18th Annual Conference of the
British HIV Association (BHIVA)

Professor Georg Behrens

Hannover Medical School, Germany

18-20 April 2012, The International Convention Centre, Birmingham

18th Annual Conference of the
British HIV Association (BHIVA)

Professor Georg Behrens

Hannover Medical School, Germany

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Professor Georg Behrens:	Professor Behrens has received payment for attending Advisory Board meetings by conference sponsors. In addition, he has received speaker fees and grants used for research from conference sponsors
Date	**April 2012**

18-20 April 2012, The International Convention Centre, Birmingham

ART now, ART to come

Spoilt for Choice? Switching Antiretrovirals

Georg Behrens
Department for Clinical Immunology and Rheumatology
Hannover Medical School, Hannover, Germany

HIV therapy: A matter of choices?

- Our choice of tolerable, safe and effective HIV drug combinations

  versus

- HIV‘s choice of resistance mutation development

Spoilt for choice? 26 drugs + FixDoseCombinations

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

NNRTI
- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine
- Rilpivirine

PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Fusion Inhibitor
- Enfuvirtide (T-20)

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Combinations
- 6 available, combining 2 or 3 drugs

Spoilt for choice? **14** drugs

NRTI
- Zidovudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI
- Nevirapine
- Efavirenz
- Etravirine
- Rilpivirine

PI
- Lopinavir
- Atazanavir
- Darunavir

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Don‘t start with, nor switch to

- 3TC + FTC
- AZT + d4T
- ddI + d4T
- TDF + ddI
- TDF + ABC

Spoilt for choices? **NO!**

- Just enough choices to keep HIV in check
- Need for even more options in the future
- New drug classes are desirable

  - HIV epidemic will spread in humans during the next decades, if not centuries!
  - Think of TB and development of MDR TB!

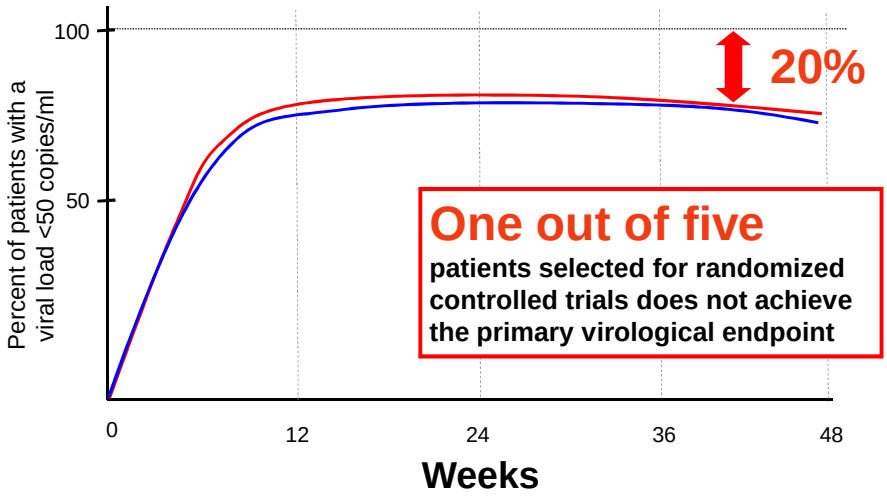
Randomized trials: No choices

- We request for data from trials, in which we have no choice and cannot switch
  - Difficult to extrapolate
- How to best treat 100 patients versus how to best treat the patient in front of me

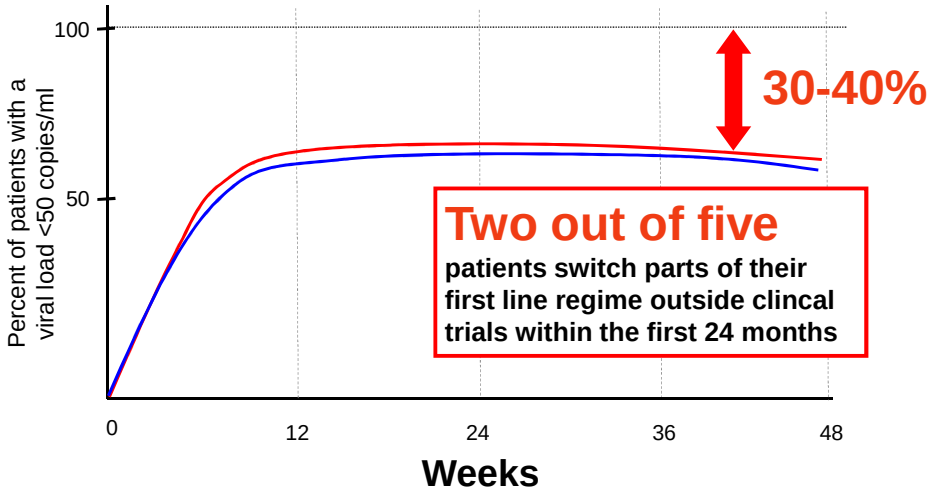
Randomized trials vs. "real live scenario"

- Efficiency is determined by the fact, whether or not the patient is able to take the drugs
  - Doctors decisions become more important
- Does a doctor‘s therapy decision for patients perform better then randomised trials?

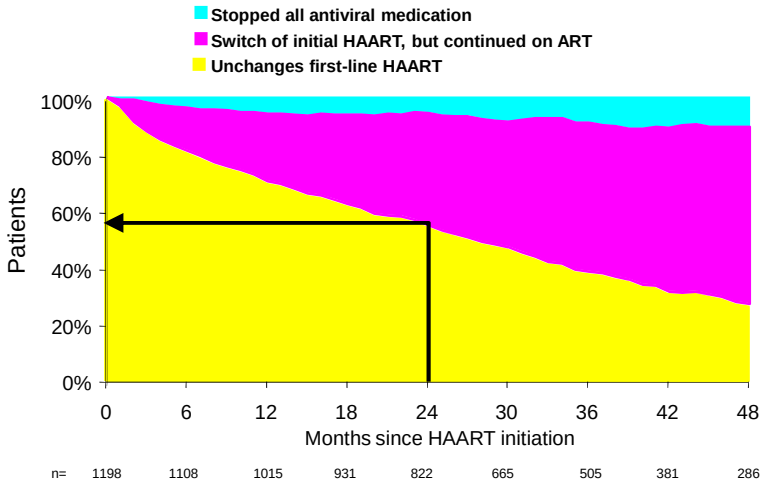
Antiretroviral efficacy studies



Outside antiretroviral efficacy studies



Switch of first line HIV therapy regimens



Mocroft et al. AIDS Res Hum Retroviruses 2005;9:743-752

Even the “best” regimens result in some level of discontinuation

TDF+FTC+EFV[1]

12/257 (5%) because of toxicity

ABC/3TC+LPV/r[2]

24/444 (5%) because of adverse event

1. Gallant JE, et al. IAC 2006. Abstract TUPE0064. 2. Eron JJ Jr, et al. Lancet. 2006;368:476-482.

Even the “best” regimens result in some virological failures

TDF+FTC+EFV[1]

4/255 (1,6%) virological failure

ABC/3TC+LPV/r[2]

30/444 (6,7%) virological failure

1. Gallant JE, et al. IAC 2006. Abstract TUPE0064. 2. Eron JJ Jr, et al. Lancet. 2006;368:476-482.

Switch of antiretrovirals

- Why switch?
- What is possible?
- What has been looked at in clinical trials?
- What makes sense, what not?
- What needs to be considered?

Why switch antiretrovirals?

- Virological failure
- To respond to short term toxicity
- To avoid long term toxicity
- To avoid drug-drug interactions, to simplify treatment, to enhance adherence

Incomplete virological suppression

- **Incomplete viral suppression** will lead to resistance mutation accumulation
  - 68% with new mutations after median of 22 months[1]
  - 33% with new TAMs, 2% K65R during 96 wks of FU[2]
  - 60% with new mutations after median of 9.3 months but no shift on virtual phenotype[3]

Lafeuillade A, et al. IAC 2004. Abstract WeOrB1293.
Margot NA, et al. J AIDS. 2003;33:15-21. 3. Napravnik S, et al. J Acquir Immune Defic Syndr. 2005;40:34-40.

Virological failure

- How resistance-sensitive is the present therapy? NNRTI, 3TC/FTC, RAL: change quickly
- The lower the VL, the greater the prospect of success after change
- Adherence?
- Resistence test
- …

Little choices because of NRTI resistance mutations

Failing nuke backbone	**Mutations**
TDF+3TC/FTC	K65R and/or **M184V**
ABC+3TC	L74V, less often K65R, and /or **M184V**
AZT/d4T+3TC AZT/3TC+ABC	**M184V** and then successive TAMs
AZT/d4T+ddI	TAMs, Q151M, T69ins
TDF+ABC/ddI	K65R

Different combinations of V118I, H208Y, and T215Y reverse transcriptase mutations produce NNRTI hypersusceptibility

Clark et al. AIDS. 2006 Apr 24;20(7):981-4

Changing first-line therapy

Failing initial therapy	Potentially successful change
2 NRTI + 1 NNRTI	Change NNRTI to PI/r (rapid switch) or 1-2 new NRTIs + RAL or MVC
2 NRTI + 1 PI/r	1-2 new NRTIs + NNRTI + new PI/r or RAL or MVC

TDF/FTC+EFV → TDF/FTC + PI/r M184V?

Therapeutic use of resistance mutations

- Keep 3TC/FTC because of M184V
  - Makes the virus less fit
- Add AZT because of K65R[1]
- Combine AZT + TDF because of divergent resistence pathways
- Add ddI (?)

1. Stephan et al. J Infect Dis 2010, 61(4):346-50

Changing first-line therapy

Failing initial therapy	Potentially successful change
2 NRTI + 1 NNRTI	**PI/r + RAL** (under investigation)
2 NRTI + 1 PI/r	1-2 new NRTIs + NNRTI + new PI/r or RAL or MVC

Sequencing NNRTIs? ECHO & THRIVE

Phenotypic sensitivity to NNRTIs

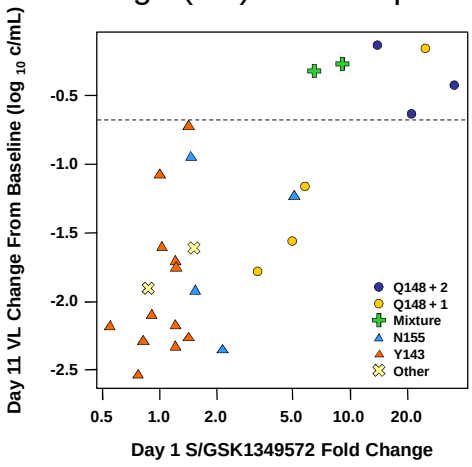
	RPV				EFV			
	BL VL ≤ 100K c/mL		BL VL > 100K c/mL		BL VL ≤ 100K c/mL		BL VL > 100K c/mL	
Time of failure, %	Resistant to RPV* N'=2	Sensitive to RVP N'=14	Resistant to RPV* N'=29	Sensitive to RVP N'=17	Resistant to EFV N'=6	Sensitive to EFV N'=6	Resistant to EFV N'=6	Sensitive to EFV N'=10
Resistant to RPV	-	**-**	-	**-**	**0**	**0**	0	**0**
Resistant to NVP	0	**0**	48	**0**	**100**	**0**	100	**20**
Resistant to ETR	50	**7**	93	**12**	**0**	**0**	0	**0**
Resistant to EFV	50	**7**	90	**6**	**-**	**-**	-	**-**

Cross-resistance determined by Antivirogram®
*RPV biological cut-off (BCO) = 3.7 (Antivirogram®)

Adapted from Rimsky L, et al. IWHHC 2011; Los Cabos, Mexico. Poster

Sequencing integrase inhibitors?

Virologic Response at DAY 11: Correlation with Baseline Fold Change (FC) in Susceptibility to S/GSK1349572



Strong correlation between baseline FC and Day 11 response (r=0.79, p value <0.001)

Patients with N155H and Y143H responded better then patients with Q148

Mixtures:
N=1 Q148H + G140S / Y143H
N=1 Q148H+ E138A+G140S / Y143H
Others:
N=1 E92Q (screen: E92Q, N155H)
N=1 none (screen: G140G/S, Q148H/Q)

Within class changes for virologival failure

- NRTI → NRTI
- NNRTI → NNRTI (etravirine)
- PI/r → PI/r
- RAL → nothing at this stage
- MVC → nothing

Spoilt for choice: NO!

To create the best combination regimen, often the (potentially) weakest active drug dictates the rest of the regimen composition.

Success of todays HIV therapy (start)

- Rapid and effective response to early virological failure (effective + simple switches)
- Choice to react to short term intolerability

→ 90% of all patients can achieve < 50 HIV-RNA copies/mL on a tolerable regimen 12 months after therapy start

Patients with TCR or TCF: some choices

	POWER	RESIST	MOTIVATE	BENCHMRK	DUET
Agent tested	DRV	TPV	MVC	RAL	ETV
Total n	245	1509	1049	701	612
Background-Therapy					
With de novo T-20, %	29–33	18–23	40–44	20	25
With darunavir, %	100	0	0	25–50	100
With tipranavir, %	0	100	14–16	19–23	0
Response at 48 Wo*					
In total, %	45 vs. 10	23 vs. 10	44 vs. 17	64 vs. 34	61 vs. 40
With de novo T-20, %	58 vs. 11	28 vs. 14	61 vs. 27	84 vs. 62	71 vs. 59
0-1 active drug, %	37 vs. 1	n.a.	37 vs. 6***	48 vs. 12	57 vs. 24

*Definition of an active drug varied considerably (different resistance scores were used);
**Response at 48 weeks defined as viral load <50 copies/ml; ***Data at week 24. n.a.=not applicable

2-3 NRTI + 1 PI/r ± (T-20) + something new (RAL, MVC, ETV)

Patients with **T**hree **C**lass **R**esistance

Week 48

- TRIO trial
  - RAL+ETV+MVC (n=103) 86% <50 copies
- Italian study
  - RAL+ETV+MVC (n=28) 92% <50 copies

Yazdanpanah Y, et al. Clin Infect Dis 2009, 49:1441-9, Nozza AIDS 2010, 24:924-8.

Side effects almost always leading to discontinuation/switch

- Severe diarrhea, severe nausea (PIs)
- Persistent sleeping disorder (EFV)
- Severe allergic manifestations with involvement of mucous membranes, fever (ABC, NVP)
- Severe anaemia (AZT)
- Pancreatitis, polyneuropathy (d4T, ddI)
- Lactic acidosis (d4T+ddI, other NRTIs)
- Renal failure, nephrolithiasis, severe hepatotoxicity, rhabdomyolysis

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

→ **NVP** 2 x 200 mg[1,2] (alternatively NVP XR) or lead in with 200 mg for two weeks?[3]

1. Winston et al. AIDS 2004;18(3):572-574. 2. Laureillard et al. HIV Med. 2008 Aug;9(7):514-8. 3. Viramune summary of product charactersistics. Boeringher Ingelheim Ltd, July 2011.

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

→ **Etravirine** 2 x 200 mg (plasma concentrations are only initially lower)[1]

1. Waters et al. AIDS. 2011 Jan 2;25(1):65-71

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

→ **Rilpivirine** 1 x 25 mg (plasma concentrations are only initially lower)[1]

1. Crauwels et al. 18th Conference on Retroviruses and Opportunistic Infections; February 27-March 2, 2011; Boston. Abstract 630.

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

→ **PI/r**	standard dose
→ **Raltegravir**	standard dose
→ **Maraviroc**	600 mg BID first week, 300 mg BID thereafter[1] (unless given together with a PI/r).

1. Waters et al. EACS 2011

React to toxicity

- **PI/r** (if viral load < 50 copies/mL)

→ **NNRTI**
→ **Raltegravir**

works well, if no prior NRTI mutation/failure

Even suppressed patients experience virologic failure when switched

PI to EFV[1]

12/156 (8%)

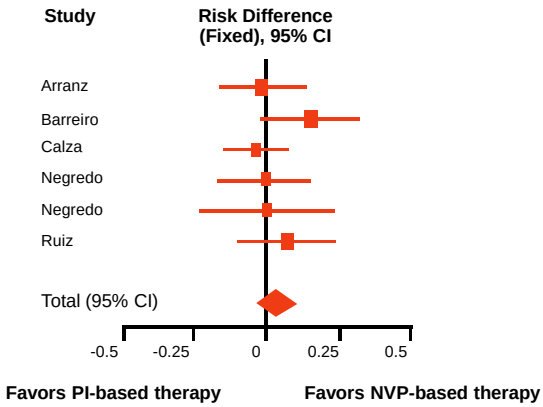
AZT/3TC to TDF/FTC[2]

6% of patients with VL >400 at week 24

1. Martinez E, et al. CROI 2006. Abstract 521. 2. DeJesus E, et al. CAHR 2006. Abstract 214.

Simplification from suppressive PI-based therapy to NVP-based regimens

- Meta-analysis of 6 randomized clinical trials (N = 550) switching suppressive PI-based therapy to NVP-based therapy or no change[1]



1. Ena J, et al. HIV Med. 2008;9:747-756. 2. EMEA Nevirapine PI.

PI → NNRTI, improves lipids

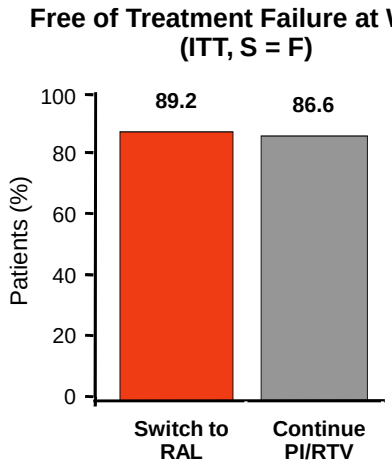
Source	n	Wk
PI to NVP		
Barreiro 2000	138	24
Ruiz 2001	106	48
Arranz-Caso 2005	160	48
PI to EFV		
Becker 2001	346	48
Molina 2005	355	48
PI to EFV vs NVP		
Negredo 2002	77	48
Calza 2005	130	48

In all studies (except Martinez 2003), randomization was against continuing PIs.

PI → ABC or RAL

Source	n	Wk	VL Effect	
PI to EFV vs NVP, ABC				
Martinez 2003	460	48	Trend against ABC	←
PI to ABC				
Clumeck 2001	211	24	Advantage	
Opravil 2002	163	84	Disadvantage (trend)	←
Katlama 2003	209*	48	n.s.	
Keiser 2002	104	28	n.s.	
PI to RAL				
Eron 2010	350	24	Disadvantage	←
Martinez 2010	139	48	n.s.	

SPIRAL: Switch to RAL noninferior to maintaining PI/RTV regimens



Martinez E, et al. AIDS. 2010;24:1697-1707.

Avoid long term toxicity

- Take out/replace thymidine analogues
  - AZT/d4T → TDF/ABC
  - AZT/d4T → **PI/r + NNRTI**

Reference	n	Switch to	Wks	Main effects of the switch
Negredo 2009 (MULTINEKA)	16*	LPV/r + NVP	48	Virologically effective, lipids and mitochondrial DNA better
Tebas 2009 (ACTG 5110)	101	LPV/r + NVP	48	Virologically effective, lipodystrophy better
Tebas 2007 (ACTG 5125)	62	LPV/r + EFV	48	Many metabolic disturbances and LA better
Fischl 2007 (ACTG 5116)	118*	LPV/r + EFV	110	Trend towards more virologic failure, more side effects

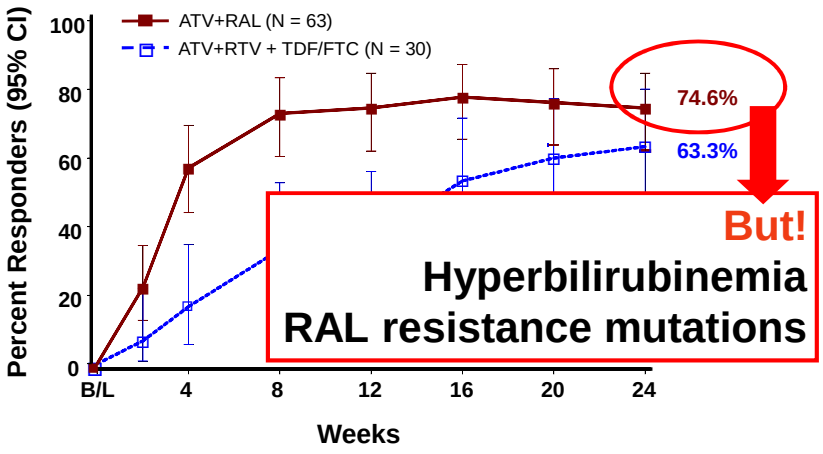
Avoid long term toxicity

- Take out/replace thymidine analogues
  - AZT/d4T out, TDF/ABC in
  - **PI/r + NNRTI**

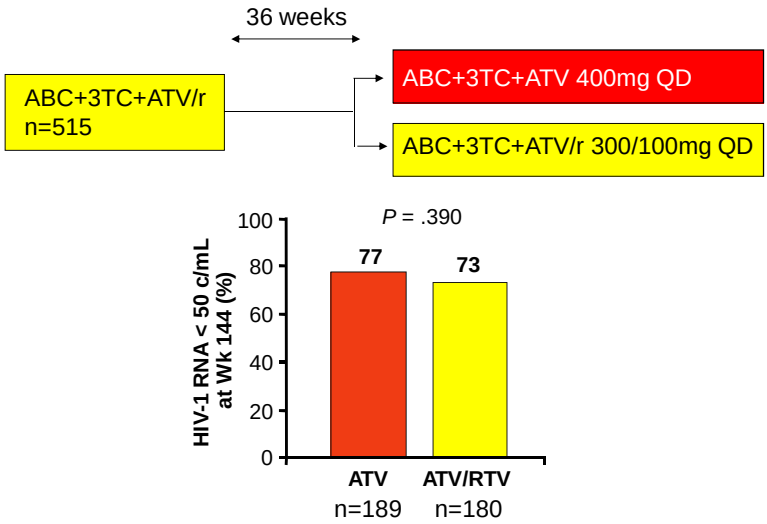
Reference	n	Switch to	Wks	Main effects of the switch
Negredo 2009 (MULTINEKA)				NA better
Tebas 2009 (ACTG 5110)				
Tebas 2007 (ACTG 5125)				ces
Fischl 2007 (ACTG 5116)				gic failure, more side effects

Don'ts
EFV/NVP + ATV unboosted
EFV/NVP + LPV/r
ETR + TPV/r

SPARTAN TRIAL: ATV (300mg BID) + RAL (400 mg BID)



ARIES: Switch From a RTV-Boosted PI to Unboosted ATV



Squires K, et al. IAS 2011. Abstract MOPE215.

Nuke-sparing: Switch to double PI

Combination	Daily Dose/comment	Source
More favorable		
Lopinavir/r + saquinavir	800/200/2000	Staszewski 2006
Atazanavir/r + saquinavir	300/200/2000	von Hentig 2007
Saquinavir/r + fosamprenavir	2000/200/1400	Boffito 2004
Lopinavir/r + indinavir	800/200/1600	Staszewski 2003
Less favorable		
Lopinavir/r + fosamprenavir	Poor PK data	Kashuba 2005
Lopinavir/r + atazanavir	Poor activity	Ulbricht 2008
Lopinavir/r + nelfinavir	Poor PK data, diarrhea	Klein 2003
Atazanavir + indinavir	Elevated bilirubin	Chisolm-Burns 2007
Atazanavir + fosamprenavir	Poor activity	Landman 2009
Atazanavir + saquinavir without /r	Poor activity	Johnson 2005
Tipranavir + LPV/APV/SQV	Poor PK data	Walmsley 2004
Indinavir + nelfinavir	Relatively poor activity	Riddler 2002

Nuke-sparing: Switch to double PI

Combination	Daily Dose/comment	Source
More favorable		
Lopinavir/r + saquinavir	800/200/2000	Staszewski 2006
Atazanavir/r + saquinavir	300/200/2000	von Hentig 2007
Saquinavir/r +		04
Lopinavir/r +		i 2003
Less favorable		
Lopinavir/r + fo		005
Lopinavir/r + a		008
Lopinavir/r + n		
Atazanavir + ir		ums 2007
Atazanavir + fosamprenavir	Poor act vity	Landman 2009
Atazanavir + saquinavir without /r	Poor act vity	Johnson 2005
Tipranavir + IPV/APV/SQV	Poor PK data	Walmsley 2004
Indinavir + nelfinavir	Relatively poor activity	Riddler 2002

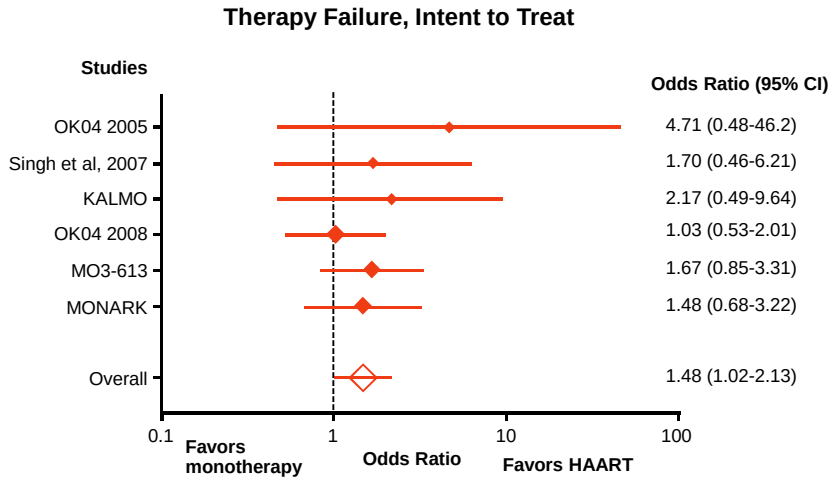
Don'ts

TPV + PI (FPV, LPV, SQV, ATV)

LPV/r + FPV

IDV + ATV

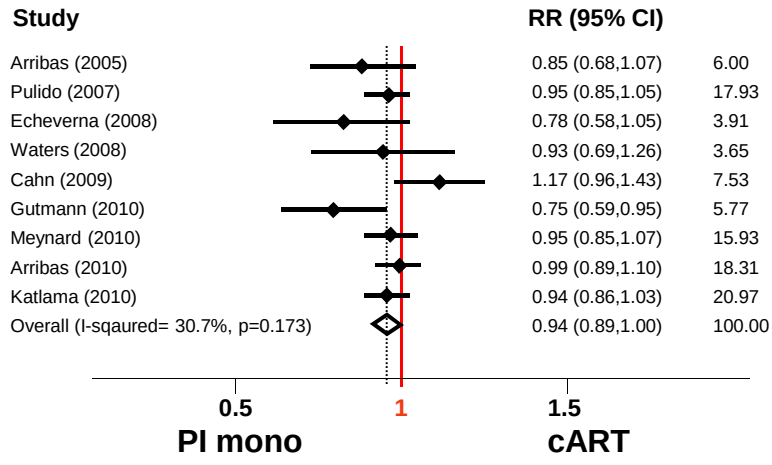
Systematic review of LPV/r monotherapy



Bierman WF, et al. AIDS. 2009;23:279-291.

Systematic review of PI monotherapy

Risk ratios for maintaining viral suppression, intention to treat analysis, 48 week follow-up, viral suppression, <50 copies/ml.

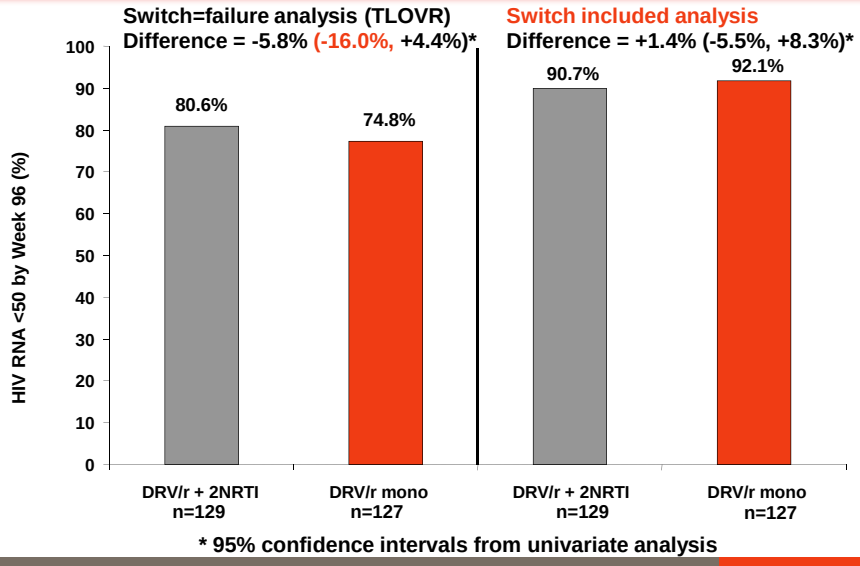


Modified from Mathis et al PlosONE 2011
NOTE: Weights are from the random effects analysis

PI monotherapy: A simple therapy?

Source	n	Maintenance	Wks	Less than 50 copies/ml?
Randomized				
Nunes 2009 (KalMo)	60	LPV/r versus 2 NRTIs+LPV/r	96	80% vs 87% (ITT, VL < 80)
Campo 2009 (M03-613)	155	LPV/r versus CBV+EFV	96	60% vs 63% (ITT), but low-level viremia more frequently
Pulido 2008 (OK04 Study)	205	LPV/r versus 2 NRTIs+LPV/r	48	85% vs 90% (ITT), Non-inferiority shown, but more frequent low level viremia
Meynard 2010 (KALESOLO)	186	LPV/r vs ART-continuation	48	84 vs 88% (ITT), Non-inferiority not shown, more frequent low viremia
Gutman 2010	60	LPV/r vs ART-continuation	24	21% VF on Mono. Especially those with low CD4-Nadir, study discontinued.
Arribas 2010 (MONET)	256	DRV/r versus 2 NRTIs+DRV/r	96	75% vs. 81% (ITT), Non-inferiority not shown
Katlama 2010 (MONOI)	225	DRV/r versus 2 NRTIs+DRV/r	48	94% vs. 99%, Non-inferiority not clearly shown (low viremia more frequently)

MONET Trial (switch to DRV/r only)

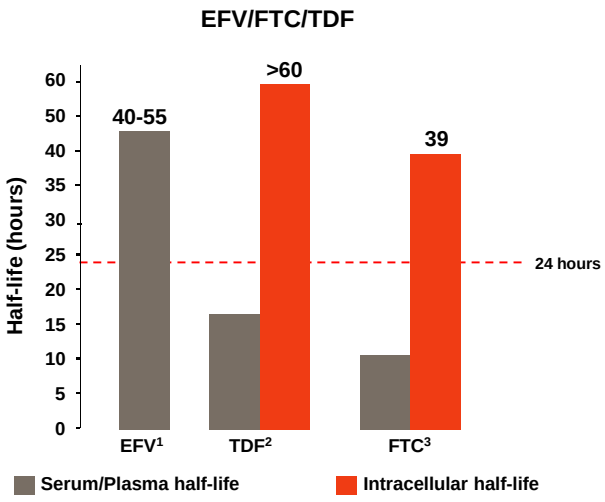


Rieger et al. WAC July 2010, Vienna [abstr TBLBB209]

PI monotherapy (LPV/r or DRV/r): Is the absence of harm a benefit?

- Data from selected patients for selected patients
- Safe (NRTI reintroduction) + cheap
- Clinical benefits not fully known

Switch to nothing: half-lives of antiretovirals



1. Sustiva (efavirenz). US Prescribing Information. Bristol-Myers Squibb. Princeton, NJ. March 2010;
2. Hawkins T, et al. J Acquir Immune Defic Syndr 2005;39:406–411; 3. Wang LH, et al. IAC 2002. #4546

Switch to nothing

- NNRTI and NRTI resistance mutations[1]
- Strategies to avoid mutation development:
  - simultaneously stop all drugs, if drugs have similar half lives
  - discontinue the drug with the longest half life first in a regimen containing drugs with short and long half lives
  - replace all drugs with i.e. a protease inhibitor[1]
- HBV/HIV coinfection: no stop of TDF, FTC, 3TC!

1. Fox et al. AIDS 2008, 22:2279-2289.

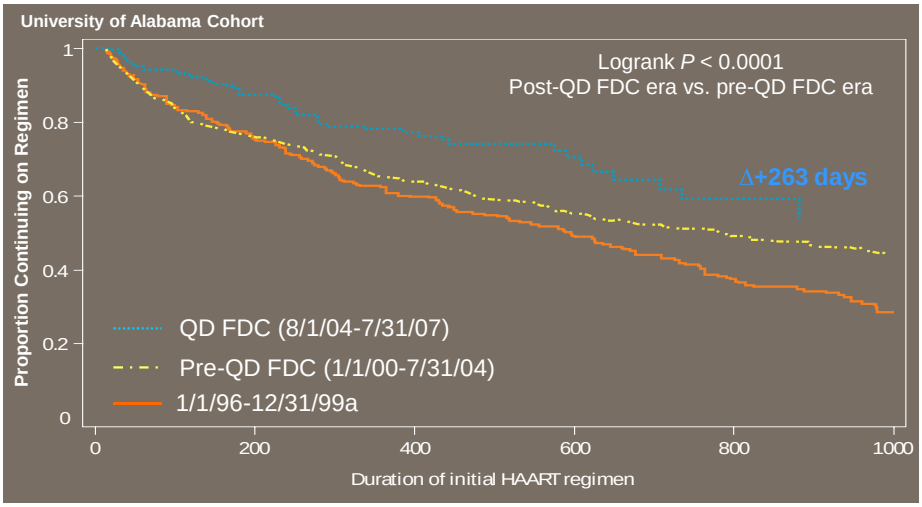
Switch to simplify the regimen

- Current regimens are either twice or once daily
  - Little evidence suggests that clinical outcomes actually improve from twice to once daily
  - Concomittant treatments may have twice-daily dosing

Switch to simplify the regimen

- Current regimens are low pill burden
  - NRTI FDC + EFV: 1-3 pills
  - NRTI FDC + ATV: 2-4 pills
  - NRTI FDC + boosted PI: 4-6 pills
- Will patients who cannot take 2 or 4 per day really adhere better on 1 pill per day?

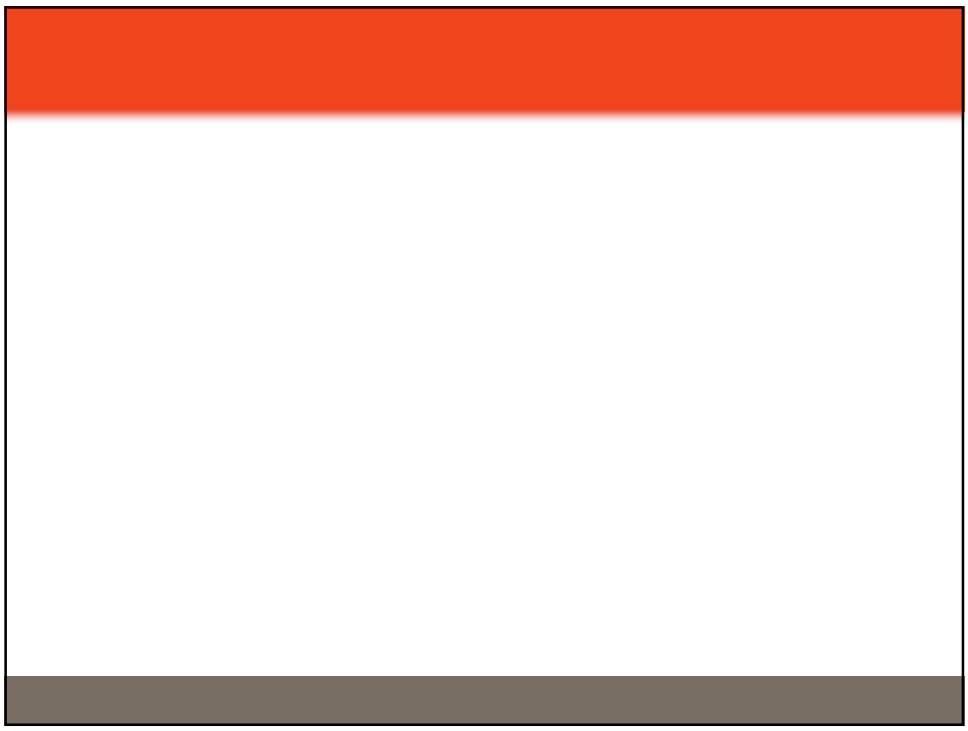
Durability of initial ART before and after availability of QD FDC NRTI backbones



Adapted from Willig JH, et al. AIDS 2008;22:1951-1960

Spoilt for choices? NO!

- Just enough choices to keep HIV in check
  - 1-2 switches lead to long-lasting efficiency in most, but not all patients
  - Choices/switch ratio goes down from ~5/1 to almost 1 (salvage no choice)
- Need for even more options in the future
  - More resistance mutations (ressource-limited seetings)
  - Patient‘s histories become more complex, patients move
  - Comorbidity, co-medication
- New drug classes are desirable



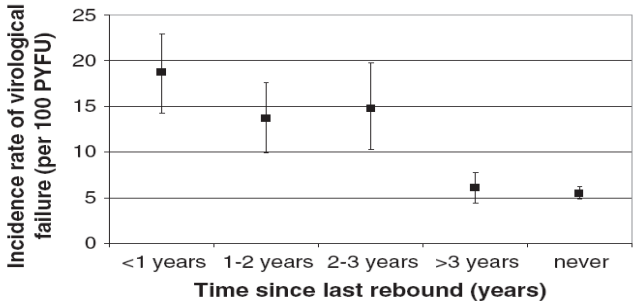
If It Ain’t Broke, Don’t Fix It!

Why Do We Need New Antiretroviral Agents?

- Resistance
  - Primary drug resistance occurs in 5% to 15% of patients[1-3]
  - Multiclass resistance in a substantial proportion of highly treatment–experienced patients[4,5]
- Toxicity/tolerability issues with current classes
  - Metabolic: lipodystrophy, lipoatrophy, dyslipidemia, insulin resistance
  - Other: bone, hematologic, renal, CNS, reproductive, gastrointestinal
- Need for lifelong therapy

1. Bennett D, et al. CROI 2002. Abstract 372-M. 2. Bennett D, et al. CROI 2005. Abstract 674. 3. Wheeler W, et al. CROI 2007. Abstract 648. 4. Phillips AN, et al. Lancet. 2007;370:1923-1928. 5. Napravnik S, et al. AIDS. 2007;21:825-34.

Eurosida: History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change

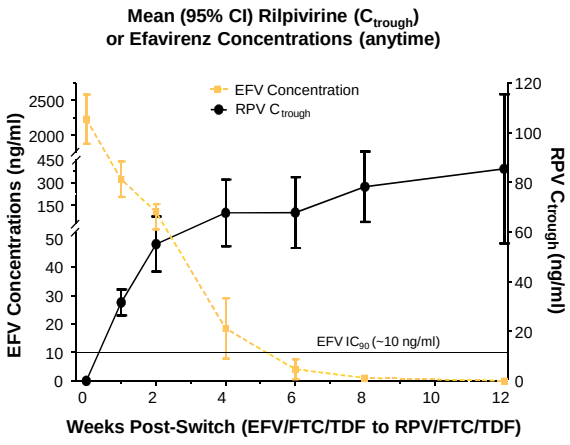


Time since last rebound (years)	<1	1-2	2-3	>3	Never
Number virologically failed after baseline	22	49	42	50	238
PYFU	386	357	284	823	4305

Fig. 3 Rate of virological failure after baseline by time since last rebound after combination antiretroviral therapy (cART) initiation prior to baseline. PYFU, person-years of follow-up.

Reekie, Mocroft et al. HIV Med. 2010;11:469-478

GS 111 Secondary Endpoint: RPV PK after Switching from EFV



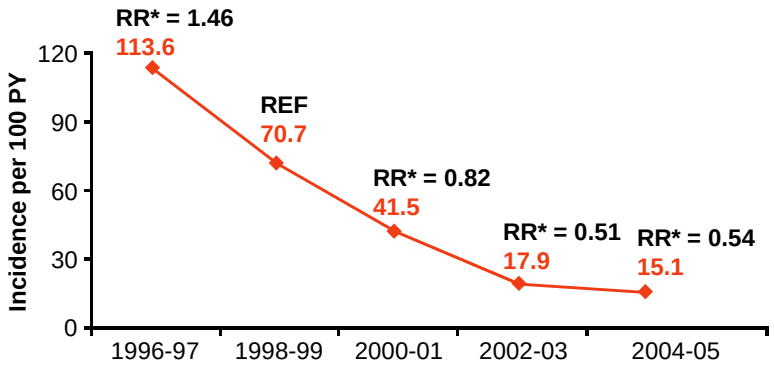
- EFV mean C_{trough} above IC_{90} (~10 ng/ml*) up to ~4 weeks
- No subject had RPV below quantifiable levels at any visit
- RPV mean C_{trough} within historic range by 2 weeks

Week	RPV C_{trough} Mean (%CV), ng/ml
2	52 (47)
4-12	66 (51) - 84 (76)

*protein-binding adjusted; Corbett JW, et al. J Med. Chem 2000:43;2019-2030

Cohen C, et al. EACS 2011; Belgrade, Serbia. Oral #PS10/4

Incidence of Second Virologic Failure Declining Over Time



*Adjusted for time from HAART initiation, sex, age, AIDS, CD4+ cell count, HIV-1 RNA level at HAART initiation and switch, and type of HAART.

Deeks S, et al. CROI 2008. Abstract 41.