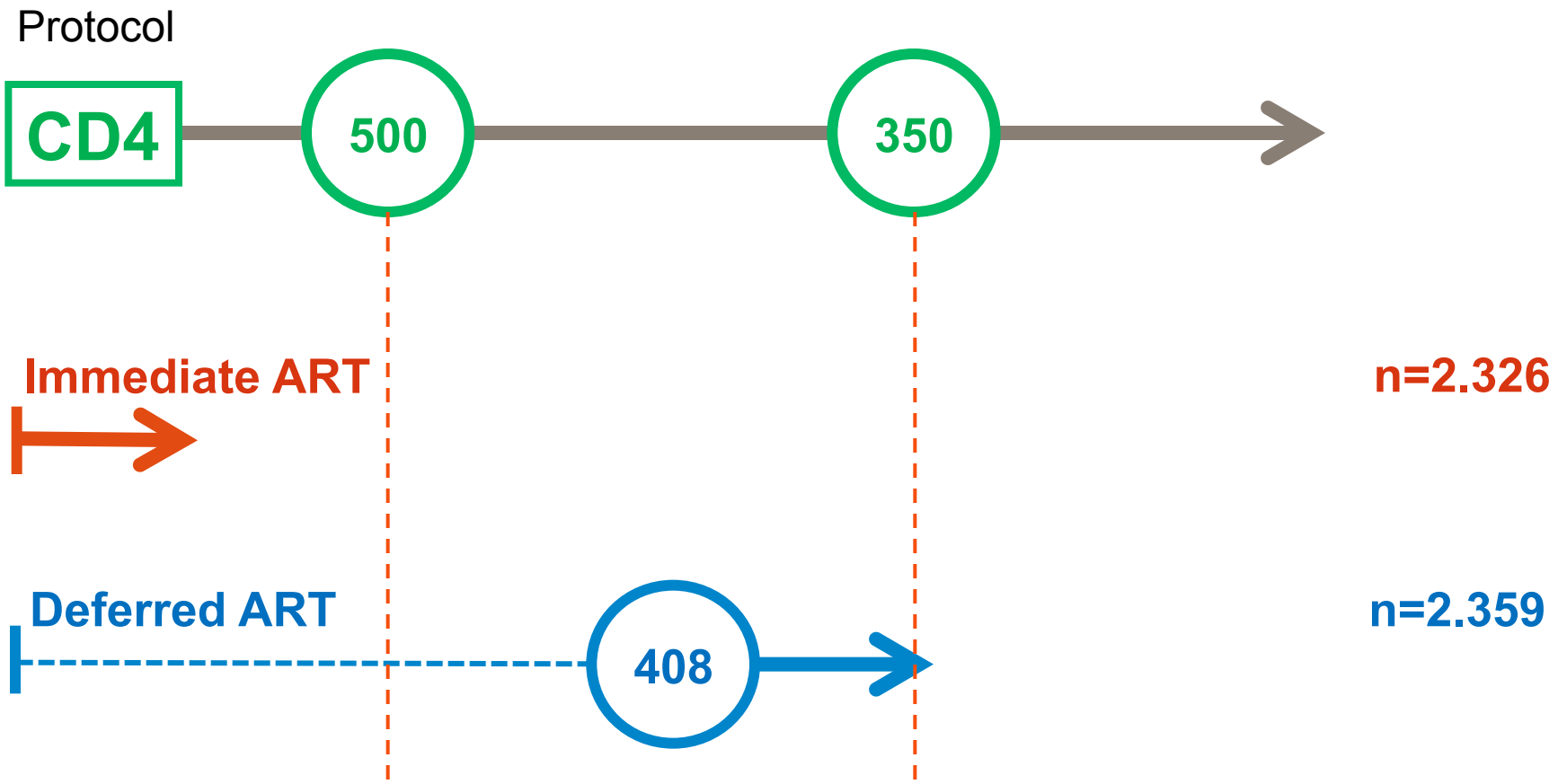
When to start ART?



START Study

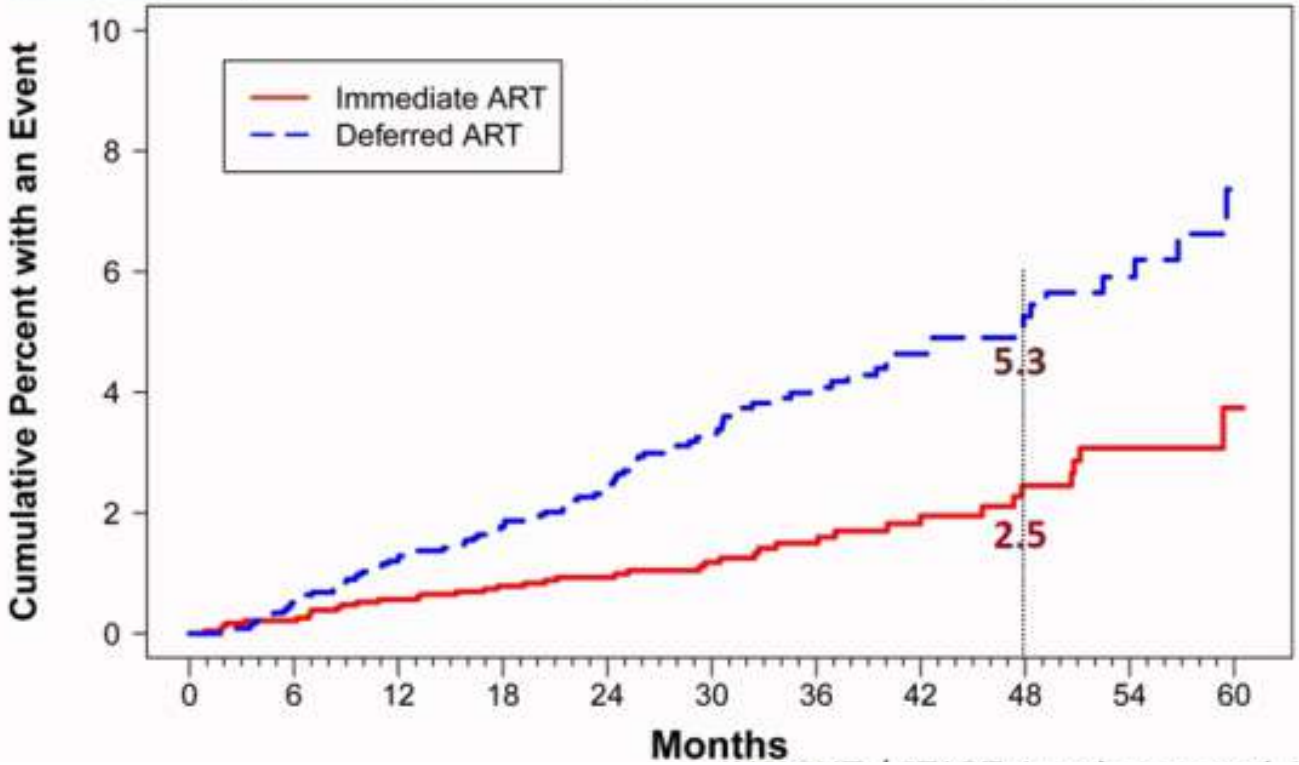

Protocol
CD4
500
350
Immediate ART
n=2.326
Deferred ART
n=2.359

START Study


Protocol
CD4
500
350
Immediate ART
n=2.326
Deferred ART
408
n=2.359

Primary End Points in START

	Immediate ART	Deferred ART
No. with Event (%)	42 (1.8%)	96 (4.1%)
Rate/100PY	0.60	1.38
HR (Imm/Def)	0.43 (95% CI: 0.30 to 0.62, p <0.001)	



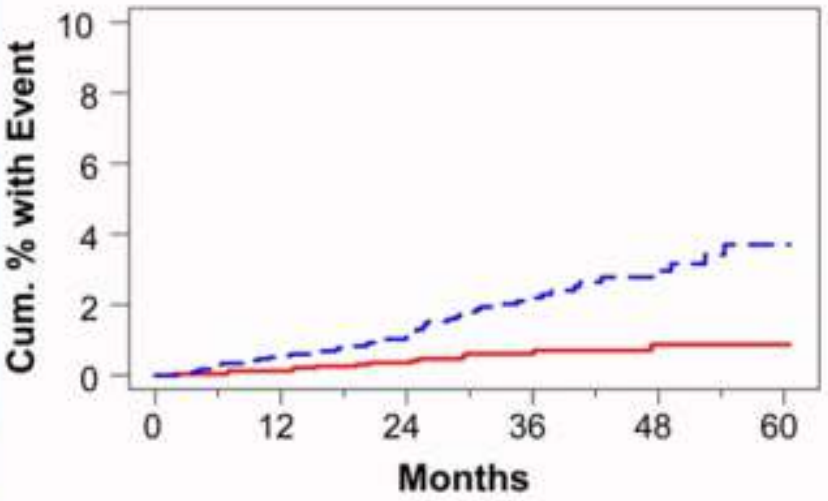
START: Serious AIDS Events

AIDS Events	Imm. ART	Def. ART
TB, pulm or extrapulm.*	6	20
Lymphoma, HL or NHL	3	10
Kaposi's sarcoma	1	11
PCP	1	5
Herpes zoster, diss.	0	3
Other**	3	1
Any Serious AIDS	14	50

*: Participants from Africa: 16/26 (62%) of TB cases

**: Cervical carcinoma, extra-pulm. cryptococcosis, CMV, recurrent bacterial pneumonia

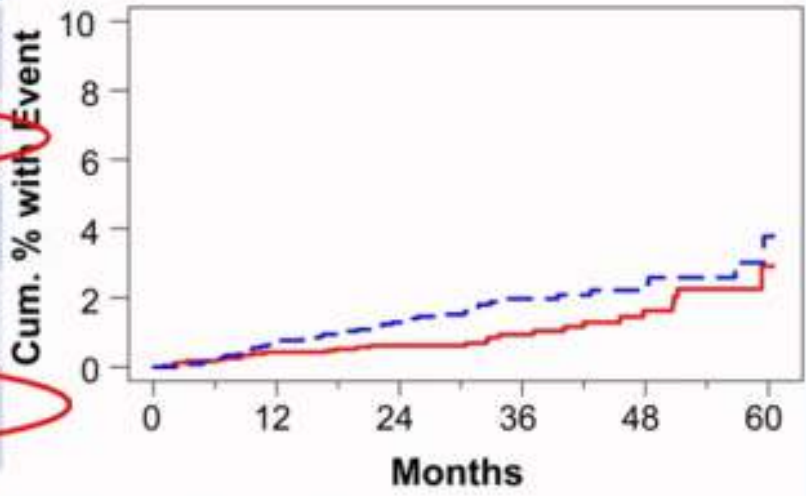
HR (Imm/Def):
0.28
(95% CI: 0.15 to 0.50, p <0.001)



START: Serious Non-AIDS Events

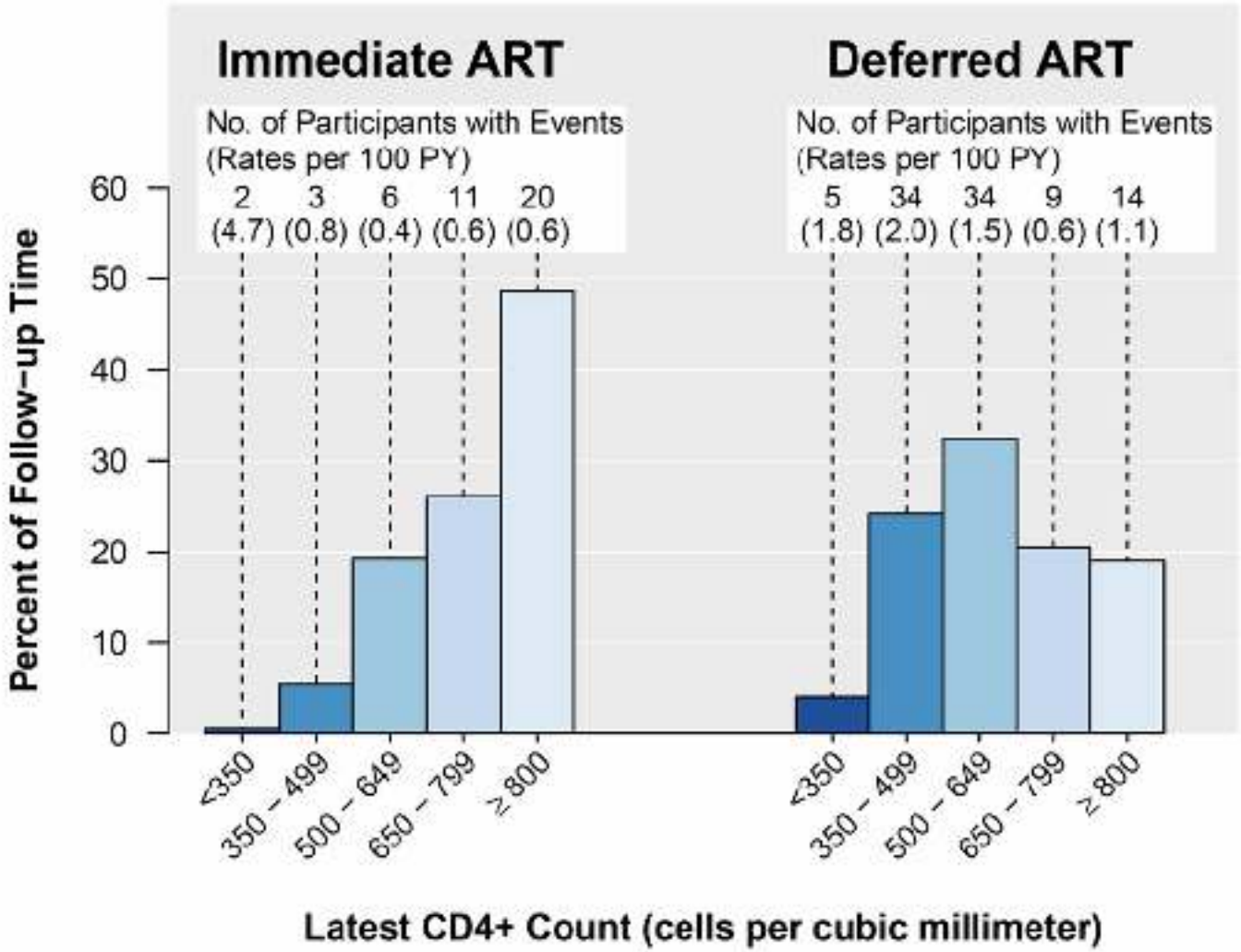
Non-AIDS Event	Imm. ART	Def. ART
Cancer, non-AIDS*	9	18
Cardiovascular disease*	12	14
Liver or renal disease	1	2
Death, other	7	13
Any Serious Non-AIDS	**29**	**47**

HR (Imm/Def):
0.61 (95% CI: 0.38 to 0.97, p=0.04)



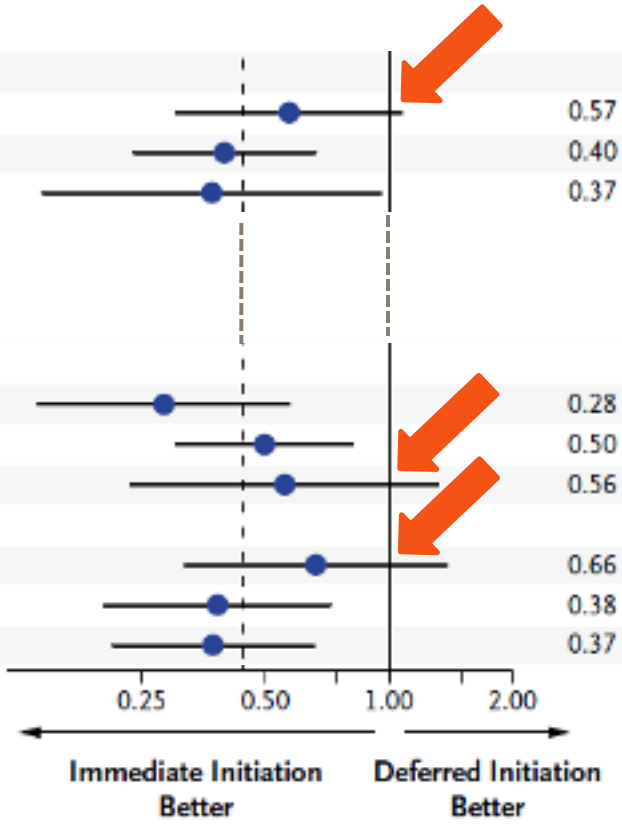
Participants from Australia, Europe, Israel and USA (46% of entire cohort):
22/27 (81%) of cancer cases
19/26 (73%) of CVD cases

The START study



START study: Subgroup analysis for primary endpoint

Subgroup	Percentage in Group	Immediate Initiation	Deferred Initiation	P Value for Interaction
		no. of patients with event (rate per 100 person-yr)		
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
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



Recommendation for treatment initiation

Recommendations are graded while taking into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

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

SR = Strongly Recommended
R = Recommended

Treatment of primary HIV infection

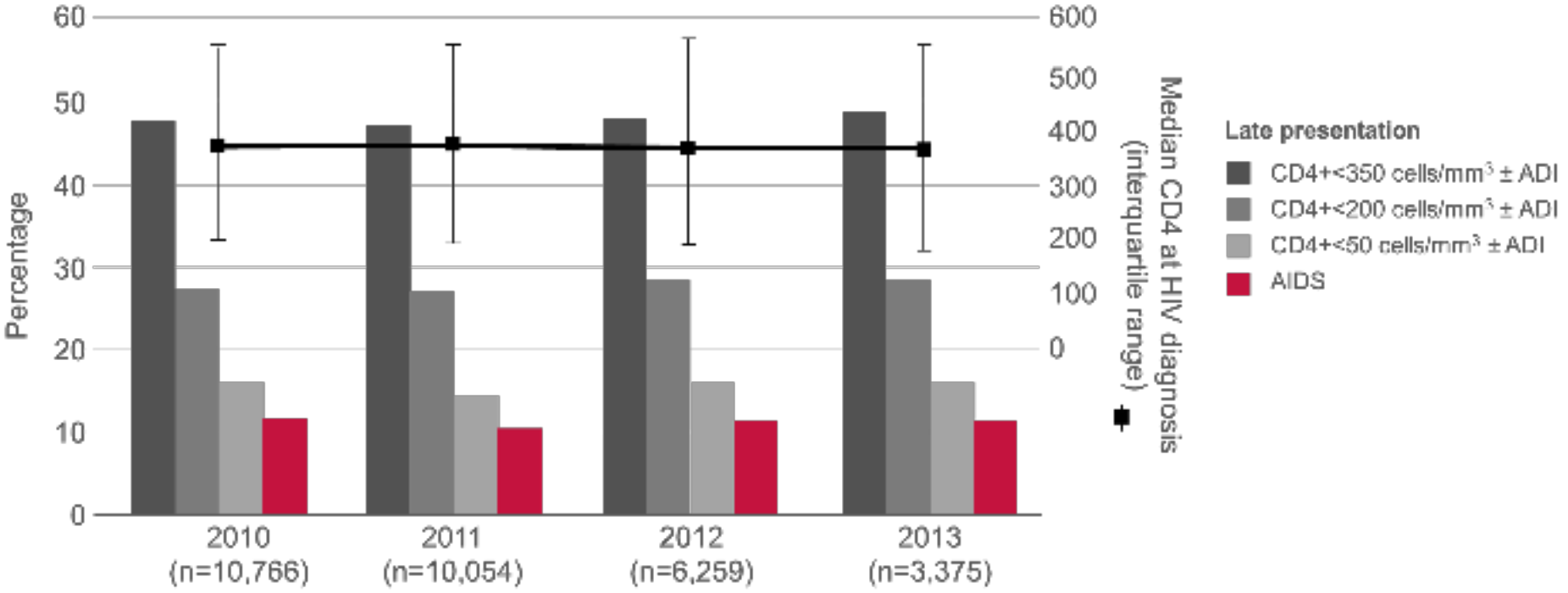
Treatment of PHI[vi-viii]

Circumstances	
Severe or prolonged symptoms	SR
Neurological disease	SR
Age ≥ 50 years	SR
CD4 count < 350 cells/μL	SR
Asymptomatic CD4 count > 350 cells/μL	R

SR=Strongly Recommended
R=Recommended

Late presentation is still common in Europe

Cohere study (N=30,454): 1st presentation to care, 2010-2013



ADI, AIDS defining illness within 6 months of diagnosis

Euro Surveill 2015;20(47). doi: 10.2807/1560-7917.ES.2015.20.47.30070

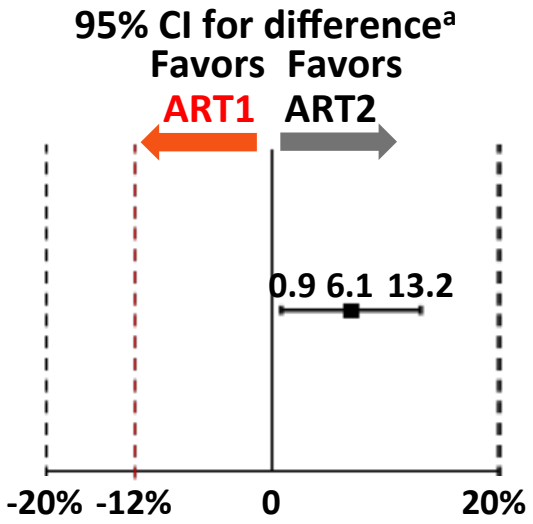
Primary Endpoint

0

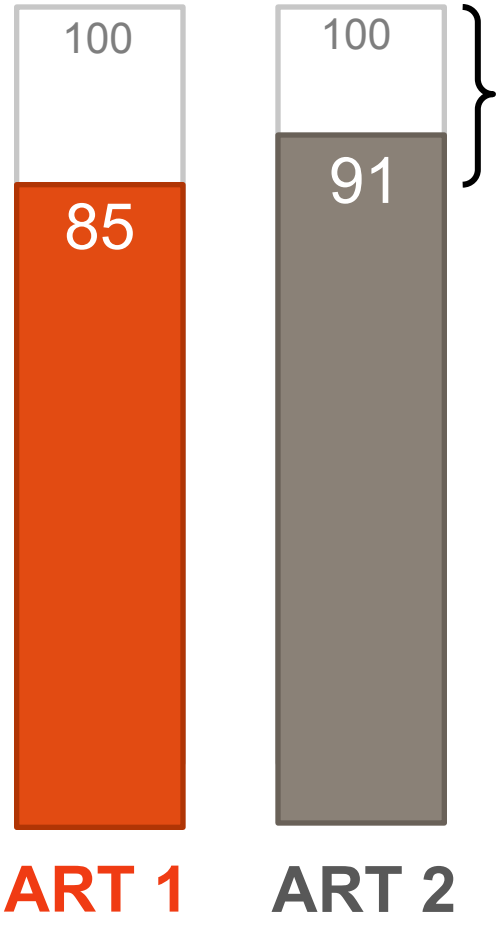
1

Non-inferiority trials (0:0)

Non-inferiority design



Test for superiority: *P*=0.045

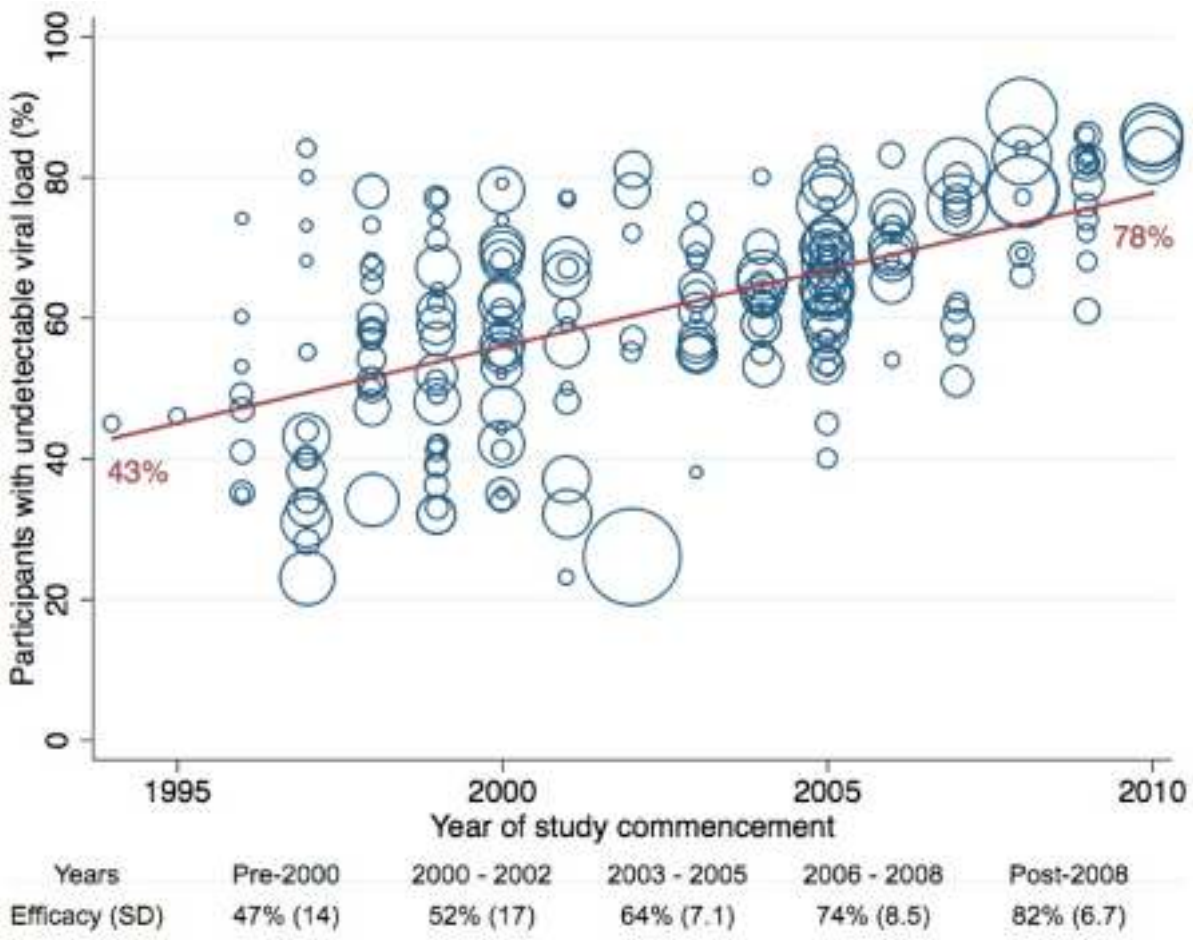


6/15 Patients benefit!

Treatment response in 1st line (114 trials)

A. Robben

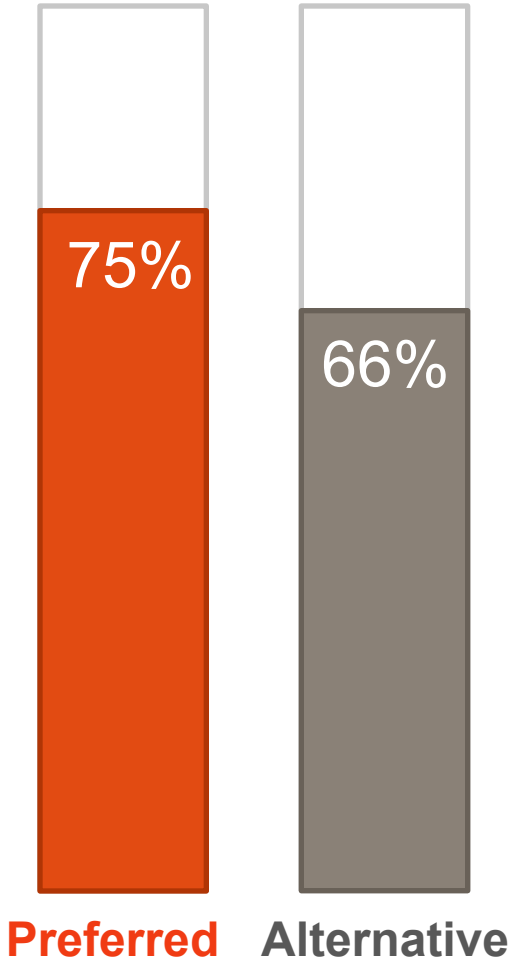
G. Netzer



Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Efficacy (SD)	47% (14)	52% (17)	64% (7.1)	74% (8.5)	82% (6.7)

Lee et al. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. Plos One 2014

Treatment response *Preferred* versus *Alternative*



'Preferred' regimen efficacy was 75% (SD 7.9) over a mean follow up of 99 weeks (SD 41), compared to 66% (SD 6.6) over 82 weeks (SD 35) with **'Alternative' regimens** (difference 10%; 95%CI 7.6 to 15.4; p,0.001)

Lee et al. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. Plos One 2014

Virologic Response Rates

Study (reference)	Study arm (N)	Regimen	HIV RNA <50 at 96 wks
ECHO/THRIVE[1]	682	2 NRTI + EFV	78%
	686	2 NRTI + RPV	78%
SPRING-2[2]	411	2 NRTI + **DTG**	**81%**
GS-US-236-0103[3]	353	TDF/FTC/**EVG**/c	**83%**
ACTG 5257[4]	605	2 NRTI + ATV/r	63%
	601	2 NRTI + DRV/r	73%
	603	2 NRTI + **RAL**	**80%**

1. Cohen AIDS 2013, 2. Raffi Lancet Infect Dis 2013, 3. Rockstroh JAIDS 2013, 4. Lennox Ann Intern Med 2014

Initial Regimens: Recommended

INSTI based	▪ DTG/ABC/3TC; only if HLA-B*5701 negative (AI) ▪ DTG (QD) + TDF/FTC (AI) ▪ EVG/COBI/TDF/FTC; only if pre-ART CrCl >70 mL/min (AI) ▪ EVG/COBI/TAF/FTC; only if pre-ART CrCl ≥30 mL/min (AI) ▪ RAL + TDF/FTC (AI)
PI based	▪ DRV/r (QD) + TDF/FTC (AI)

Note:
3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

2015: EACS-Guidelines for 1st line

TDF/FTC

DRV/r

RVP

RAL

EVG

DTG

ABC/3TC

13 → 6

1. EACS Guidelines 2015; Available at: http:// (Accessed Jan 2015).

2015: EACS-Guidelines for 1st line

TDF/FTC

DRV/r

RVP

RAL

EVG

DTG

ABC/3TC

1. EACS Guidelines 2015; Available at: http:// (Accessed Jan 2015).

Recommended regimens

A) Recommended regimens (one of the following to be selected)[*,**]

Regimen	Dosing
2 NRTIs + INSTI	
ABC/3TC/DTG[i, ii]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd
TDF/FTC[iii, iv] + DTG	TDF/FTC 300[vii]/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd
TDF/FTC/EVG/c[iii, iv, v]	TDF/FTC/EVG/c 300[vii]/200/150/150 mg, 1 tablet qd
TDF/FTC[iii, iv] + RAL	TDF/FTC 300[vii]/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid
2 NRTIs + NNRTI	
TDF/FTC/RPV[iii]	TDF/FTC/RPV 300[vii]/200/25 mg, 1 tablet qd
2 NRTIs + PI/r	
TDF/FTC[iii, iv] + DRV/r	TDF/FTC 300[vii]/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd

Alternative regimens

B) Alternative regimens (to be used when none of the preferred regimens are feasibl

Regimen	Dosing
2 NRTIs + INSTI	
ABC/3TC[I, II] + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid
2 NRTIs + NNRTI	
ABC/3TC[I, II] + EFV[VI]	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd
TDF/FTC/EFV[II, IV]	TDF/FTC/EFV 300[V]/200/600 mg, 1 tablet qd
2 NRTIs + PI/r or PI/c	
ABC/3TC[I, II] + ATV/r	ABC/3TC 600/300 mg, 1 tablet qd + ATV 300 RTV 100 mg, 1 tablet qd
TDF/FTC[II, IV] + ATV/r	TDF/FTC 300[V]/200 mg, 1 tablet qd + RTV 1 tablet 100 mg qd
ABC/3TC[I, II] + ATV/c	ABC/3TC 600/300 mg tablet qd + COBI 150 mg, 1 t
TDF/FTC[II, IV] + ATV/c	TDF/FTC 3 V 300 mg, 1 tablet qd + C
ABC/3TC[I, II] + DR	g, 1 tablet qd + DRV 800 mg, 1 tablet qd 100 mg qd
ABC/3TC[I, II] + DRV/c	600/300 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd OBI 150 mg, 1 tablet qd
TDF/FTC[II, IV] + DRV/c	TDF/FTC 300[V]/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd
TDF/FTC[II, IV] + LPV/r	TDF/FTC 300[V]/200 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid

Always triple ART in 1st line

A perfect treatment works efficiently

1) in everyone and
2) has no side effects

Why then individualised therapy?

NRTI options are limited and not always guideline recommended

Treatment considerations	TDF/FTC	ABC/3TC
*High viral load[1,2]	Acceptable	Caution / Acceptable**
High CVD risk[1,2]	Acceptable	Caution
Renal impairment[2]	Caution	Acceptable
Decrease in BMD[2,3]	Caution	Acceptable
HLAB*5701 positive[1,2]	Acceptable	Avoid

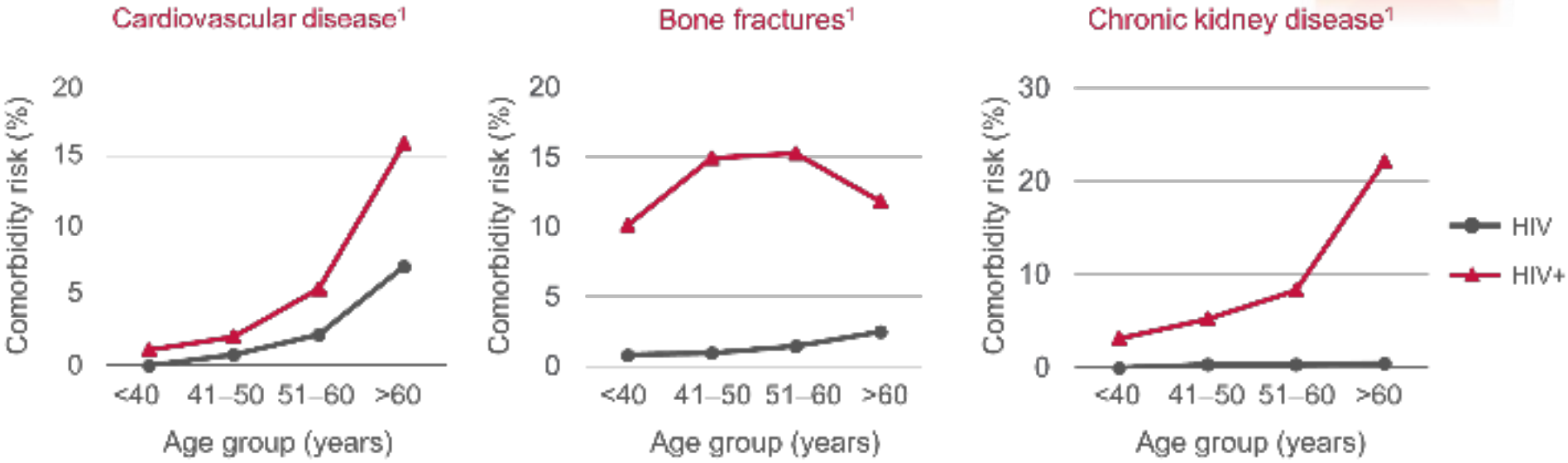
*>100,000 copies/mL; BMD: bone mineral density; CVD: cardiovascular disease
** No viral load restriction for DTG/ABC/3TC use, according to May 2014 DHHS guidelines[2]

1. EACS Guidelines 2013; Available at: http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf (accessed Mar 2014). 2. DHHS Guidelines 2014; Available at: www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed May 2014); 3. Thompson MA, et al. JAMA 2012;308:387–402.

What guidelines don‘t know for sure:

- What to start with in a patient with CD4 cell counts of 683/µl?
- What ART is best for patients with AIDS?
- What is the best treatment strategy in the long run?
- …

Part III Prevention and Management of Co-morbidities in HIV-positive Persons



1. Guaraldi G et al. Clin Infect Dis 2011;53:1120–6

Kideny disease in HIV

Kidney Disease: Definition, Diagnosis and Management

Diagnosis of kidney disease

		eGFR[i]		
		≥ 60 mL/min	30-59 mL/min	< 30 mL/min
Proteinuria[ii]	UP/C[iii] < 50	Regular follow-up		• Check risk factors for CKD and nephrotoxic medicines including ART[iv] • Discontinue or adjust drug dosages where appropriate[v] • Perform renal ultrasound • Urgent referral to nephrologist
	UP/C[iii] 50-100	• Check risk factors for CKD[v] and nephrotoxic medicines including ART[iv, v] • Discontinue or adjust drug dosages where appropriate[v] • Perform renal ultrasound • If haematuria present with any level of proteinuria refer to nephrologist • Refer to nephrologist if new CKD or progressive decline in eGFR		
	UP/C[iii] > 100			

Management of HIV-associated kidney disease[vi]

Prevention of progressive renal disease	Comment
1. ART	Start ART immediately where HIV-associated nephropathy (HIVAN) [vii] or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. Renal biopsy to confirm histological diagnosis recommended
2. Start ACE inhibitors or angiotensin-II receptor antagonists if:	Monitor eGFR and K^+ level closely on starting treatment or increasing dose

i For eGFR: Use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated >60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see http://www.hivpv.org/.
Definition CKD: eGFR < 60 ml/min for > 3 months (see http://kdigo.org/home/guidelines/ckd-evaluation-management). If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of DTG, COBI and RTV boosted PIs is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proxi-mal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

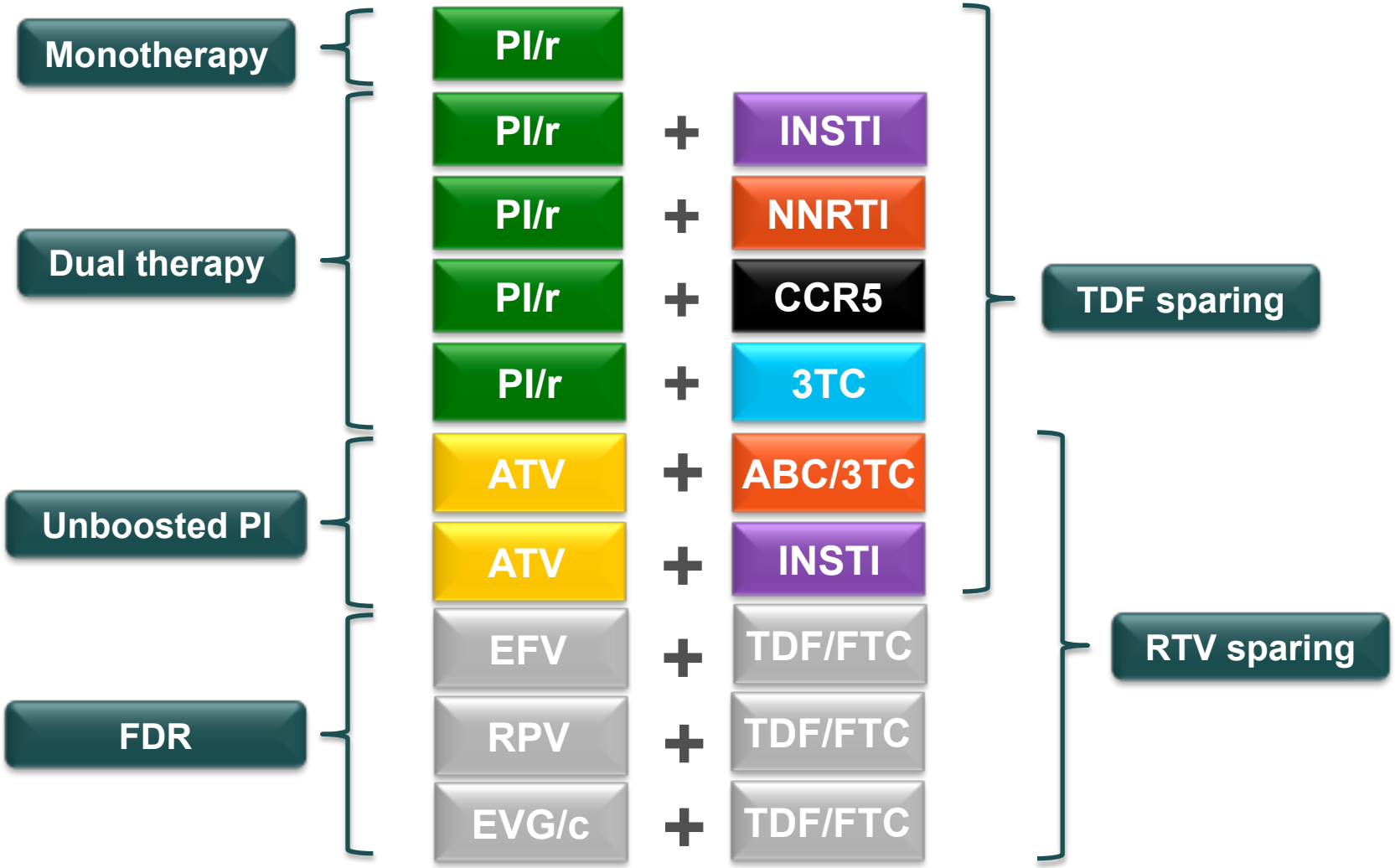
ii Urinalysis: use urine dipstick to screen for haematuria. To screen for proteinuria, use urine dipstick and if ≥ 1+ check urine protein/creatinine (UP/C), or screen with UP/C. Proteinuria defined as persistent if con-

Drug-drug interactions

Drug-drug Interactions between Contraceptives/Hormone Therapy Replacem Treatment and ARVs

		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Estrogens	ethinylestradiol	↓19%[a]	↑	↓44%[a]	↓42%[b]	↔[d]	↑22%	↓20%[b]	↑14%	↔	↑3%	↓25%[e]	↔	↔	↔	↔	↔	↔
	estradiol	↓[f]	↑	↓[f]	↓[f]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Progestins	desogestrel	↑[g,h]	↑[g,h]	↑[g,h]	↑[g,h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[g,h]	↔	↔	↔	↔	↔	↔
	drospirenone	↔[h]	↑[h,n]	↑[h]	↔[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
	dydrogesterone	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	etonogestrel	↓[h]	↑[n]	↑[h]	↑52%[b]	↓63%[c]	↓[n]	↓[n]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
	gestodene	↓[h]	↑[n]	↑[h]	↓[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
	levonorgestrel	↓[h]	↑[n]	↑[h]	↓[h]	↓[e]	↓[e]	↓[e]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
	medroxypro-gesterone (IM)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	medroxypro-gesterone (oral)	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	norelgestromin	↑	↑[n]	↑[j]	↑83%[j]	↓[j]	↓[j]	↓[j]	↔	↔	↔	↑[j]	↔	↔	↔	↔	↔	↔
	norethisterone	↓[k]	↑[n]	↓14%[j]	↓17%[j]	↓[j]	↓5%	↓19%[j]	↓11%	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
	norgestimate	↑85%[h]	↑[n]	↑[h]	↑[h]	↓[j]	↓[j]	↓[j]	↔	↔	↔	↑126%[j]	114%	↔	↔	↔	↔	↔
	norgestrel	↓[h]	↑[n]	↑[h]	↓[h]	↓[j]	↓[j]	↓[j]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔
Other	levonorgestrel (EC)	↑	↑	↑	↑	↓58%[l]	↓[l]	↓[l]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mifepristone	↑	↑	↑	↑	↓	↓	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	ulipristal	↑	↑	↑	↑	↓[m]	↓[m]	↓[m]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Keeping it simple: Simplifying treatment regimens



Maintenance of HIV therapy

Reactive

Proactive

Switch of HIV therapy

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV), diarrhoea (PI/r) and jaundice (ATV).
2. **Prevention of long-term toxicity.** Example of this proactive switch: prevention of lipoatrophy in patients receiving d4T or AZT.
3. **Avoid serious drug-drug interactions**
4. **Planned pregnancy**
5. **Ageing and/or co-morbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification:** to reduce pill burden, adjust food restrictions and improve adherence.

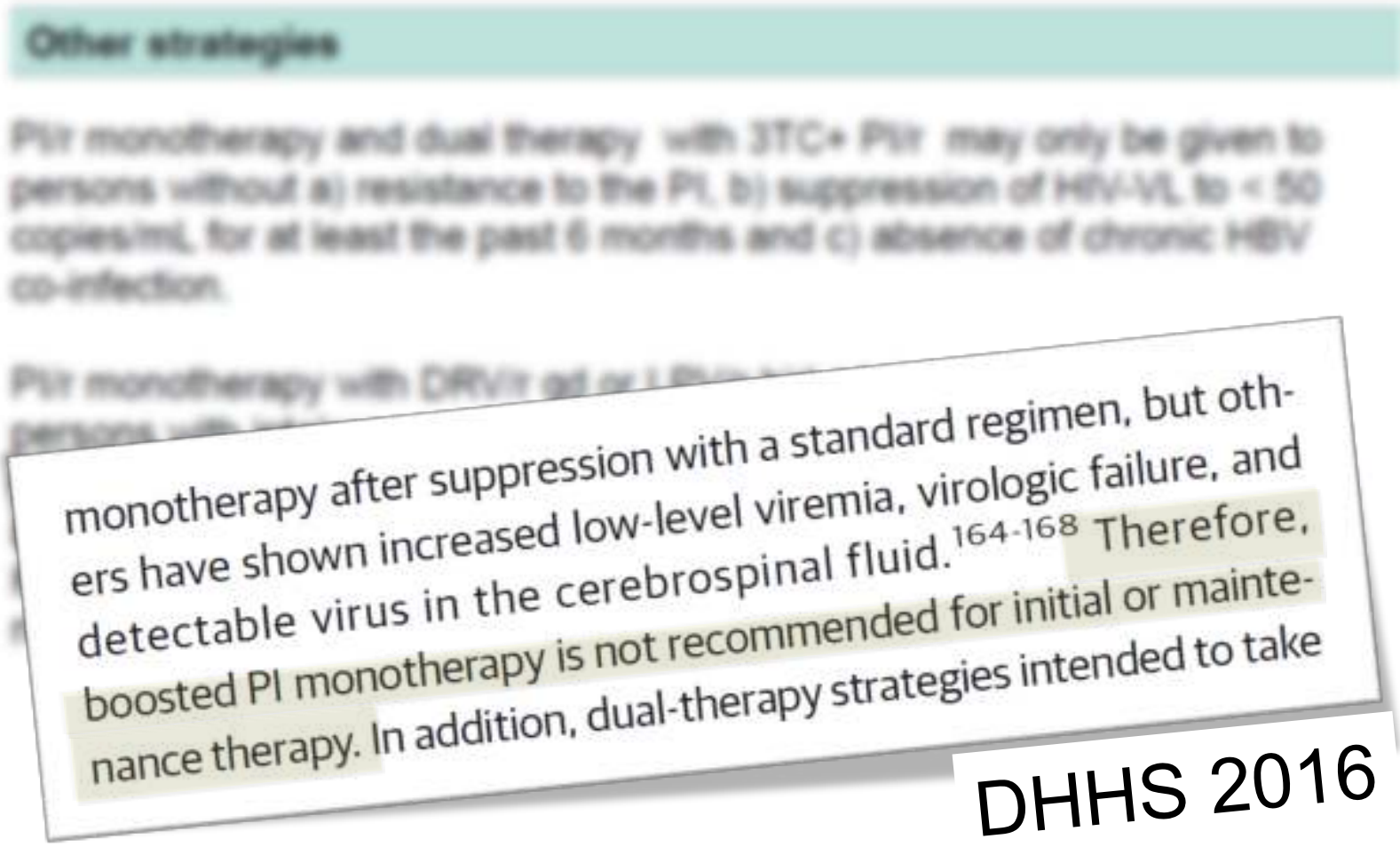
Switch of HIV therapy

Other strategies

PI/r monotherapy and dual therapy with 3TC+ PI/r may only be given to persons without a) resistance to the PI, b) suppression of HIV-VL to < 50 copies/mL for at least the past 6 months and c) absence of chronic HBV co-infection.

PI/r monotherapy with DRV/r qd or LPV/r bid might represent an option in persons with intolerance to NRTIs or for treatment simplification or in illicit drug users with documented frequent interruption of cART. This strategy is associated with more virological rebounds than continuing triple therapy. However, resistance occurs rarely, and suppression can be regained with nucleoside reintroduction.

Switch of HIV therapy



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PI/r monotherapy with DRV/r qd or LPV/r

monotherapy after suppression with a standard regimen, but others have shown increased low-level viremia, virologic failure, and detectable virus in the cerebrospinal fluid.[164-168] Therefore, boosted PI monotherapy is not recommended for initial or maintenance therapy. In addition, dual-therapy strategies intended to take

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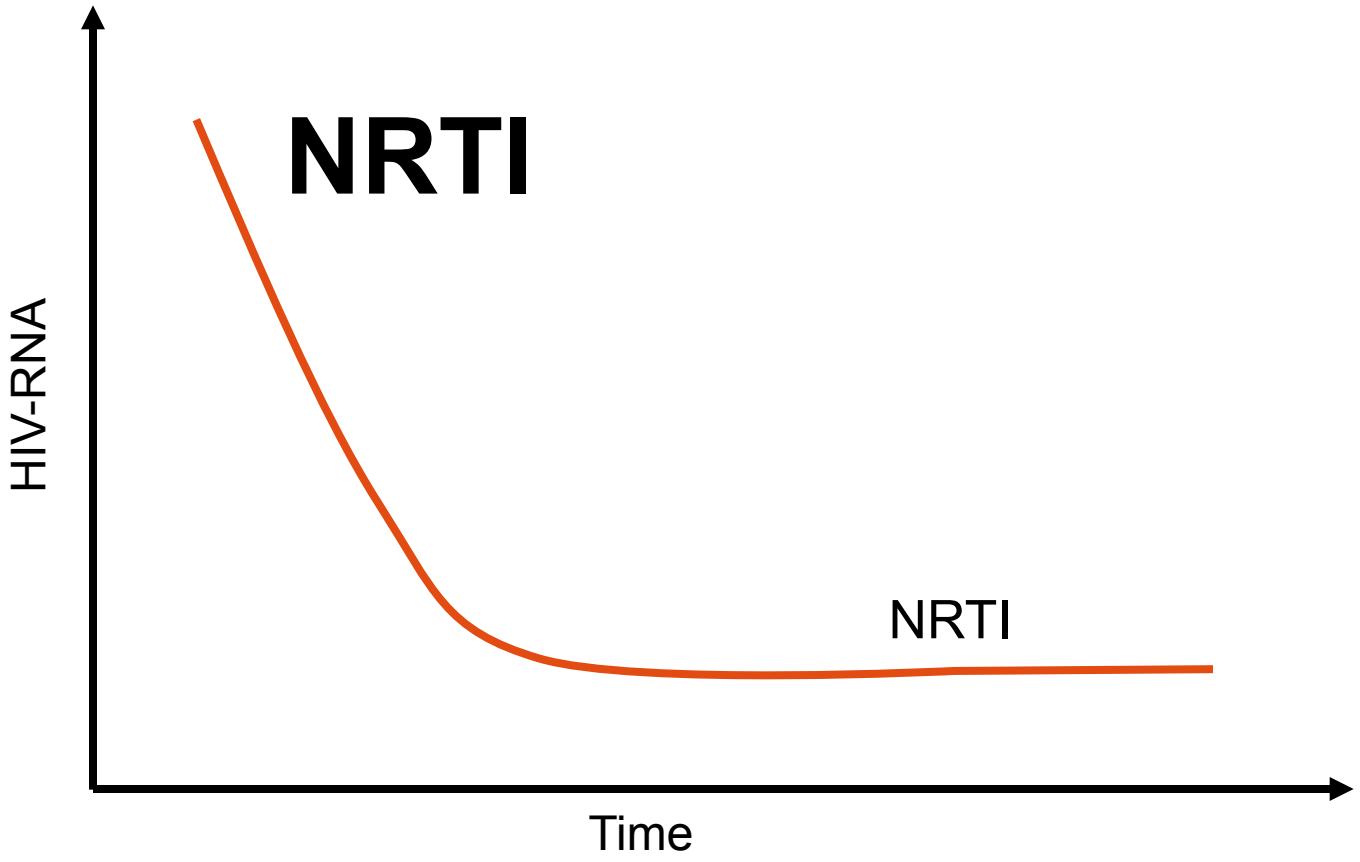
Nukes are particularly valuable at treatment initiation



NRTI remain backbones of 1st line ART

- Dual therapy strategies without NRTI (LPVr/+EFV, **ACTG 5142**[1], IDV+EFV, **DMP-266-006**[2], DRV/r+RAL, **NEAT001**[3] and others did not demonstrate similar efficacy as standard triple ART
- NRTI remain as part of 1st line ART in national and international treatment guidelines
- NRTI-sparing regimens have proven efficacy following treatment failure (**SECOND-LINE** Study (LPV/r+RAL)[4], **EARNEST** Study (LPV/r+RAL)[5] or for treatment switch in succesfully treated patients

1. Riddler S et al. N Engl J Med 2008; 358:2095-2106; 2. Staszewski S et al. 39th ICAAC, September 26-29, 1999, San Francisco; 3. Raffi F et al. Lancet 2014; 384:1942-51; 4. Second Line Sudy Group et al. Lancet. 2013 Jun 15;381(9883):2091-9; 5. Paton N et al. N Engl J Med 2014;371:234-47.

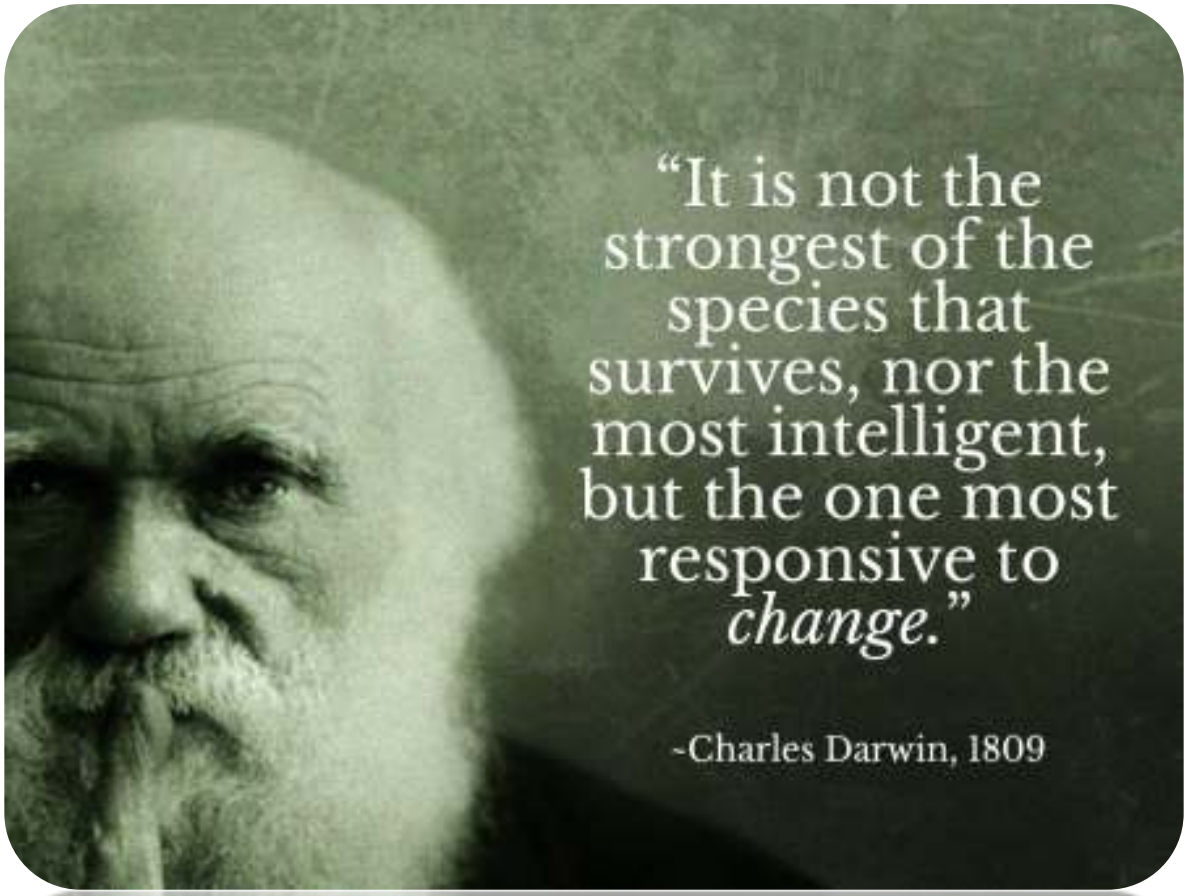
HIV Treatment Guidelines

How are they made?

For whom?

According to which principles?

What do they say?


"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*."
-Charles Darwin, 1809