Switching Therapy and other considerations for Successful Antiretroviral Therapy (ART)

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HIV: a success story

- Suppression of viral load >90% of treated patients
- Immune restoration
- Better ART drugs
- Simplified treatment
- Improved survival
- Transmission reduced

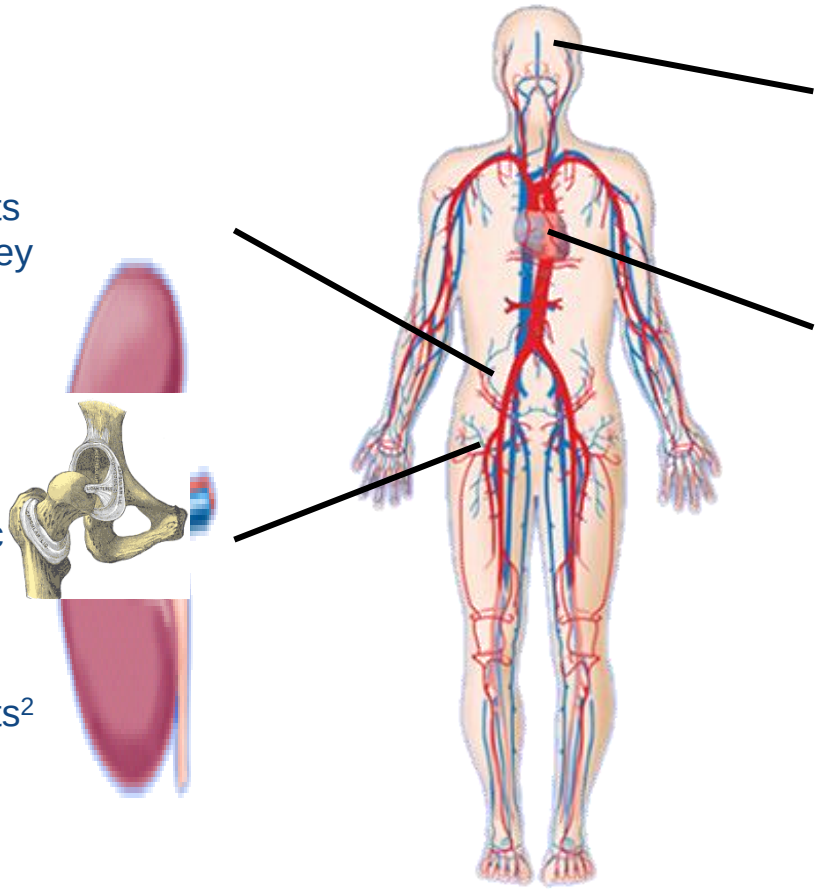
Emerging co-morbidities in HIV

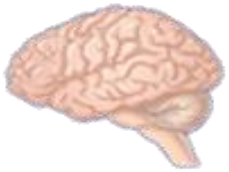
Renal dysfunction

30% of HIV+ patients have abnormal kidney function[1]

Reduced bone mineral density

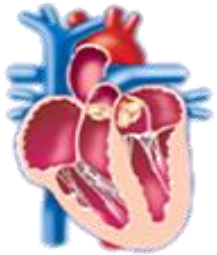
Increased prevalenc of osteoporosis or osteopenia in spine, hip or forearm:
63% of HIV+ patients[2]





Neurocognitive dysfunction

Neurological impairment present in ≥50% HIV+ patients[3]



Cardiovascular disease

75% increase in risk of acute MI[4]

Cancer

Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal[5]

Frailty

Increased frailty phenotype if HIV infected 3-14x; Associated with CD4 count

1. Gupta SK *et al. Clin Infect Dis* 2005;**40**:1559–85.
2. Brown TT *et al. J Clin Endocrinol Metab* 2004;**89**(3):1200–06.
3. Clifford DB. *Top HIV Med* 2008;**16**(2):94–98.
4. Triant VA *et al. J Clin Endocrinol Metab* 2007;**92**:2506–12.
5. Patel P *et al. Ann Intern Med* 2008;**148**:728–36.

Toxicities today

NRTIs

- Mitochondrial toxicity
- Abacavir: hypersensitivity and cardiovascular risk
- Tenofovir: renal and bone

NNRTIs

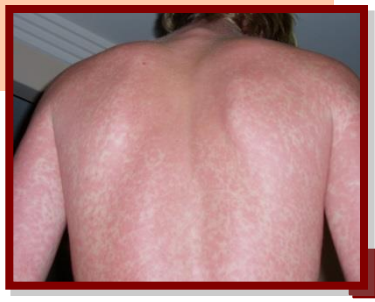
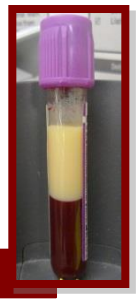
- Rash and hepatotoxicity
- Efavirenz: CNS disturbance

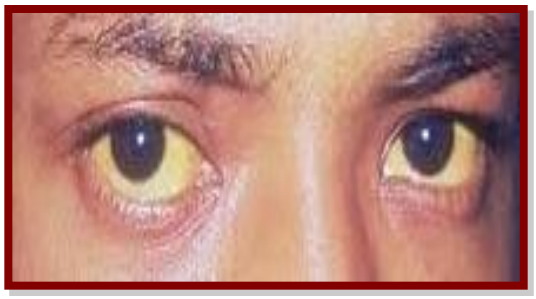
PIs

- GI/metabolic disturbance/ hyperlipidaemia
- Atazanavir: jaundice/ hyper-bilirubinaemia
- Darunavir: rash

INIs

- Myalgia

CNS, central nervous system; GI, gastrointestinal; INI, integrase inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; NRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor. Ziagen eMC Summary of Product Characteristics, October 2013; Viread eMC Summary of Product Characteristics, November 2013; Sustiva eMC Summary of Product Characteristics, June 2013; Reyataz eMC Summary of Product Characteristics, January 2014; Prezista eMC Summary of Product Characteristics, March 2014; Isentress eMC Summary of Product Characteristics, August 2013; Images adapted from: http://commons.wikimedia.org/wiki/File:Jaundice_eye_new.jpg; http://host.web-print-design.com/statspin/lipoclear.htm; http://upload.wikimedia.org/wikipedia/commons/b/bd/Severerash.jpg; http://upload.wikimedia.org/wikipedia/commons/8/8d/Hyperlipidaemia_-_lipid_in_EDTA_tube.jpg

Outline

- Why do patients/clinicians modify therapy?
- How do we monitor patients?
- How do we (safely) switch therapy?

Swiss cohort: reasons for discontinuation of HAART

Patients starting HAART:

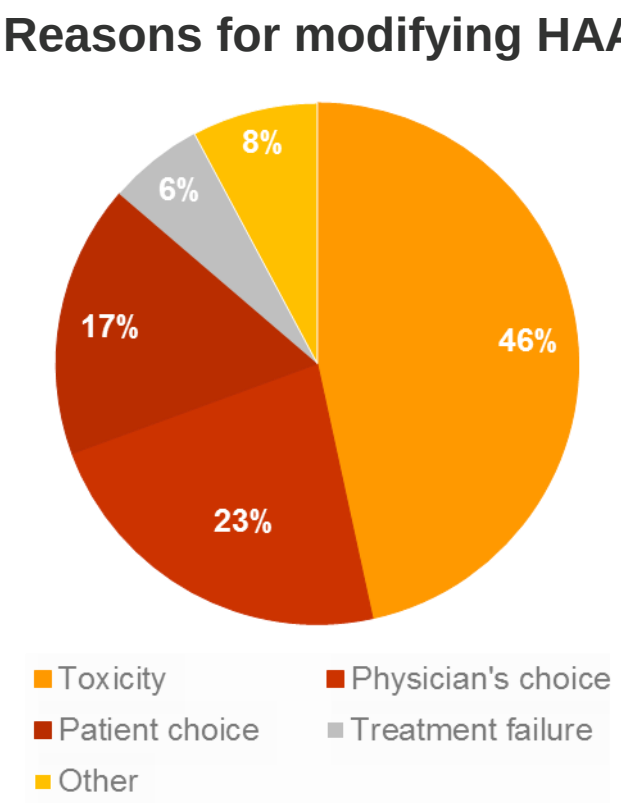
N=1318

Patients modifying HAART within 1 year:

n=391 (29.7%)

Switched:
n=297 (76.0%)

Discontinued for ≥4 weeks:
n=94 (24.0%)



Most frequent toxicities:

- Gastrointestinal intolerance (28.9%)
- Hypersensitivity (18.3%)
- CNS adverse events (17.3%)
- Hepatic events (11.5%)

HAART, Highly active antiretroviral therapy; CNS, central nervous system

Adapted from Elzi, *et al. Arch Intern Med* 2010;**170**:57–65

Why do patients switch therapy?

- Virological failure

Why do patients switch therapy?

- Virological failure
- Toxicity/tolerability
  - REACTIVE ('real' toxicity): after occurrence of an adverse event or a drug-drug interaction
  - PROACTIVE ('potential' toxicity): to avoid an adverse event/ drug interaction
- Simplification: to improve adherence
- 'Potentially better' regimens
- Cost?

Do you consider proactive switching ART in stable patients for possible benefit in terms of potential co-morbidity (e.g. cardiovascular disease?), and when?

In the clinic: Monitoring

- What are we asking the patient about?
- What are we looking for?
- What triggers a switch in ART?
- Don’t always blame the drugs!

Guidelines

DOI: 10.1111/j.1468-1293.2011.00971.x
HIV Medicine (2012), 13, 1–44

BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011

D Asboe, C Aitken, M Boffito, C Booth, P Cane, A Fakoya, AM Geretti, P Kelleher, N Mackie, D Muir, G Murphy, C Orkin, F Post, G Rooney, C Sabin, L Sherr, E Smit, W Tong, A Ustianowski, M Valappil, J Walsh, M Williams and D Yirrell on behalf of the BHIVA Guidelines Subcommittee*
British HIV Association (BHIVA), BHIVA Secretariat, Mediscript Ltd, London, UK

EACS European AIDS Clinical Society

GUIDELINES

Version 7.0
October 2013

Part III

Routine monitoring on ART (1)
(adapted from BHIVA monitoring guidelines 2011)

- History (patient reported outcomes):
  - Tolerability, toxicity
  - Adherence: assess and support
- Targeted physical examination
  - Plus annual weight/BP/BMI
- Investigations
  - Efficacy
  - Safety
- Other assessments
  - CVD risk (annual)
  - Fracture risk (FRAX score 3 yearly) +/- BMD

Routine monitoring on ART (2)
(adapted from BHIVA monitoring guidelines 2011)

- Investigations
  - Efficacy: Viral load and CD4 count
  - Safety:
    - FBC (12 monthly)
    - Creatinine, eGFR, liver function, glucose, bone profile (3-6 monthly)
    - Lipids (6-12 monthly)
    - Urinalysis (all routine visits if on TDF, otherwise 12 monthly)
    - Urine protein:creatinine ratio (uPCR) (12 monthly)

Screening for co-morbidities: EACS guidelines

	Assessment	At HIV diagnosis	Prior to starting cART	Follow up frequency		Comment
				with cART	without cART	
History	• Past and current co-morbidities • Family history (eg premature CVD, diabetes, hypertension, CKD) • Concomitant medications[i] • Current lifestyle (alcohol use, smoking, diet, aerobic exercise	+ + + +	+ + + +	 every visit 6-12 m	 every visit annual	On transfer of care repeat assessment Premature CVD: Cardiovascular events in a first degree relatives: male <55, female <65 years Adverse lifestyle habits should be addressed more frequently
Body composition	• Body-mass index • Clinical lipodystrophy assessment	+ +	+ +	annual annual		Annual assessment on ART only
Cardiovascular disease	• Risk assessment (Framingham score[ii]) • ECG	+ +	+	annual	annual	Should be performed in every older patient without CVD (Men > 40 years; Women >50 yrs)
Hypertension	• Blood pressure	+	+	annual	annual	
Dyslipidaemia	• TC, HDL-c, LDL-c, TG[iii]	+	+	annual		Repeat in fasting state if used for medical intervention (i.e. ≥8h without caloric intake)
Diabetes mellitus	• Serum glucose	+	+	6-12 m		Consider oral glucose tolerance test if repeated fasting glucose levels of 6.1-6.9 mmol/L (110-125 mg/dL)
Liver disease	• Risk assessment[iv] • ALT/AST, ALP	+ +	+ +	annual 3-6 m	annual 6-12 m	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs
Renal disease	• Risk assessment[v] • eGFR (aMDRD)[vi] • Urine Dipstick analysis[vii]	+ + +	+ + +	annual 3-6 m annual	annual 6-12 m annual	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs[viii] Every 6 months if eGFR <60 ml/min; If proteinuria ≥1+ and/or eGFR<60 ml/min perform UP/C or UA/C[viii]
Bone disease	• Risk assessment[ix] FRAX®x in patients >40 years) • 25-OH vitamin D	+ +	+	2 yrs	2 yrs	If not using FRAX®, consider DXA of spine and hip in specific patients Repeat according to risk factors
Neurocognitive impairment	• Questionnaire	+	+	1-2 yrs	1-2 yrs	Perform screening assessment in at risk patients
Depression	• Questionnaire	+	+	1-2 yrs	1-2 yrs	Perform screening assessment in at risk patients
Cancer	• Mammography • Cervical PAP • Others			1-3 yrs 1-3 yrs	1-3 yrs 1-3 yrs	Women 50-70 years Sexually active women, frequency depending on CD4, Controversial

EACS guidelines, 2009

Routine monitoring – discussion points

- Little evidence around optimal frequency of monitoring
- Should monitoring frequency depend on the drugs used?
- What to do with fluctuating values?
- Cost implications of monitoring

Virtual clinic (St Mary's) May-July 2014

- 67 patients discussed in 3 month period
- 39/67 (58%) 'undetectable' viral load on ART
- Reasons for discussion
  - Simplification (38%)
  - Renal dysfunction (19%)
  - CNS/neurocognitive impairment (13%)
  - GI/liver (8%)
  - Potential interaction (5%)
  - CV/lipids (5%)
  - Lipoatrophy (2%)
  - Other (10%)

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  - Other including **bone** (10%)

Renal

HIV and the kidney

- Mild abnormalities very common
- Several ARV associated with a higher risk of renal impairment (tenofovir, atazanavir, indinavir)
- Usually multi-factorial
  - Co-morbidities?
  - Other drugs? It's not always tenofovir!
- 2 urgent situations:
  - Fanconi's syndrome (severe proximal tubule dysfunction)
  - Acute or chronic kidney injury requiring ARV dose adjustments

How do we measure renal function?

- Creatinine
  - Dependent on skeletal muscle mass
- Creatinine-based formulae
  - Cockroft Gault
  - Modification of Diet in Renal Disease (MDRD)
- Urine
  - Proteinuria (uPCR vs uACR)
- Other blood markers
  - Phosphate

Impact of tenofovir (TDF) on renal function (1)

- **Increased creatinine**
  - Filtered by glomerulus (TDF probably not glomerulo-toxic)
  - Smaller amounts secreted across proximal tubule
    - Proximal tubule injury may cause modest eGFR changes
  - TDF causes small, non-progressive increase in creatinine
  - More common in real life than trials but moderate/severe increases uncommon (2.2%/0.6% in one cohort[1])

1. Nelson MR et al. AIDS 2007

Impact of TDF on renal function (2)

- **Proximal tubule (PT) dysfunction**
  - Main target of TDF nephrotoxicity: ‘leaky kidneys’
  - Most severe = Fanconi’s syndrome or acute renal injury
  - Urine protein key marker
- **Distal tubule dysfunction (nephrogenic DI)**
- **Phosphate leak**
  - TDF can increase urinary phosphate excretion
  - Can lead to osteomalacia
  - PT handling of phosphate very sensitive to mitochondrial toxicity

HIV drugs that increase creatinine

- Tenofovir
- Rilpivirine
- Ritonavir
- Cobicistat
- Dolutegravir

Fanconi's syndrome

- TDF and proximal tubule dysfunction
- eGFR and proteinuria assessment routine
- 3 essential features of Fanconi's
  - Proteinuria
  - Glycosuria
  - Hypophosphataemia
- Hypophosphataemia in a well patient with normal urine is NOT an emergency

BHIVA monitoring guidelines 2011 (1)

- **Baseline:**
  - eGFR, urine dip + UPCR
- **During clinical follow-up:**
- **Not on ART**
  - eGFR, urine dip + UPCR (annual)
- **On ART (not TDF)**
  - eGFR, urine dip + UPCR (annual)
- **On ART-containing TDF**
  - eGFR, urine dip + UPCR (all routine visits; 3-4x/yr)
  - Serum phosphate (all routine visits; 3-4x/yr; fasting if low)
  - More frequently if progressive decline in eGFR or persistent severe hypophosphataemia

BHIVA monitoring guidelines 2011 (2)

- Check concomitant medication
- Care with drug doses in renal impairment
- Manage BP, glucose, lipids
- HIVAN will improve on any HAART
- Renal referral / joint clinics

BHIVA monitoring guidelines 2011

- When to stop TDF?
  - New onset or worsening proteinuria and/or glycosuria may indicate tubular injury
  - Monitor carefully
  - If abnormalities persist:
    - Additional biochemistry including fasting serum/urine phosphate
    - Additional investigations
    - Discontinue TDF and/or refer to nephrology

Bone

Prevalence of Reduced BMD Higher in HIV+ than HIV- Subjects

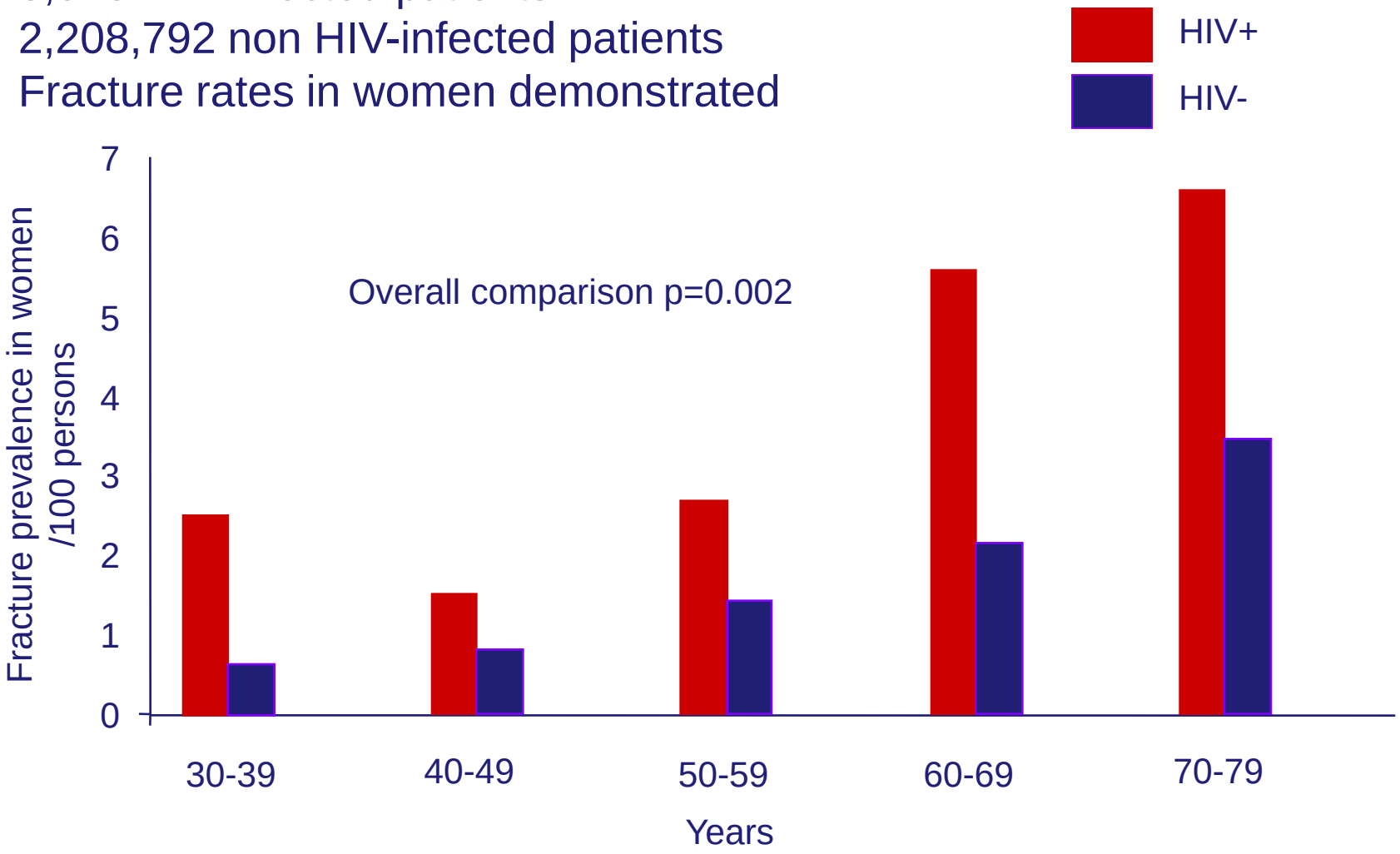
Publication	Number of patients		Overall prevalence of reduced BMD, %	
	HIV+	HIV–	HIV+	HIV–
Amiel *et al* 2004	148	81	82.5	35.8
Brown *et al* 2004	51	22	63	32
Bruera *et al* 2003	111	31	64.8	13
Dolan *et al* 2004	84	63	63	35
Huang *et al* 2002	15	9	66.6	11
Knobel *et al* 2001	80	100	87.5	30
Loiseau-Peres *et al* 2002	47	47	68	34
Madeddu *et al* 2004	172	64	59.3	7.8
Tebas *et al* 2000	95	17	40	29
Teichman *et al* 2003	50	50	76	4
Yin *et al* 2005	31	186	77.4	56

Brown et al, AIDS 2006

Derived from Brown TT & Qaqish RB. *AIDS* 2006; **20:**2165-2174

Fractures are more common in HIV+ patients

Healthcare Registry study
8,525 HIV-infected patients
2,208,792 non HIV-infected patients
Fracture rates in women demonstrated



Triant VA et al, JCEM 2008;93:3499-3504

Potential causes of low BMD

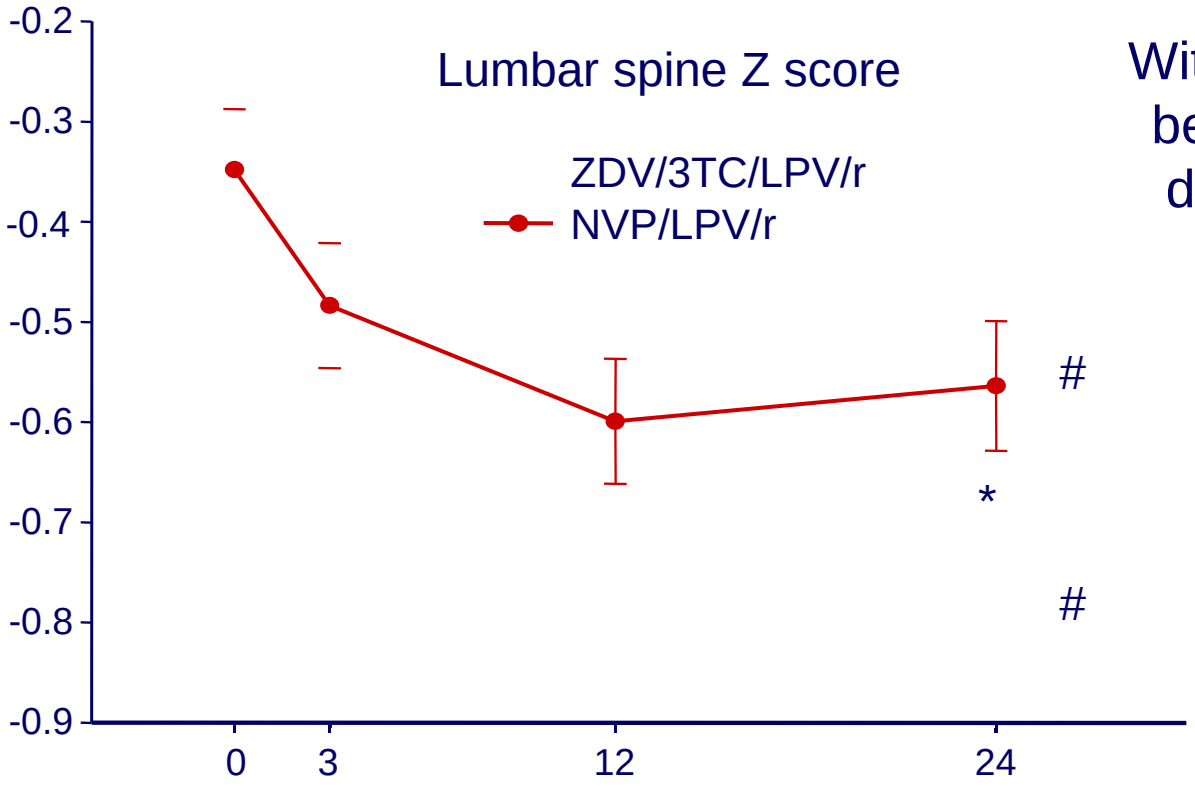
- HIV infection*
- Traditional osteoporosis risk factors (poor nutrition, low weight, physical inactivity)
- High rates smoking and alcohol/opiate use
- Low Vit D levels
- Antiretroviral therapy

*ART-naïve subjects also have high prevalence of osteopenia –

?effect of uncontrolled viraemia and systemic inflammation on bone remodelling

ART initiation is associated with bone loss

Greater loss in BMD with ART containing NRTI



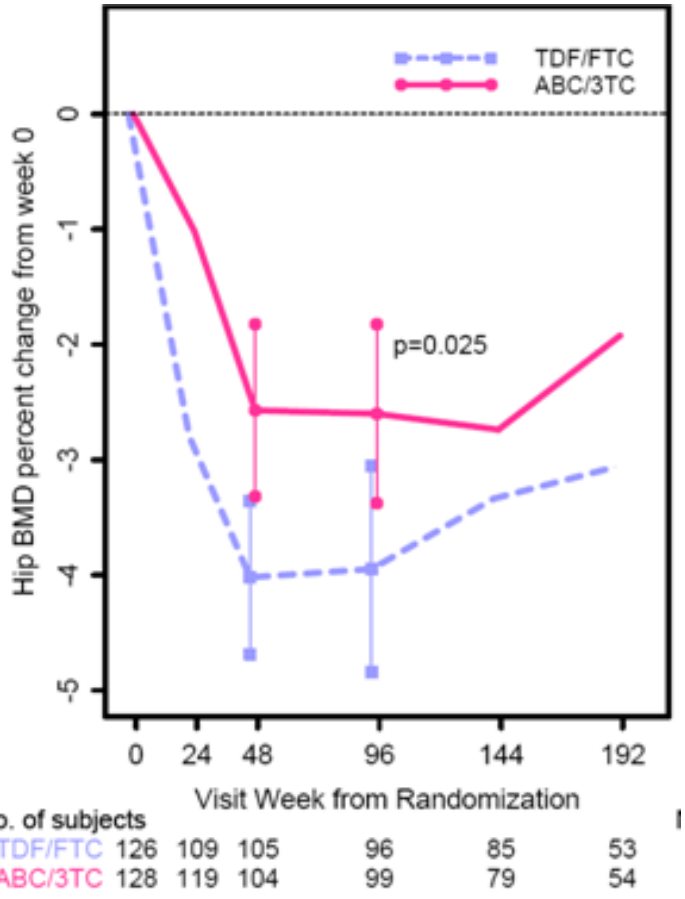
Within group and between-group differences all $P<0.05$

- Changes in BMD accompanied by increases in markers of bone turnover

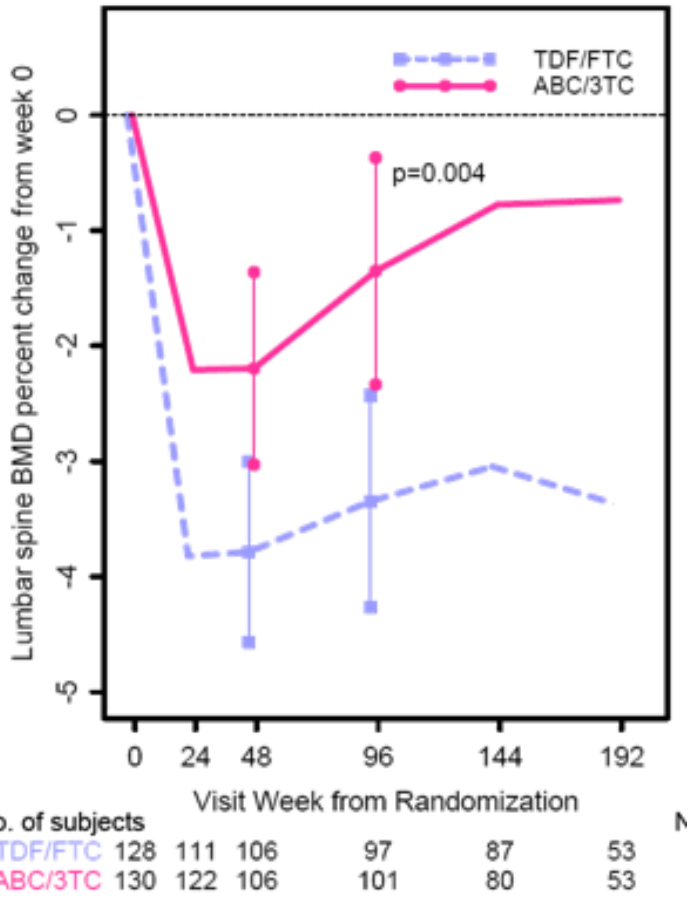
von Voderen M. et al. AIDS 2009; 23(11): 1367-1376

ART and bone loss - ABC/3TC vs TDF/FTC

Hip



Lumbar Spine



McComsey GA et al. CROI 2010

BMD monitoring: BHIVA 2011

- Assess risk factors for reduced BMD at diagnosis and prior to ART
- Reas… 3 years
- BMD …
  - All r…
  - All w…
  - Con… e to high FRAX scor…
- Biochemi… markers (calcium, phosphate, alkalin… phosphatase) have limited use as screening tools for reduced BMD

Conservative approach compared with EACS who recommend DXA in all postmenopausal women and men ≥ 50 years

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: Date of birth: Y: M: D:
2. Sex Male Female
3. Weight (kg)
4. Height (cm)
5. Previous fracture No Yes
6. Parent fractured hip No Yes
7. Current smoking No Yes
8. Glucocorticoids No Yes
9. Rheumatoid arthritis No Yes
10. Secondary osteoporosis No Yes
11. Alcohol 3 or more units per day No Yes
12. Femoral neck BMD (g/cm²)
    Select DXA

Clear Calculate

Weight Conversion

Pounds → Kgs

Convert

Height Conversion

Inches → Cms

Convert

www.nos.org.uk

National Osteoporosis Society

Having trouble with the FRAX tool?

If you experience any problems with the FRAX tool please upgrade your version of Adobe Flash. Click here to upgrade.

Should we switch ART?

- Little evidence to suggest switching will improve BMD and decrease fracture risk
- ?some data suggesting discontinuing TDF associated with improvements in BMD (Bloch HIV med 2014)
- ??preliminary data suggesting TDF-associated BMD reductions may translate into increased fracture risk (Bedimo AIDS 2012)

When to stop TDF – EACS version 7.0 (2013)

- Recommend DXA, vitamin D and PTH if patients on TDF with hypophosphateamia and phosphaturia
- **Consider stopping TDF if:**
  - Progressive eGFR decline; no other cause found
  - Confirmed significant hypophosphateamia of renal origin; no other cause found
  - Significant osteopenia ***in the presence of*** phosphaturia/renal tubulopathy

Central nervous system (CNS)

HIV and the CNS

- Persistent CNS side effects related to ART, particularly efavirenz
- HIV associated neurocognitive disorders (HAND)

CNS adverse events

- Central Nervous System (CNS) adverse events (AE) are common on EFV based regimens
- Many CNS AE are transient
- BUT a significant proportion of individuals experience on-going CNS AE

UK cohort studies of efavirenz

- Brighton[1]
  - Bimodal discontinuation of efavirenz
    - 39% discontinued EFV (59% due to AE)
    - 12% in first 6 weeks
    - 47% 6 weeks–12 months
    - 41% >12 months
- Chelsea and Westminster[2]
  - 71% switched therapy due to CNS AEs
    - 10% in first 4 weeks
    - 6% in first 3 months
    - 48% 3–12 months
    - 36% > 12 months

Zhou et al, HIV Medicine 2011; Scourfield et al, AIDS 2012

CNS

- Central Nervous System (CNS) adverse events (AE) are common on EFV based regimens
- Many CNS AE are transient
- BUT a significant proportion of individuals experience on-going CNS AE
- Differentiating drug AE from other causes of CNS problems can be difficult
- Remember to ask about other drugs including alcohol and recreational drugs

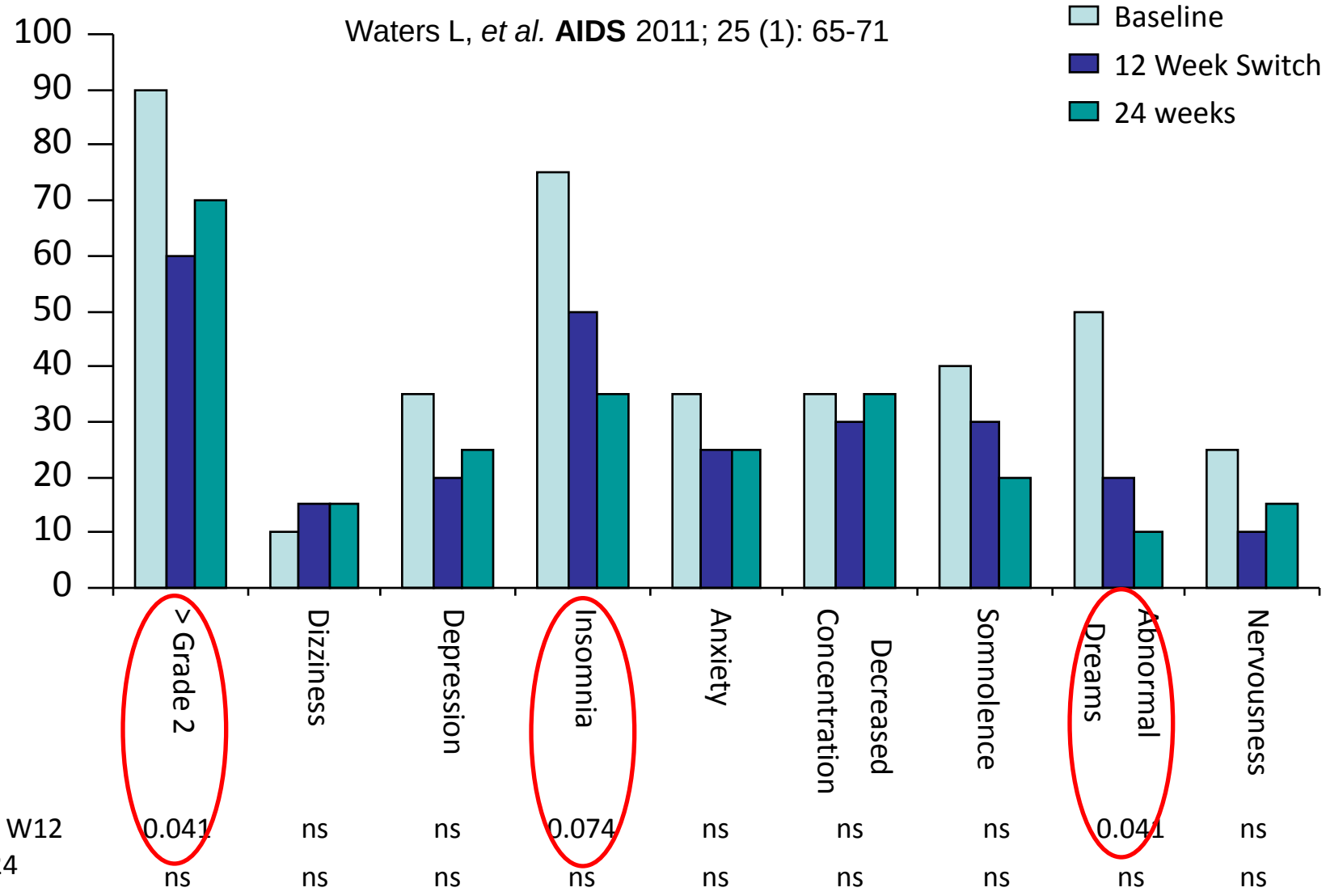
Switching from efavirenz

- Concerns re enzyme induction
- Few good studies to guide clinical practice
- Early toxicity switch when still detectable VL
  - Switch to bPI recommended
- Switch when VL<50
  - Nevirapine[1]:
    - packet insert recommends dose escalation. BHIVA also endorses switch to full dose[2, 3]
  - bPI/raltegravir/etravirine/rilpivirine[4]:
    - Straightforward switch

[1]Ward et al AIDS Patient Care STDS 2006; [2]Winston *et al* AIDS 2004; [3]Laureillard *et al* HIV Med 2008; [4]Crauwels *et al* CROI 2011

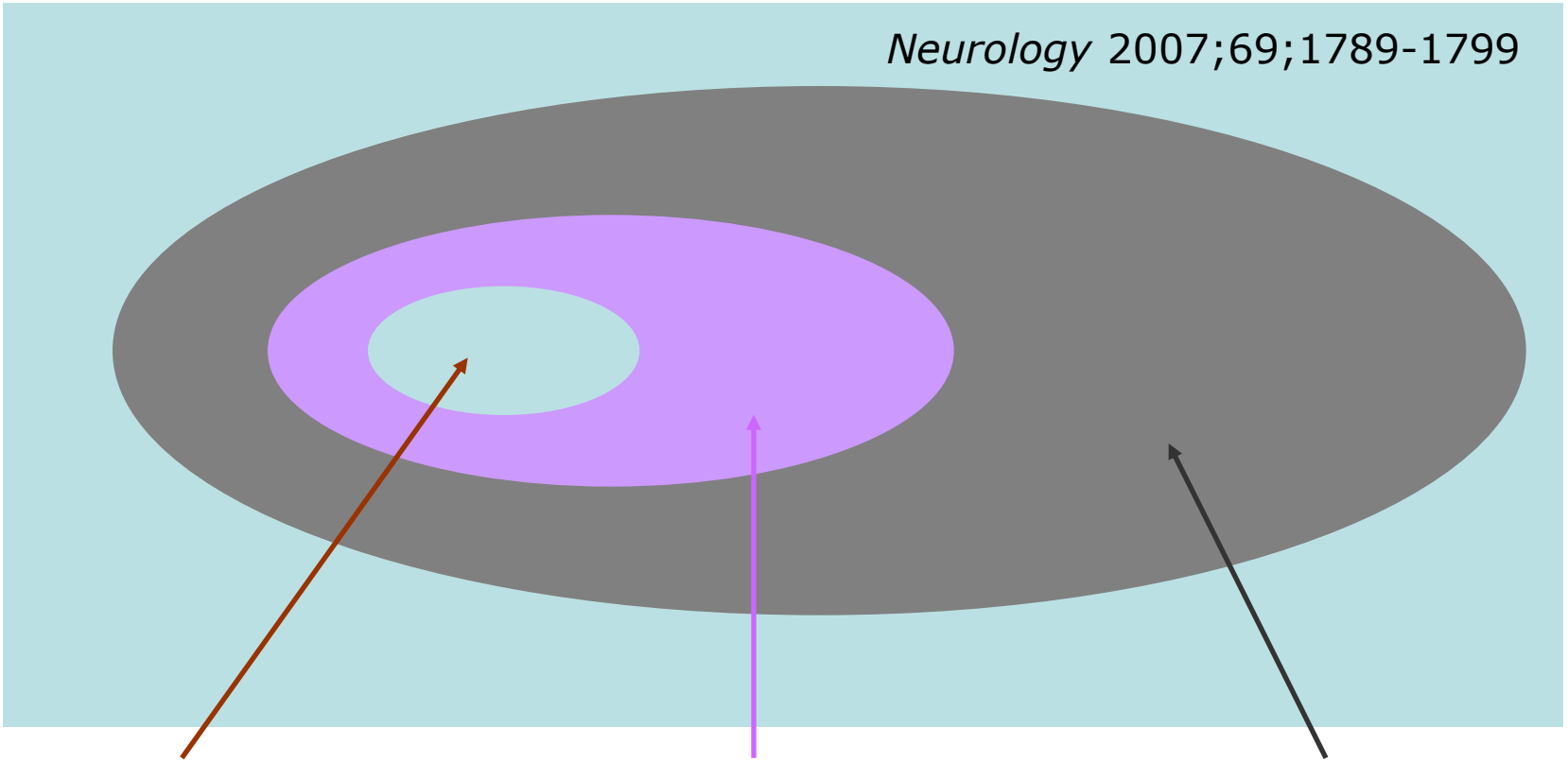
A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine

Waters L, *et al.* **AIDS** 2011; 25 (1): 65-71



	> Grade 2	Dizziness	Depression	Insomnia	Anxiety	Concentration Decreased	Somnolence	Abnormal Dreams	Nervousness
Baseline to W12	0.041	ns	ns	0.074	ns	ns	ns	0.041	ns
W12 to W24	ns	ns	ns	ns	ns	ns	ns	ns	ns

HIV associated neurocognitive disorders (HAND)



HAD (HIV associated dementia)

- ***Marked interference with daily life***

Symptomatic NCI (neurocognitive impairment)

- ***interferes with daily life***

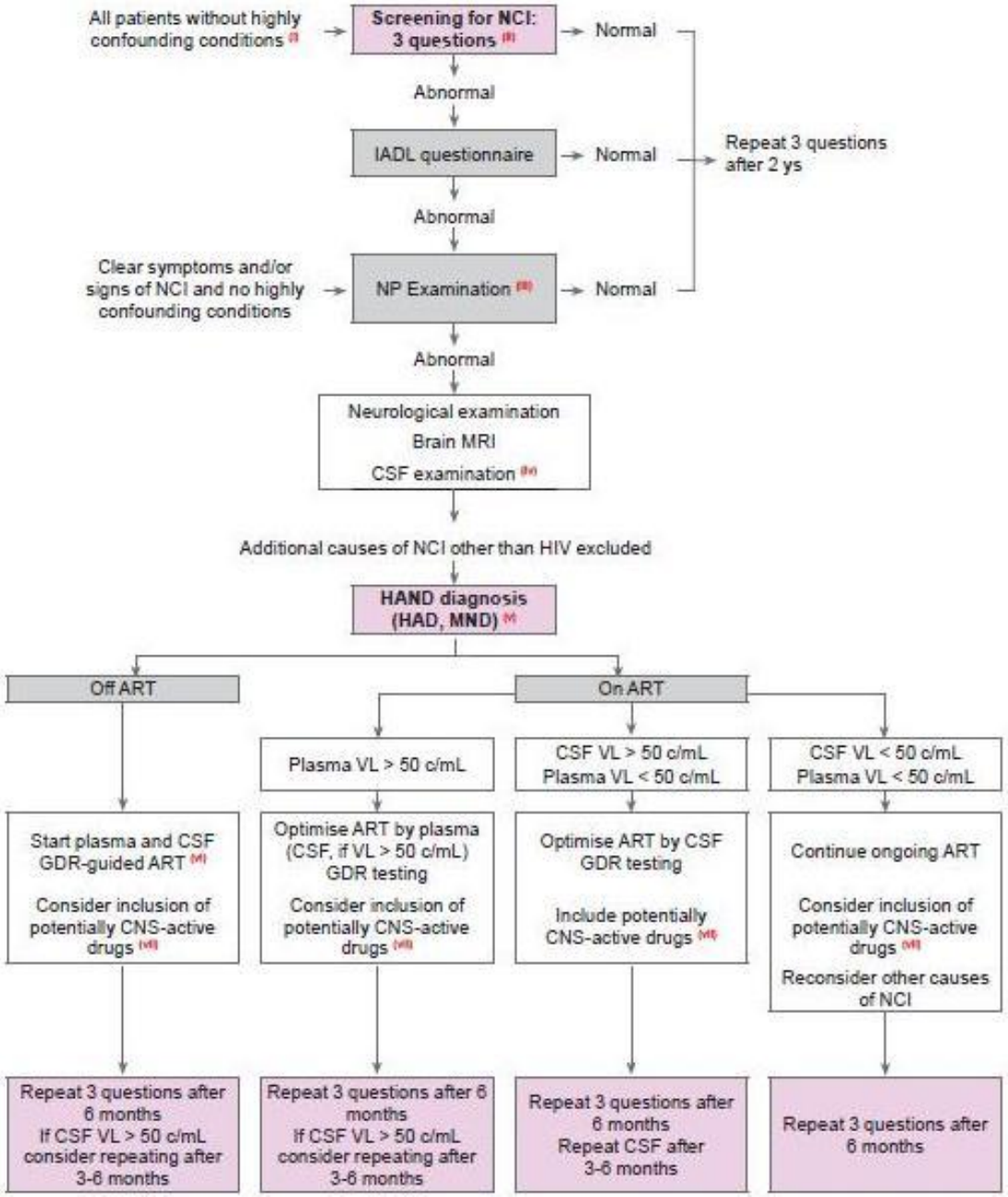
Asymptomatic NCI

- ***does not interfere with daily life***

HIV associated neurocognitive impairment (BHIVA 2013)

- Start ART (any CD4) if symptomatic HIV-associated neurocognitive disorders
- Suggest avoidance of PI monotherapy in neurologically symptomatic patients
- Ongoing or worsening NC impairment despite ART
  - re-assessment for confounding conditions
  - assessment of CSF HIV RNA with genotyping
  - modifications to ART should be based on plasma and CSF genotypic results

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)



EACS 2013 Guidelines – algorithm for NCI

3 screening questions (ref. Simioni et al., AIDS 2009)

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?

2. Do you feel that you are slower when reasoning, planning activities, or solving problems?

3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely.
Patients are considered to have an "abnormal" result when answering "yes, definitely" on at least one question.

Highly confounding conditions
1. Severe psychiatric conditions
2. Abuse of psychotropic drugs
3. Alcohol abuse
4. Sequelae from previous CNS-OIs or other neurological diseases
5. Current CNS-OIs or other neurological diseases

What to switch to – general principles

Considerations in switching ART

- ***'do no harm'***

- Patient preference and clear discussion

Considerations in switching ART

Table 1. Switching and simplifying antiretroviral therapy in a patient with controlled HIV replication.

Treatment Aspect	Potential Advantages of Switching or Simplification	Potential Disadvantages of Switching or Simplification
Efficacy	Improved d	irological control
Pill burden	Reduce (improve	doses or number
Toxicity	Prevent	ew drug may be greater than toxicity of existing rugs have less long-term safety data than older
		not reverse
		ay be less effective than other approaches, e.g., ypercholesterolaemia, smoking cessation for ar risk
Drug interactions	Prevent	new interaction
Co-morbid disease	Prevent	eraction, e.g., lipid increase in patient with cular disease
Pregnancy	Prevent toxicity to	New toxicity to mother or foetus
Costs	Reduce costs f improve community coverage with same re expenditure	Increase costs because of greater virological failure, toxicity with new therapy
		Future market prices may change
Confidentiality	Improve confidentiality by not requiring pill refrigeration or dosing at work	
Treatment options	Enable use of a drug previously avoided because concerns about medication safety or efficacy no longer apply	Reduce future options—the number of new HIV drugs in clinical development is small and reducing
Pharmacy	Lower pharmacy costs	Patient takes the wrong dose or pills
		Pharmacy prescribes the wrong agent
		Forgotten drug interactions or superimposed toxicities

"maintain virological suppression"

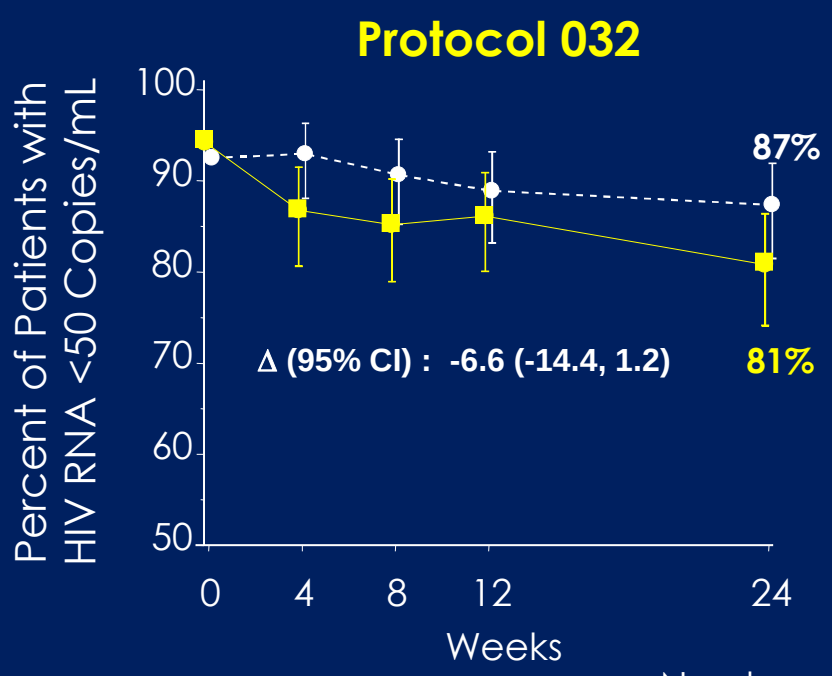
Carr *et al*. PLoS Medicine 2012; 9(7): 1-4

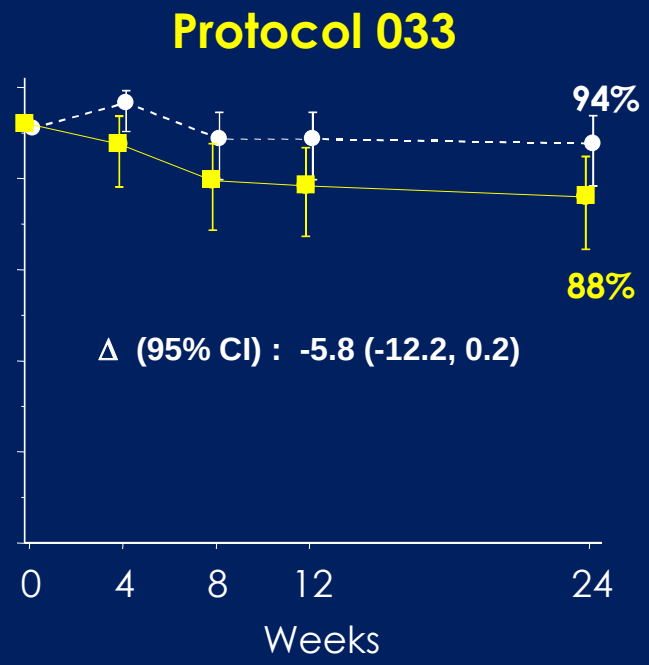
SWITCHMRK 1 and 2 (P032 & 033) Study Design

- Identical, multicenter, double-blind, randomized, active-controlled studies
- Study population
  - Well controlled on a stable LPV/r regimen (b.i.d.) in combination with at least 2 NRTIs (and no other active PI) for ≥ 3 months
    - HIV RNA <50 copies/mL (US PCR) or <75 copies/mL (bDNA)
    - Patients were not required to be intolerant of LPV/r
    - Patients with prior virologic failure were not excluded
      - No limit on number of prior ART regimens
  - No lipid lowering therapy for at least 12 weeks
- Randomized (1:1) to continue LPV/r or switch to RAL

NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor

Protocols 032, 033
Percent of Patients (95% CI) With HIV RNA <50 Copies/mL (NC = F)





Number of Contributing Patients

RAL + ARTs	174	166	169	173	172	176	176	176	176	175
LPV/r + ARTs	174	171	171	171	174	178	178	177	177	178

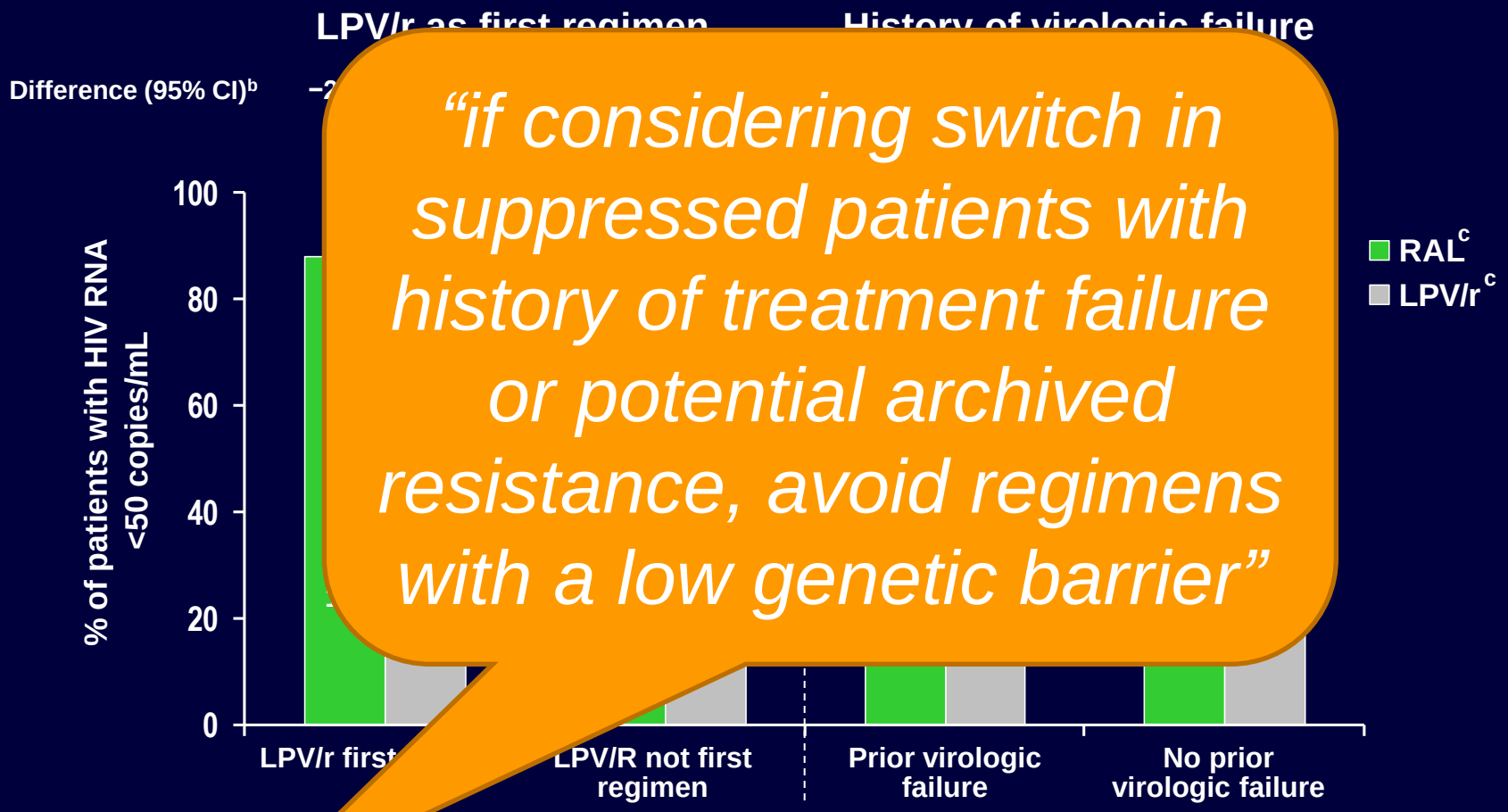
In P032,

- 149 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 134/149 (90%) remained suppressed (< 50 copies/mL) at Week 24.
- 152 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 145/152 (95%) remained suppressed (< 50 copies/mL) at Week 24.

In P033,

- 157 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 148/157 (94%) remained suppressed (< 50 copies/mL) at Week 24.
- 167 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 161/167 (96%) remained suppressed (< 50 copies/mL) at Week 24.

Efficacy at 24 Weeks: Subgroup analysis – SWITCHMRK-1 and -2 combined data1[a]



"if considering switch in suppressed patients with history of treatment failure or potential archived resistance, avoid regimens with a low genetic barrier"

CI = confidence interval; LPV/r = lopinavir/ritonavir; RAL = raltegravir.
[a]All patients who did not complete the study were regarded as failures.
[b]Calculated by the method of Miettinen and Nurminen.
[c]Plus existing baseline regimen.

2. Eron JJ et al. Lancet. 2010; Vol. 375, No. 9712 pp 396-407.

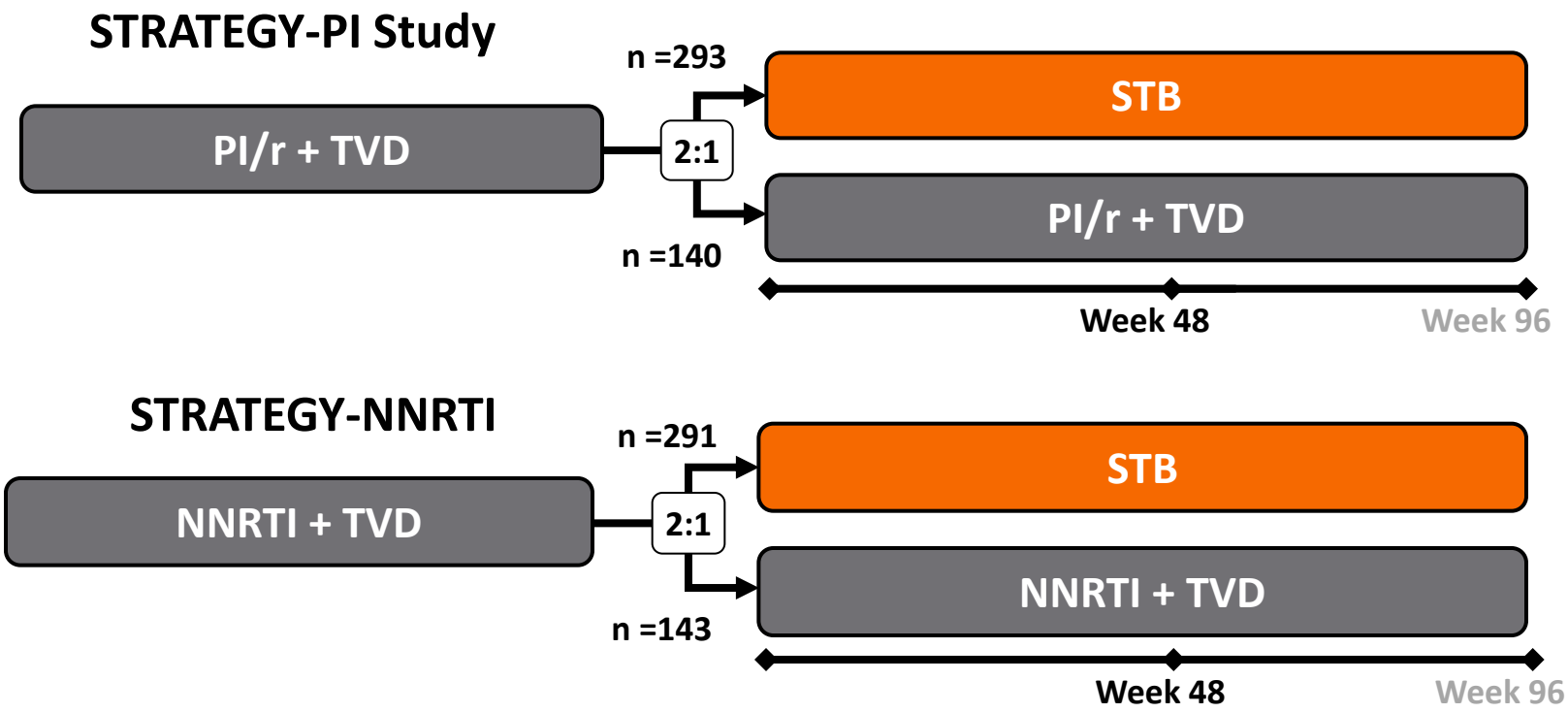
"What to switch to will be dependent on the reason for the switch"

How to switch and with what

- Virological failure
  - Based upon resistance testing
  - Ideally 3 drugs that are effective, at least 1 new class
- Toxicity
  - Switch within class: if drug-specific
  - Switch between class: if class-specific
- Potential drug-drug interactions
  - Dependent upon interaction
- Better treatment options
  - New agents/formulations with better tolerability/toxicity/adherence profile

Switch studies

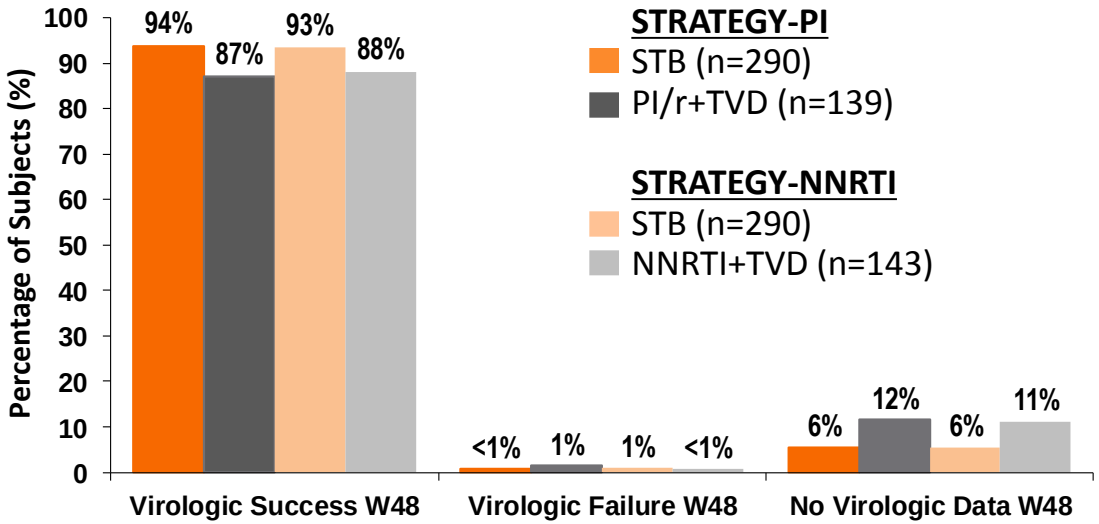
Study Design

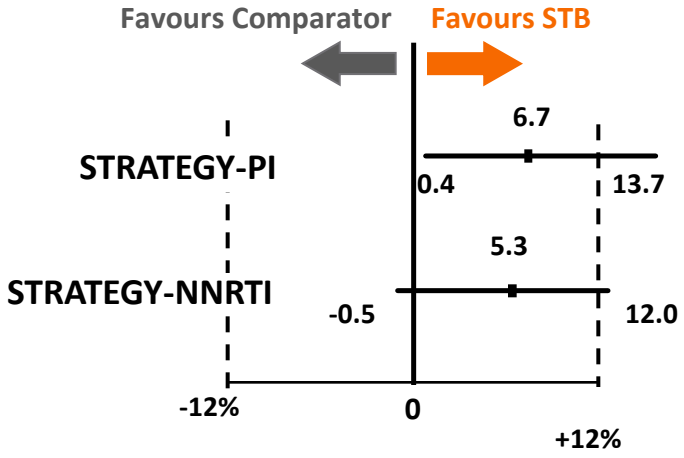


STB = Stribild® = EVG/COBI/FTC/TDF
TVD = Truvada® = FTC/TDF

Mills A, et al. IAC 2014. Melbourne, Australia. #WEPE092

Primary Endpoint: HIV-1 RNA < 50 c/mL





	STRATEGY-PI		STRATEGY-NNRTI	
CD4 Cell Count (cells/mm³)	STB	PI/r+TVD	STB	NNRTI+ TVD
Baseline (mean)	603	625	586	593
ΔWeek 48 (mean)	+40	+32	+56	+58
P-value (Δ W48-BL)	<0.001	0.025	<0.001	<0.001

In STRATEGY-PI, pre-specified sequential testing demonstrated statistical superiority (p = 0.025)

- Driven by a higher rate of discontinuation in the PI group due to non-virologic reasons

No subject in either treatment arm developed treatment-emergent resistance

Mills A, et al. IAC 2014. Melbourne, Australia. #WEPE092

Conclusions

Switching to STB from PI/r+TVD or NNRTI+TVD at Week 48:

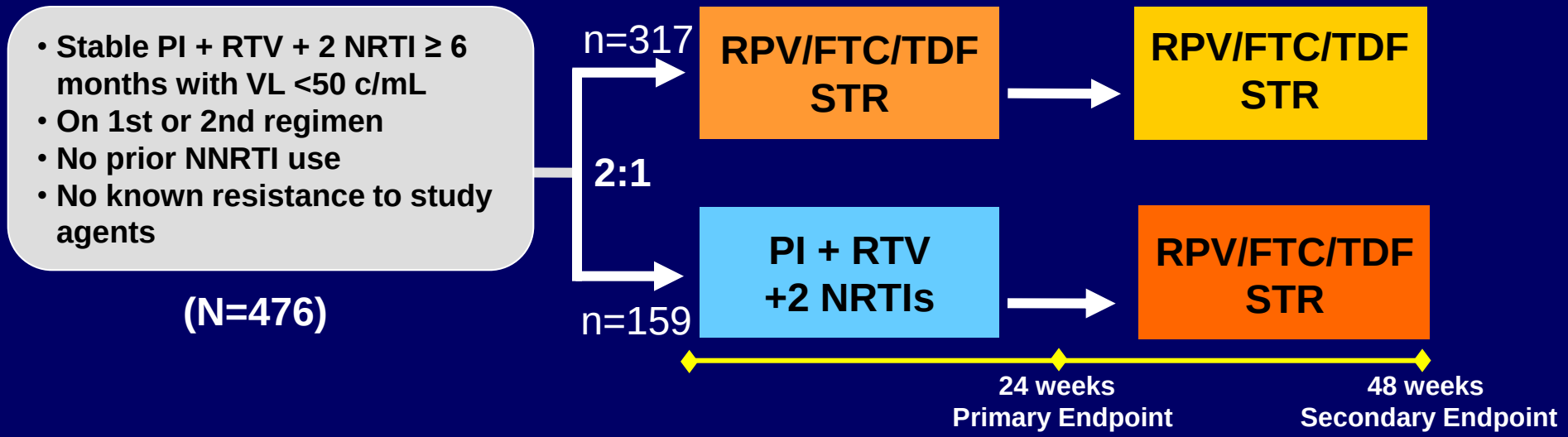
- STB was non-inferior in maintaining virologic suppression
  - 94% STB (statistically superior) vs. 87% PI/r+TVD
  - 93% STB vs. 88% NNRTI+TVD
- No treatment-emergent resistance after switching to STB
- STB was well-tolerated with adverse events consistent with known safety profile
  - Adverse events leading to discontinuation were uncommon
  - Rates of investigator-reported AEs were similar between STB and PI/r+TVD; and higher rates of headache and nausea were reported in the STB compared to NNRTI+TVD group
  - Patient-reported symptoms of diarrhoea and bloating symptoms were lower after switching to STB from an PI/r+TVD regimen and lower rates of neuropsychiatric symptoms were reported in those who switched from an EFV-based regimen
  - Changes in SCr and CrCl were small and non-progressive; consistent with the known cobicistat inhibition of MATE-1 transporters, which mediate renal creatinine secretion

Mills A, et al. IAC 2014. Melbourne, Australia. #WEPE092

GS-264-106: SPIRIT

Study Design

Switching boosted PI to Rilpivirine In-combination with Truvada as a STR
Multicenter, international, randomized, open-label, Phase 3b, 48-week study



Primary Endpoint: Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks[2]

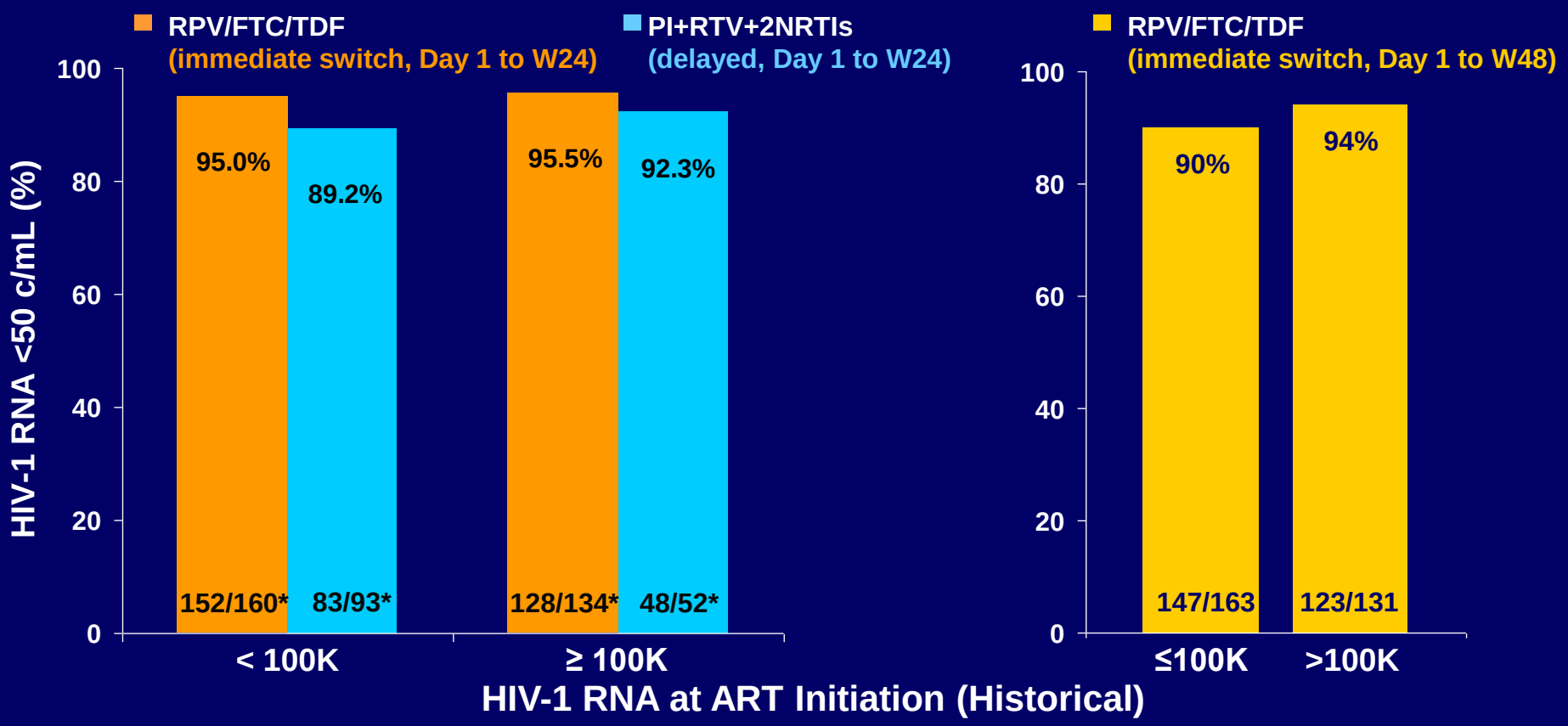
Secondary Endpoints: Proportion of subjects who have HIV1 RNA <50 copies/mL (missing=excluded) through Week 48, change in fasting lipid parameters and CD4 cell count at 24[2,3] and 48[1] weeks, safety and tolerability to PI+RTV+2NRTIs at 24[2,3] and 48[1] weeks

Adherence & Patient Reported Outcomes: Visual Analog Scale Adherence, HIV Symptom Index and HIV Treatment Satisfaction Questionnaire[3]

Ad Hoc Analysis: Outcome at 24 weeks for patients with pre-existing resistance mutations[4]

1. Fisher, M, et al. HIV-11 2012. Glasgow, UK. #P285
2. Palella F, et al. IAC 2012. Washington, DC. Oral #TUAB0104
3. Tebas P, et al. LIPO 2012. Washington, DC. #018
4. White K, et al. IHDRW 2012. Stiges, Spain. #P49

Week 24 and 48 Virologic Suppression (Snapshot Analysis) Stratified by HIV-1 RNA at ART Initiation



Switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs regardless of HIV-1 RNA while ARV naïve (a post-hoc analysis)

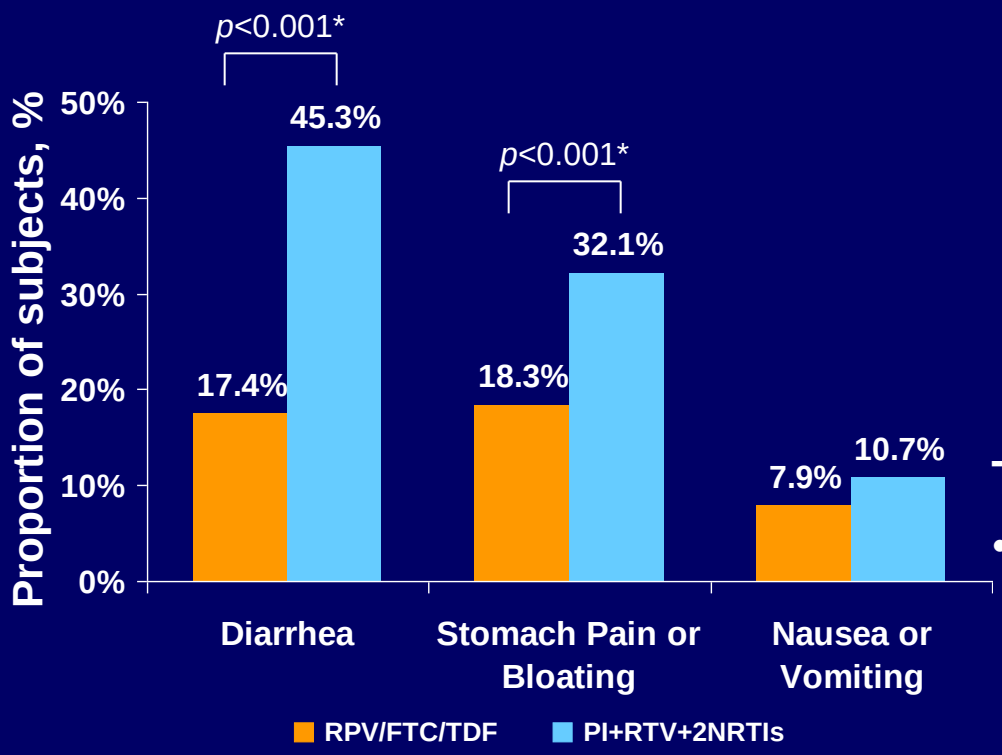
*23 (8%) RPV/FTC/TDF and 14 (9%) PI+RTV+2NRTI subjects were excluded from this analysis due to unavailable HIV-1 RNA while ARV naive

1. Palella F, et al. IAC 2012; Washington, DC. Oral TUAB0104
2. Data on file, Gilead Sciences, Inc.

SPIRIT

Patient Reported Outcomes at Week 24

Gastrointestinal Symptom



HIV Symptom Index

- Subjects that switched to RPV/FTC/TDF were significantly less likely to report the following symptoms compared to baseline:
  - Fatigue (p=0.002)
  - Memory loss (p=0.022)
  - Headache (p=0.003)
  - Depression (p<0.001)

Treatment Satisfaction Questionnaire

- Reported higher satisfaction with their treatment regimen by HIV-TSQ than those who stayed on PI+RTV+2NRTIs (p<0.001†)

* *P*-value for comparison between treatment groups at Week 24 using Chi-square

† *P*-value for comparison between treatment groups at Week 24 from ANCOVA
HIV TSQ: HIV Treatment Satisfaction Questionnaire

Tebas P, et al. LIPO 2012. Washington, DC. #018

Novel strategies

PI monotherapy – BHIVA guidelines (2013)

- Recommend against the use of protease inhibitor monotherapy as **initial therapy** for treatment-naïve patients*. (1C)

However as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

***Same applies to PI based dual therapy**

PI monotherapy – BHIVA guidelines (2013)

- Recommend continuing standard combination ART as the **maintenance strategy** in virologically suppressed patients (1C)

No significant clinical benefit of PI monotherapy vs standard cART, which might offset the disadvantage of a lower rate of viral suppression with PI monotherapy. For this reason PI monotherapy should not be used in unselected patient populations

PI monotherapy – EACS guidelines (2013)

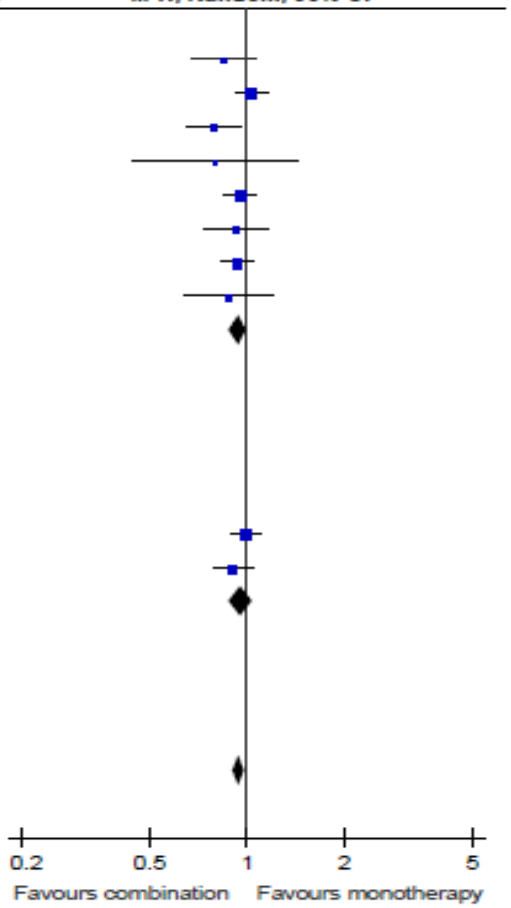
- PI/r monotherapy with od DRV/r or bd LPV/r might represent an option for:
  - Persons with intolerance to NRTIs
  - Treatment simplification
- This only applies to:
  - those without a history of failure on prior PI-based therapy
  - VL<50 cp/ml for ≥ 6 months
  - Those who do not have hepatitis B

PI monotherapy

Forest plots for comparisons of PI monotherapy versus combination therapy.

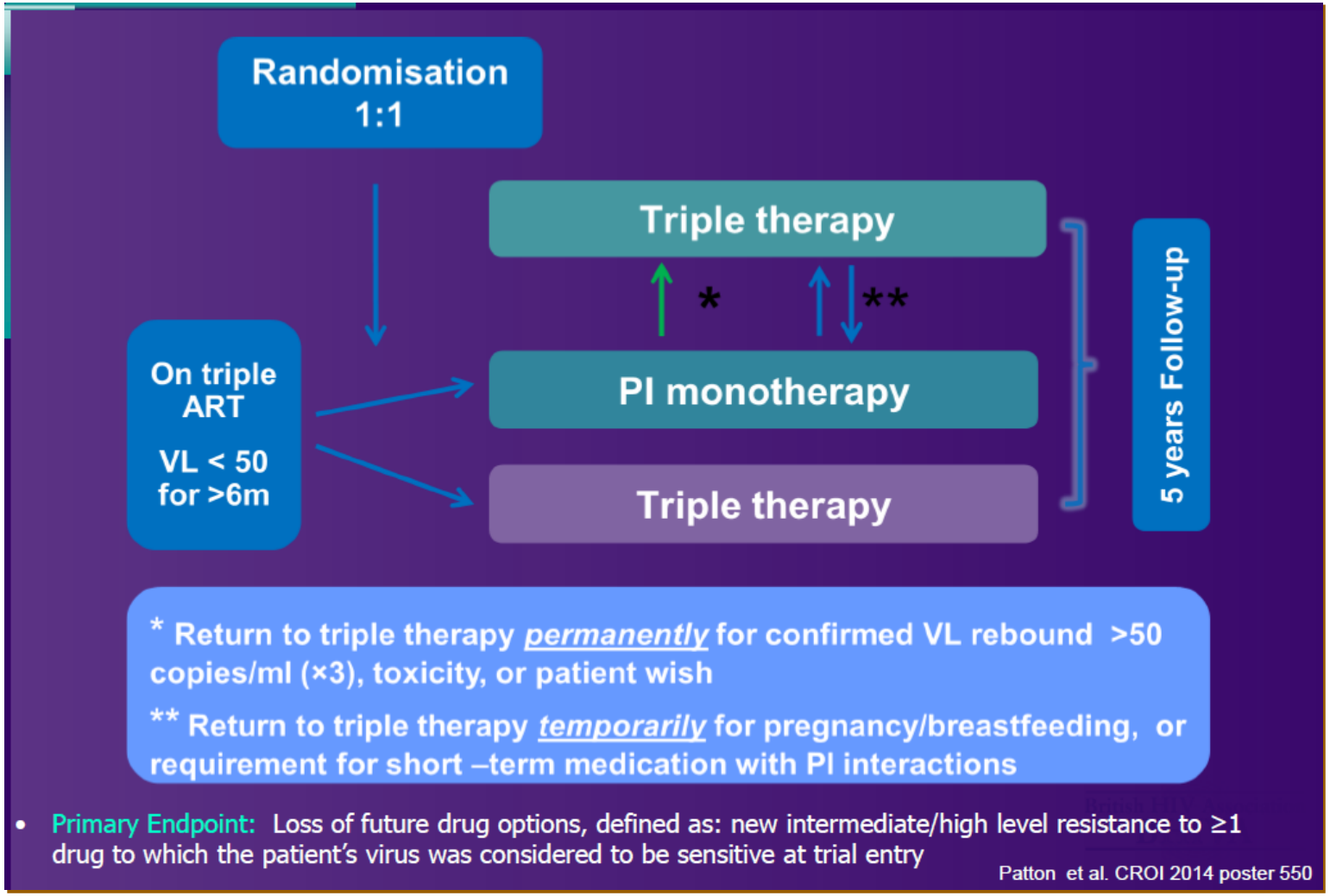
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.1 Virological suppression.

Study or Subgroup	PI monotherapy Events	Total	Combination therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Lopinavir						
Arribas 2005 (OK Pilot)	17	21	20	21	4.3%	0.85 [0.68, 1.07]
Cahn 2011 (wk51.4)	39	41	36	39	17.3%	1.03 [0.92, 1.16]
Gutmann 2010 (MOST)	23	29	31	31	6.0%	0.80 [0.66, 0.97]
Hasson 2011 (KAMON 2)	8	15	10	15	0.6%	0.80 [0.44, 1.45]
Meynard 2010 (KALESOLO)	73	87	87	99	16.3%	0.95 [0.85, 1.07]
Nunes 2009 (KalMo wk 96)	24	30	26	30	4.3%	0.92 [0.74, 1.16]
Pulido 2008 (OK04 wk48)	85	103	90	102	17.4%	0.94 [0.83, 1.05]
Waters 2008 (wk48)	18	26	22	28	2.2%	0.88 [0.64, 1.21]
Subtotal (95% CI)		352		365	68.4%	0.94 [0.89, 1.00]
Total events	287		322			
Heterogeneity: Tau² = 0.00; Chi² = 6.99, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
1.1.2 Darunavir						
Arribas 2010 (MONET wk48)	107	127	110	129	20.8%	0.99 [0.89, 1.10]
Katlama 2010 (MONOI)	82	112	91	113	10.8%	0.91 [0.79, 1.05]
Subtotal (95% CI)		239		242	31.6%	0.96 [0.88, 1.04]
Total events	189		201			
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		591		607	100.0%	0.95 [0.90, 0.99]
Total events	476		523			
Heterogeneity: Tau² = 0.00; Chi² = 7.91, df = 9 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.28 (P = 0.02)						
Test for subgroup differences: Not applicable						



Combination therapy was superior to monotherapy for virological suppression.

PIVOT


Randomisation
1:1
On triple ART
VL < 50 for >6m
Triple therapy
*
**
PI monotherapy
Triple therapy
5 years Follow-up
* Return to triple therapy permanently for confirmed VL rebound >50 copies/ml (×3), toxicity, or patient wish
** Return to triple therapy temporarily for pregnancy/breastfeeding, or requirement for short –term medication with PI interactions
• Primary Endpoint: Loss of future drug options, defined as: new intermediate/high level resistance to ≥1 drug to which the patient's virus was considered to be sensitive at trial entry
Patton et al. CROI 2014 poster 550

PIVOT – baseline characteristics

Characteristic	OTT (n=291)	PIm (n=296)	Overall
Age (years)*	43 (37-49)	45 (39-50)	44 (38-49)
Mode of infection			
MSM	175 (60%)	176 (60%)	351 (60%)
Heterosexual	108 (37%)	108 (36%)	216 (37%)
Other	8 (3%)	12 (2%)	17 (3%)
Female	64 (22%)	73 (25%)	137 (23%)
Ethnicity			
White	206 (71%)	195 (66%)	401 (68%)
Black	73 (25%)	90 (30%)	163 (28%)
Other	12 (4%)	11 (4%)	23 (4%)
HCV infected (Ab +ve)	7 (2%)	14(5%)	21 (4%)
Baseline CD4*	512 (386, 658)	516 (402, 713)	513 (392, 682)
CD4 nadir*	181 (90,258)	170 (80, 239)	178 (86, 250)
Years since ART start*	3.9 (2.0,6.4)	4.2 (2.4, 6.9)	4.0 (2.2, 6.7)
No. drugs ever received *	5 (3,6)	4 (3,6)	4 (3,6)
PI or NNRTI at entry			
PI	134 (46%)	139 (47%)	273 (47%)
NNRTI	127 (54%)	155 (53%)	314 (53%)

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PIVOT - Outcomes

Characteristic	OTT (n=291)	PIm (n=296)	Difference PIm–OTT (95% CI)	p-value
VL rebound ≥ 50 copies/ml, confirmed - n (%) [1]	8 (3.2%)	95(35.0 %)	31.8% (24.6 to 39.0%)	<0.001
Loss of future drug options [by 36 months] - n (%) [2]	2 (0.7%)	6 (2.1%)	1.4% (-0.4 to 3.4%)	0.15
Loss of future drug options [by end of trial] - n (%) [2]	4 (1.8%)	6 (2.1%)	0.2% (-2.5 to 2.6%)	0.85
By drug class – n				
NRTI	3	1	-	-
NNRTI	3	2	-	-
PI	1	3	-	-
CD4 change, cells/mm^3 mean (SE) [3]	+91 (9)	+108 (9)	+17 (-10 to +43)	0.21
Serious disease complication n (%)	8 (2.8%)	15 (5.1%)	2.3% (-0.8% to 5.4%)	0.15
Grade 3/4 adverse event n (%) [5]	159 (55%)	137 (46%)	-8.4% (-16.4% to 0.3%)	0.043
Neurocognitive function [NPZ-5] change -mean (SE)[3]	+0.51 (0.04)	+0.50 (0.04)	-0.01 (-0.11 to +0.09)	0.86
Cost of ART drugs, £ mean (SE)[4]	30,230 (860)	21,260 (700)	-8970 (-6,790 to -11,160)	–

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PI monotherapy – discussion points

- Will results of PIVOT change prescribing guidelines?
- Who are the best candidates for PI monotherapy?
- Cost effectiveness of PI monotherapy when total management/monitoring costs factored in as well as drug costs

NRTI-sparing regimens – the search goes on?

Study	Strategy
ACTG 5142 (2008)	bPI + NNRTI
PROGRESS (2011)	bPI + RAL
SPARTAN (2012)	bPI + RAL
ACTG 5262 (2012)	bPI + RAL
NEAT 001/ANRS 143 (2014)	bPI + RAL
A4000178 (2011)	bPI + MVC
MODERN (2014)	bPI + MVC

When would you consider using such novel strategies?

In conclusion

- Patients are living longer – this is good news!
- Emerging co-morbidities and drug toxicities
- Aggressive management of modifiable risk factors
- It's not always the antiretrovirals!
- Reviewing the patient in front of you is key!
- Switch ART safely and wisely

Thank you