Issues in Adult Second-line ART

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The clinical problem

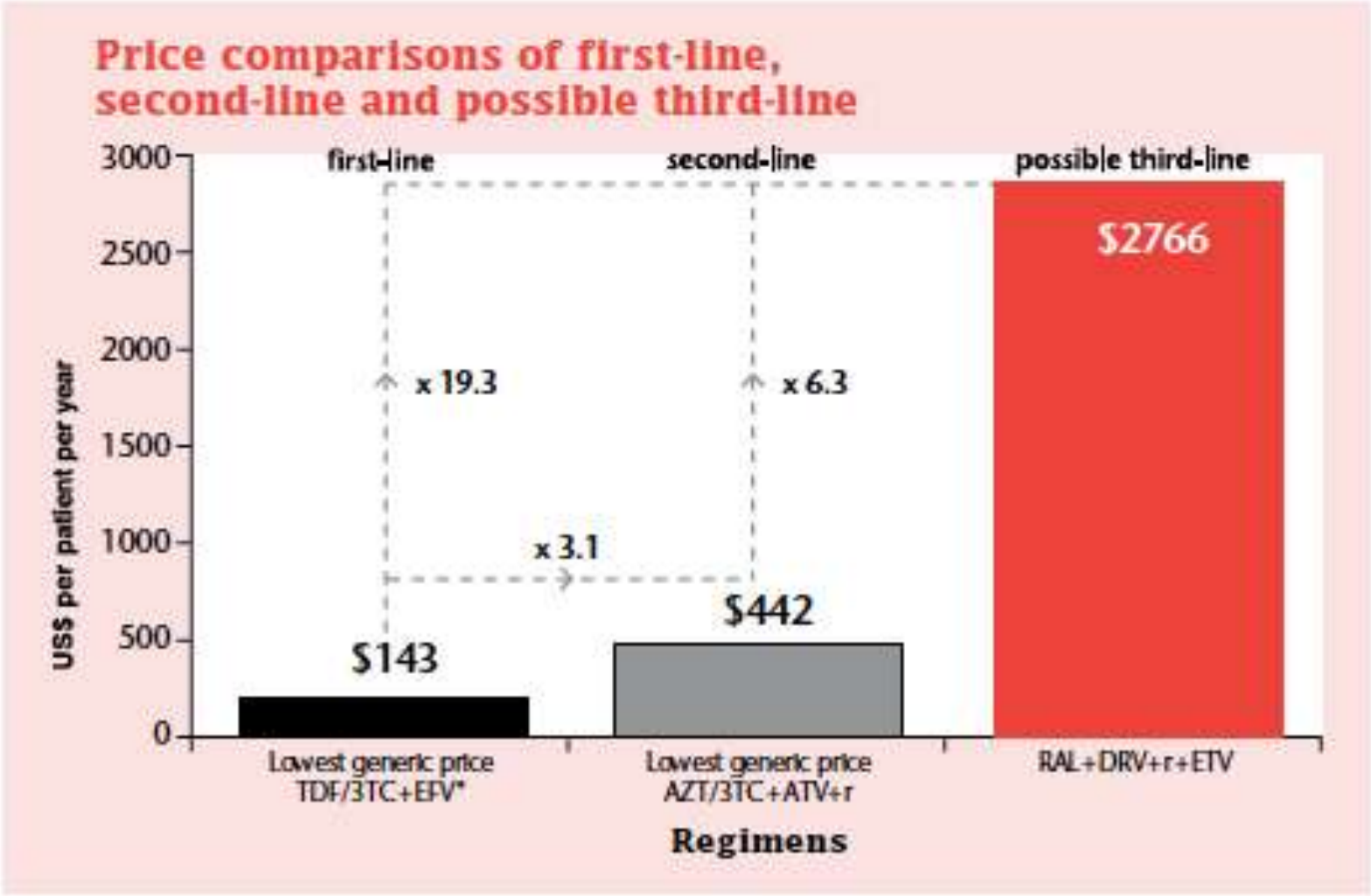
How large is the potential need for 2nd-line ART?

The WHO estimates that, in low and middle-income countries, more than 100,000 persons currently receive 2nd-line ART.

The need for 2nd-line ART is predicted to reach beyond 500,000 by the end of 2012.

- The number receiving 2nd-line ART is far smaller than the global need
  - *Poor sensitivity of immunological monitoring in detecting VF*
  - *Cost of 2nd-line ART remains high*

Comparison of first-line, second-line and potential third-line ART in RLS by price



MSF Access Campaign “Untangling the Web”, 2011

Virologic failure

In South Africa, 2 consecutive viral loads >1000 copies/ml after 6 months of ART, despite adherence counseling , with viral loads separated by 3 months.

SA Dept of Health 2010 HIV Treatment Guidelines

Second-line ART

2010 South African recommendations

PI recommendation:

• RTV-boosted lopinavir (400 /100 mg) twice daily

PI alternative :

• RTV-boosted atazanavir (300/100 mg) daily

- Raised fasting glucose > 6 mmol/l
- Inability to take LPV/r due to GI side-effects
- Raised total cholesterol > 6 mmol/l (230 mg/dl)

NRTI recommendation:

• If prior nucleosides were D4T + 3TC or AZT+ 3TC → TDF + 3TC/FTC

• If prior nucleosides TDF + 3TC/FTC → AZT + 3TC

Second-line ART

Lopinavir/r and atazanivar/r compared in the CASTLE study both in combination with TDF/FTC

Methods

- Soft gel formulation of LPV/r used during first 48 weeks of trial
- ATZ/r a once daily boosted PI

Not fully applicable to resource-constrained settings given that patients were ART-naïve and the soft gel LPV/r formulation used is associated with a somewhat more pronounced side effect profile

Castle Study: Lancet 2008; 372: 646–55

Adverse effects of boosted PIs

ATZ/r associated with less hyperlipidemia vs. LPV/r

	Atazanavir/ritonavir	Lopinavir/ritonavir
Total bilirubin elevation (≥2·6×ULN)	146/435 (34%)	1/431 (<1%)
Alanine aminotransferase increase (≥5·1×ULN)	8/435 (2%)	6/431 (1%)
Aspartate aminotransferase increase (≥5·1×ULN)	9/435 (2%)	2/430 (<1%)
Total cholesterol (≥240 mg/dL) >6.2 mmol	30/434 (7%)	77/428 (18%)
Triglycerides (≥751 mg/dL) >8.5 mmol	2/434 (<1%)	15/428 (4%)

Data are n/N (%). ULN=upper limit of normal.

Table 5: Selected grade 3–4 laboratory abnormalities in ≥2% patients through week 48

- Higher triglycerides & TC were observed in LPV/r arm but LDL levels similar
- 2-5x more GI toxicity in LPV/r arm (soft gel) but more hyperbili in ATZ/r arm

Castle Study: Lancet 2008; 372: 646–55

CASTLE Study (2008)

- Rate of virologic failure at 48 weeks was the same in the two groups at 6%
- 2 patients in the ATZ/r arm, 0 in LPV/r failed with PI resistance
- 96 week findings similiar

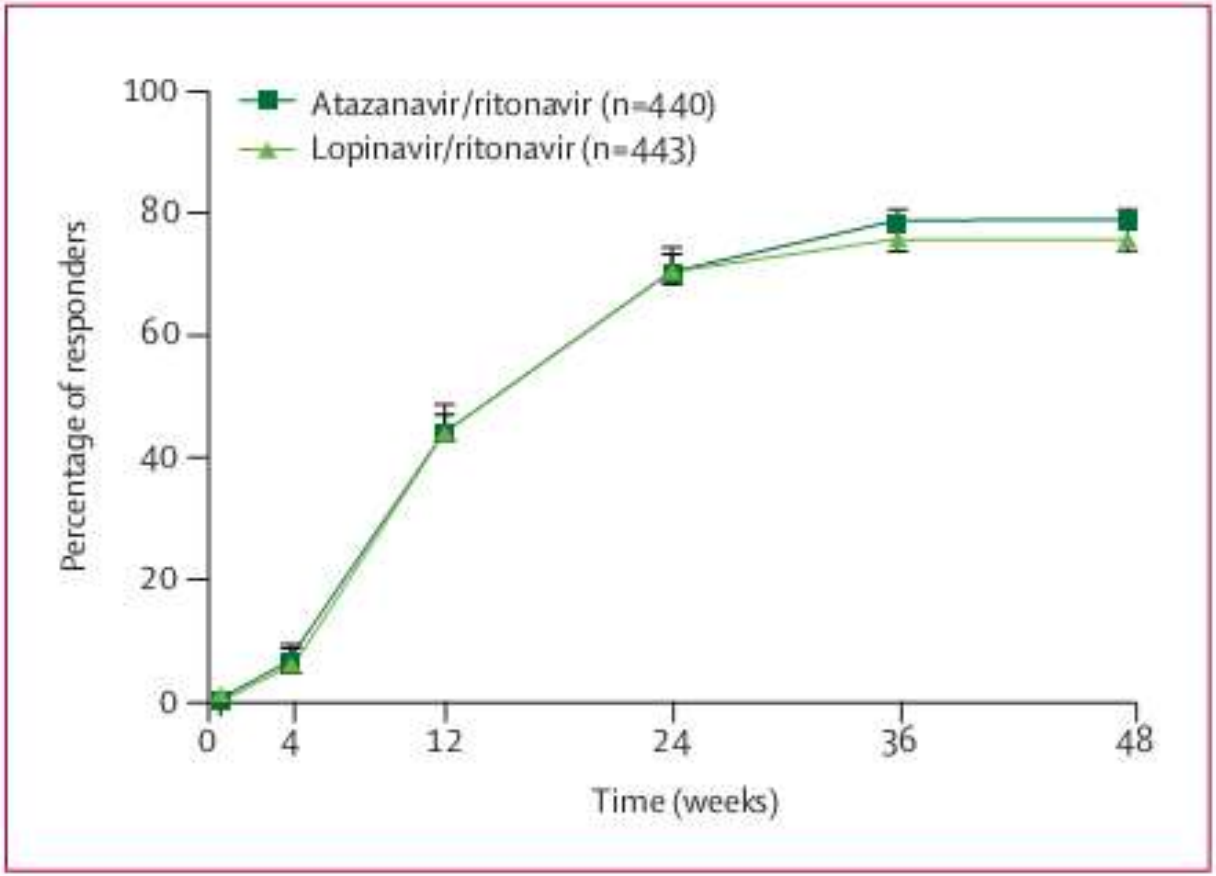


Figure 2: **Proportion of patients with HIV RNA below 50 copies per mL at week 48 (ITT; CVR, NC=F analysis)**

Second-line ART

2010 South African recommendations

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NRTIs used with ritonavir-boosted PIs in resource constrained settings

Hamers *et al* compared outcome of 2nd-line ART in those with "fully-active" and "partially-active" 2nd-line regimens.

The PI was LPV/r in nearly all patients but a variety of NRTIs used 3TC/FTC: 182, TDF: 163, AZT: 68, DDI: 40, ABC 39

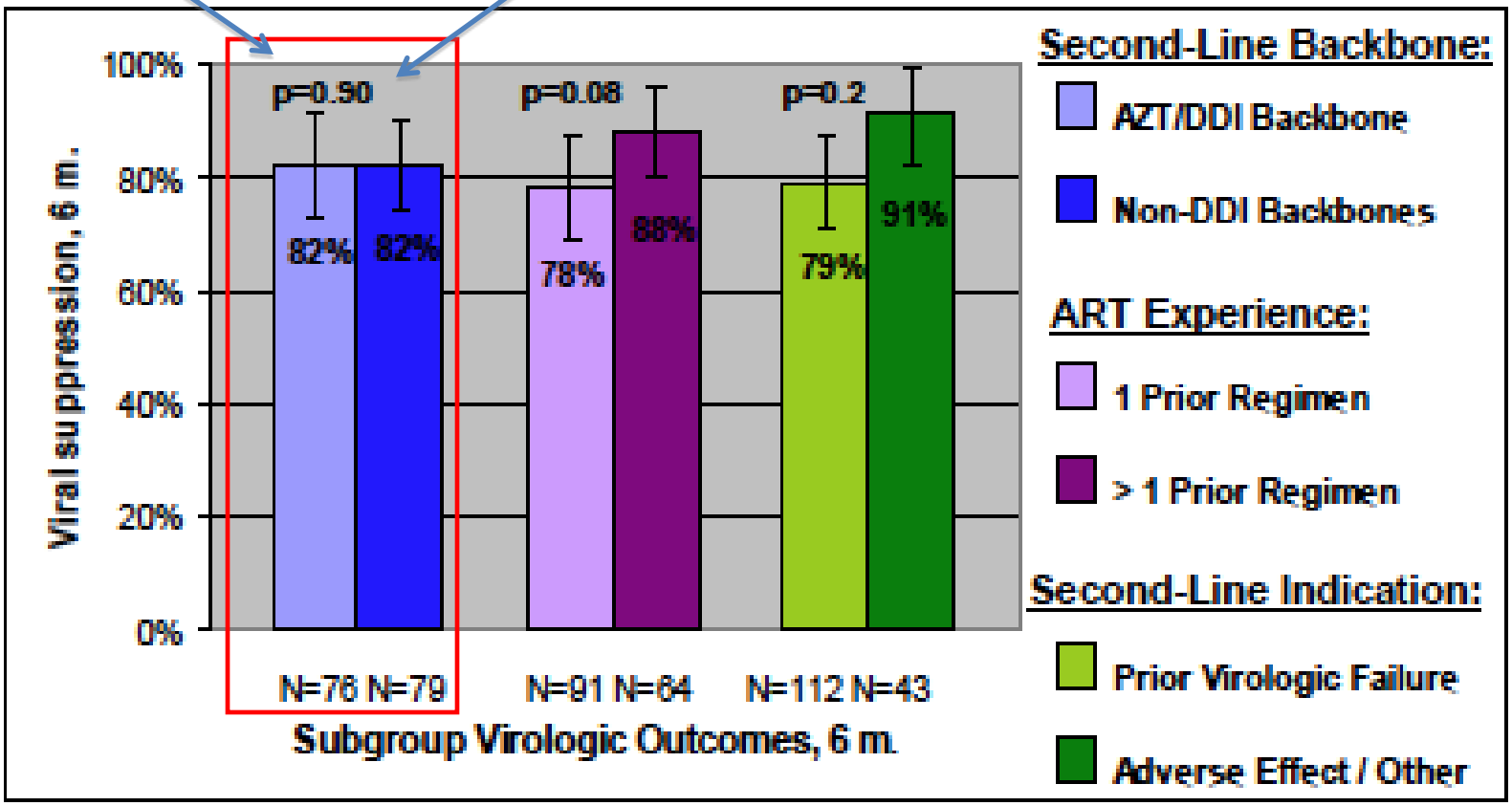
- NRTIs used empirically not informed by resistance testing

- 104 patients received a fully active 2nd line regimen
  - **12 month: 86% viral suppression <400 c/ml**
- 128 partially active 2nd line regimen
  - **12 month: 85% viral suppression < 400 c/ml**

CROI 2012: Hammers and colleagues

Virologic outcome according to NRTIs used with lopinavir/ritonavir-based 2nd-line ART

(AZT/DDI) (AZT+3TC OR D4T+3TC)



CROI 2009 McCord / Sinikithemba Second-line ART Outcomes

PI monotherapy in resource-constrained settings

What is the evidence?

Despite some prior evidence of reduced efficacy of LPV/r monotherapy from prior studies, the simplicity and cost benefits prompted a clinical trial in Africa /Asia (n=123).

Methods

Single-arm study of pts (median CD4 164 cells/mm^3) with prior failure of 1^{st}-line ART, and most had baseline resistance to 3TC (95%), EFV (98%) with no data provide on NRTIs.

Bartlett AIDS 2012

PI monotherapy in low resource settings

What is the evidence?

Outcomes:

At 24 wks, 87% on treatment with viral load <400 c/mL.

- Additional analysis showed that among 37 pts with "suppression," there was low viremia of 40-400 c/mL.

Virologic failure was observed more frequently in patients with baseline viral load of >100,000 c/mL compared to <100,000 c/mL (29% vs 10%).

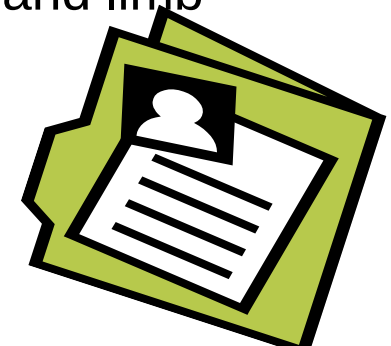
New PI mutations observed in 2 patients at LPV/r monotherapy failure: (1st patient, V82F;

2nd patient, L33F, M46I, I54V and L90M).

Bartlett et al AIDS 2012

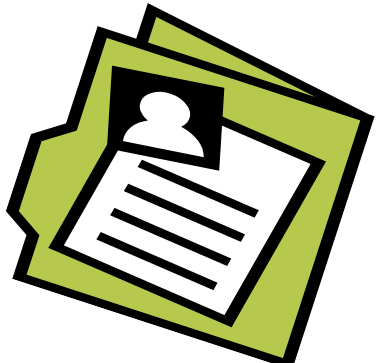
Case

- 40 year old HIV-infected male (nadir CD4 13)
  - Past medical history of DM2 (oral meds), tuberculosis (2006)
- Mar 2007 Initiated D4T + 3TC + EFV
- Aug 2007 CD4 109, VL 580
- Jan 2008 Hospitalized for lactic acidosis (lactate 7.7).
  - ART was discontinued
  - At that time HbAIC noted to be 11.2 ; he initiated insulin
  - Also noted was severe lipodystrophy with facial and limb muscle lipoatrophy &
    abdominal adiposity



Case

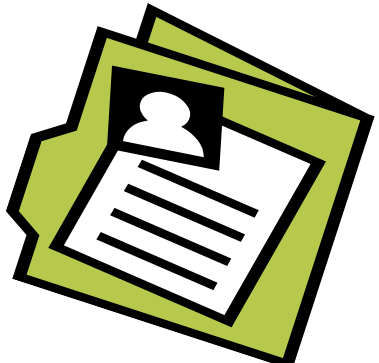
- Mar 2008 (2 months later): Started AZT + 3TC + EFV
- Jun 2008: Developed gall stone pancreatitis, discontinued regimen until August
- Mar – Oct 2008: ART interruption → CD4 126 – 241 and VL 1300 – 3800



Case

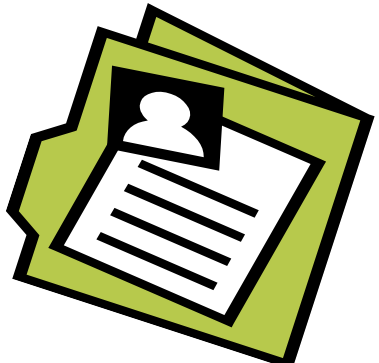
What is your 2nd-line ART regimen ?

1. AZT + 3TC + LPV/r
2. LPV/r + EFV
3. LPV/r monotherapy
4. Hold ART, monitor patient closely



Case

- Oct 2008: He initiated LPV/r + EFV
- Feb 2010: Adjusted regimen to LPV/r + EFV + 3TC



HBV coinfection

A significant number of HBV/HIV coinfected patients in South Africa do not know their HBV status.

- HBV coinfection in 5-20% of HIV patients in SA
- Routine HBV screening previously not performed
- No clear policy for 'catch-up' HBV testing

If change in regimen is considered, HBV testing key. Why?

- Patients who are withdrawn from active HBV agents (TDF, 3TC) at risk for hepatitis, sometimes severe.
- If 3TC is used alone as active agent against HBV, patients are at risk for HBV drug-resistance, HBV rebound hepatitis.

Patients with HBV should be maintained on TDF + 3TC in the 2nd- ART regimen, minimally with 3TC alone.

Mendelson, M et al. SA Journal of HIV Medicine, April 2011

NRTI-sparing regimens

Effective but lipid abnormalities frequent

LPV/r + EFV was compared with 2 NRTI + EFV and 2 NRTI + LPV/r, relative efficacy of the NRTI-sparing regimen was high but there was a high incidence of lipid abnormalities:

- Event -	2 NRTI + EFV	2 NRTI + LPV/r	LPV/r + EFV
Grade 3-4 Abnormalities			
Fasting LDL cholesterol >190 mg/dl (>4.9 mmol/l)	3%	1%	6%
Fasting triglycerides >750 mg/dl (>8.5 mmol/l) *	2%	6%	14%
* For almost 5% of patients in the LPV/r + EFV arm, elevated triglycerides were treatment limiting events			

Riddler *et al*. NEJM 358;20; 2008

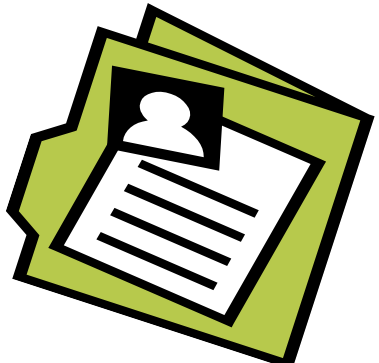
Case

The patient developed hyperlipidemia:

Cholesterol 5.2 mmol/L (201 mg/dl)→ 19.6 mmol/L (757)

Triglycerides 2.72 mmol/L (240 mg/dl)→ 5.10mmol/L (451)

He initiated atorvastatin 10 mg daily



Management questions

What impact can we expect from atorvastatin?

Singh *et al.* conducted an observational study among HIV-infected patients with dyslipidemia, 2/3 were receiving boosted PI-based ART.

Most common statins used: atorvastatin, rosuvastatin, and pravastatin.

Median dose of atorvastatin was 20mg/day.

- One year after atorvastatin therapy, changes observed:
  - Total chol. - 1.0 mmol/L (-39 mg/dl)
  - LDL-C - 0.7 mmol/L (-26 mg/dl)
  - Trigyclerides - 0.7 mmol/L (-60 mg/dl)

Low rates of toxicity in all groups, but myalgias not well documented.

Conclusion: Atorvastatin and rosuvastatin were effective with rosuvastatin slightly more so. Both may be superior to pravastatin.

Clinical Infectious Diseases 2011;52(3):387–395

Case

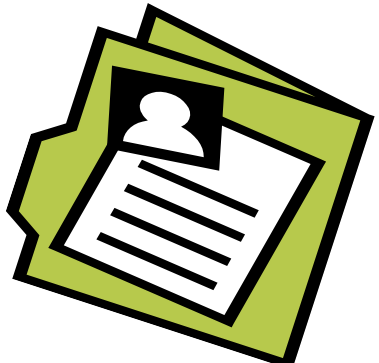
He subsequently developed VF on LPV/r + EFV + 3TC:

2 months after 2nd-line switch:

Apr 2010: CD4 134, VL 1268

10 months after 2nd-line switch:

Oct 2010: CD4 ?, VL 420 000



Management questions

What are the long-term outcomes we can expect with boosted PI 2nd line ART?

Long-term 2nd-line outcomes at Sinikithemba clinic

Immunologic, virologic and clinical outcomes after switch

	Month 6	Month 12	Month 18	Month 24
2nd-line patients remaining in follow-up	136	126	112	99
Died during prior 6 months (no.)	N/A[3]	0	0	1
Loss to follow-up prior 6 months (no.)	N/A[3]	4	7	6
Changed provider prior 6 months (no.)	N/A[3]	6	7	6
Viral load >1000 copies/mL (%)[2]	36/136 (26%)	32/126 (25%)	23/112 (21%)	25/99 (25%)

1 Baseline was the CD4 cell count within 2 months of first-line regimen failure.
2 Among patients in active follow-up. Missing=failure rule applied for patients in active follow-up but with no data at interval.
3 By definition all patients included in this analysis completed six months of second-line ART

JAIDS 2012

Characteristics of patients at McCord with 2nd-line ART failure

At 2nd-line ART failure, South African patients were found to have relatively advanced immunosuppression.

- Median CD4 cell count 84 cells/mm3 (IQR, 64-128)
- Median viral load 16,500 c/mL (IQR, 2,907-84,904).

Viral resuppression after 2nd-line failure was observed frequently, occurring in 22 (47%) of 49

- Among patients remaining in care (not LTFU), the mortality was very low.

Characteristic	Median (IQR)	N (%)
Time to failure (months)		
Median time to VF	**11 (5-16)**	
Median time to imm. fail	**11.5 (5-18)**	
Viral load at 2nd-line ART failure (copies/ml)		
Median viral load	**16,500 (2907-84904)**	
CD4 cell count at 2nd-line ART failure (cells/mm^3)		
Median CD4 cell count	**84 (64-122)**	
Viral resuppression after 2nd-line VF		
Yes		**22 (47)**
No		**27 (53)**

JAIDS 2012

Key causes of 2nd-line ART failure

- **Suboptimal adherence**
  - **Side effects**
  - **Unable to correct prior poor adherence pattern**
  - **Local factors: user fees, stock-outs, distance, ?alternative medicine**
- **Antiretroviral drug resistance**
  - **PI mutations may be important**
  - **NRTI mutations may not be**
- **Drug-drug interactions**
  - **Example: Concomitant rifampicin-containing TB therapy**
    - **Rifampicin lowers lopinavir drug concentrations**

Adherence and outcome during second-line ART in South Africa

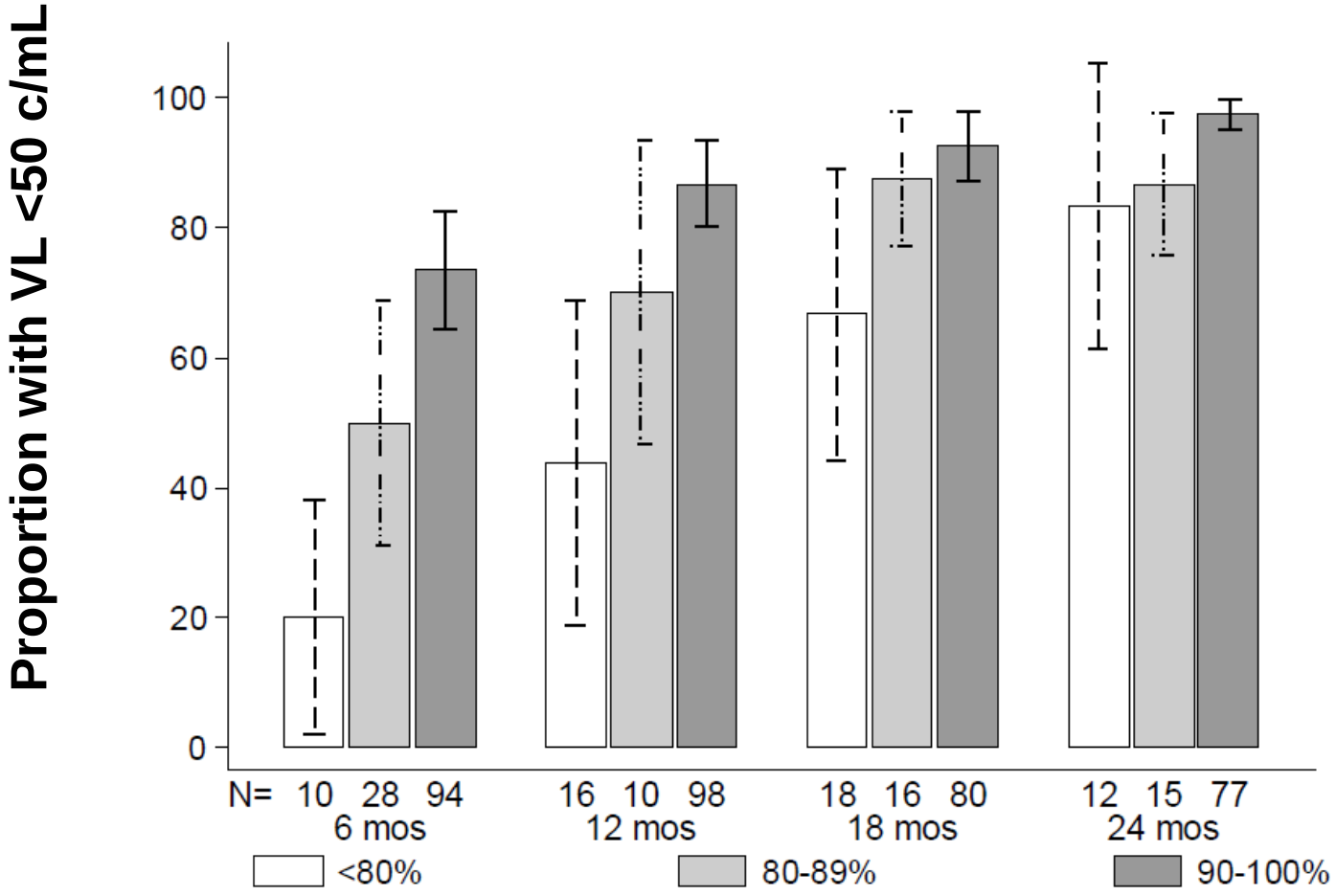
Adherence improves in the 6 months following switch to second-line ART:

- 6 months prior to switch: median adherence 67% (IQR, 33-67)
- 6 months following switch: median adherence 100% (IQR, 83-100)

Long-term 2nd-line outcomes at Sinikithemba clinic

But then what?

Virologic outcome according to adherence level over time



Factors associated with high level of adherence to second-line ART in multivariate analysis

Factor	Odds ratio	P
Age (above the median)	1.9 (0.7-5.4)	0.22
Male gender	0.8 (0.3–2.0)	0.57
Adherence during final six months of first-line ART (above the median)	4.4 (1.6–12.3)	0.004 *
CD4 cell count >100 cells/µL at second-line ART initiation	0.6 (0.2–2.2)	0.47
Viral load at second-line initiation of >4.5 log10 c/µL	0.8 (0.3–2.3)	0.68
NRTI backbone		
AZT/DDI	1	
AZT/3TC	0.6 (0.2-1.9)	0.39
Other	1.6 (0.3-9.7)	0.62

Case

- Feb 2010, HIV genotype performed after failure of 1st-line ART (D4T, 3TC, EFV and AZT, 3TC, EFV) and 2nd-line ART (LPV/r + EFV).

Case

What results do you predict for the genotype?

1. No significant resistance mutations
2. NNRTI and NRTI resistance
3. M184V alone
4. Triple class resistance with NNRTI, NRTI and PI resistance

Case

- Feb 2010, HIV genotype revealed triple class resistance
  - PI Mutations:
    - M46I, I54V, V82A, L10F
    - High level resistance: LPV/r, ATZ/r, fosamprenavir/r
    - Low level resistance: tipranavir/r
    - Susceptible: darunavir/r
  - NRTI Resistance Mutations:
    - D67N, M184V
    - Low level resistance: ABC, DDI
    - Susceptible: AZT, D4T, and TDF
    - Special: 3TC
  - NNRTI Resistance Mutations:
    - K103N, V106M
    - High-level resistance: all NNRTIs except etravirine (susceptible)

Key causes of 2nd-line ART failure

- Suboptimal adherence
  - Side effects
  - Unable to correct poor adherence during 1st-line ART
  - Local factors: user fees, stock-outs, distance, alternative med
- Antiretroviral drug resistance
  - PI mutations may be important
  - NRTI mutations may not be
- Drug-drug interactions
  - Example: Concomitant rifampicin-containing TB therapy
    - Rifampicin lowers lopinavir drug concentrations

Drug resistance mutations at the time of 2nd-line ART failure - India

Saravan et al performed a cross sectional study of patients on PI-based 2nd-line ART in Chennair, Southern India with subtype C virus

Cross sectional study of patients (n=107) 2nd-line ART with boosted ATV (48%), boosted IDV (45%) or boosted LPV (8%)

- Exposure to an unboosted PI, particularly IDV was reported in this cohort at 16 of 107 (15%)
- 77 (72%) of 107 were viremic with median VL of 5450 copies/mL

PI mutations noted associated with resistance to LPV/r:

- M46I (22 samples / 49%), I54 V/A (17 samples / 38%), V82A (17 samples / 38%), L90M (14 samples / 31%)
- It was not noted if all patients with PI mutations had prior PI exposure

TAMs noted in 71%; TAM1 (50%), TAM 2 (28%), TAM 1 + TAM 2 (22%)

Resistance at 2nd line failure:

Evidence of PI resistance in minority in South Africa

Sunpath *et al.* genotyped 21 patients with virologic failure during 2nd line LPV/r-based ART.

Among the 21 patients, 3 (14%) shown to reduce susceptibility to PIs.

Patient	PI Mutations	Predicted DRV/r activity*
1	M46I, I54L, L76V, I84V	Intermediate resistance
4	M46I, I54V, V82A	Susceptible
6	M46I, I54V, L76V, V82A	Low level resistance

*Stanford HIV Drug Resistance Database

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Boosted PI-containing ART in patients with TB coinfection

The management of TB coinfection in patients receiving a PI is a challenge because rifampicin reduces the trough concentration of most PIs.

Rifampicin induces cytochrome 3A4 and p-glycoprotein resulting in a 90% reduction in lopinavir trough concentrations.

This reduction in lopinavir can be attenutated by using higher doses of RTV or higher doses of LPV.

PI-containing ART in TB

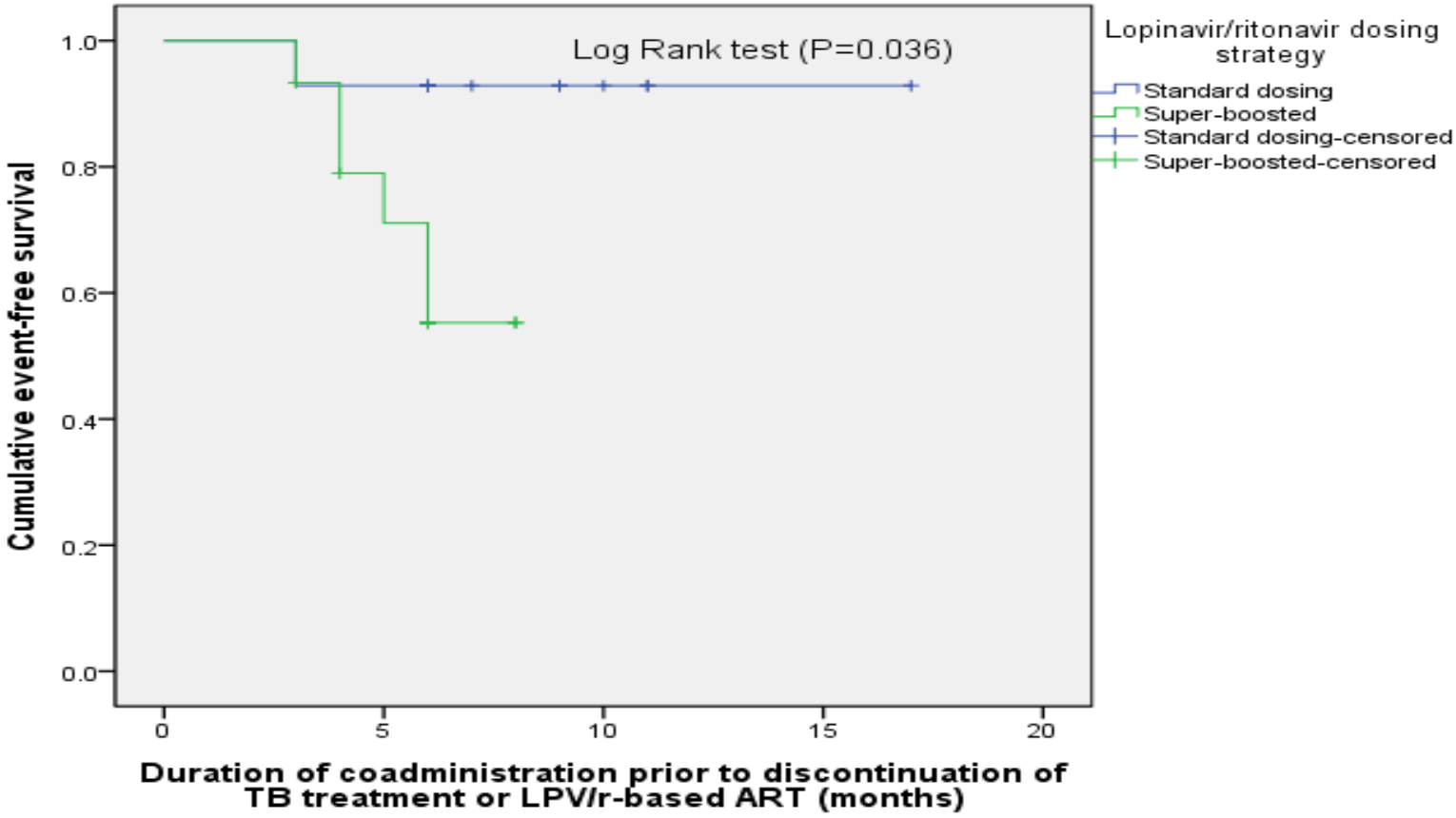
A previous recommendation in South Africa was to super-boost LPV/r in this setting:

This involved increasing RTV dose given with LPV resulting in a total dose of during TB treatment of LPV/r of 400 /400 mg twice daily.

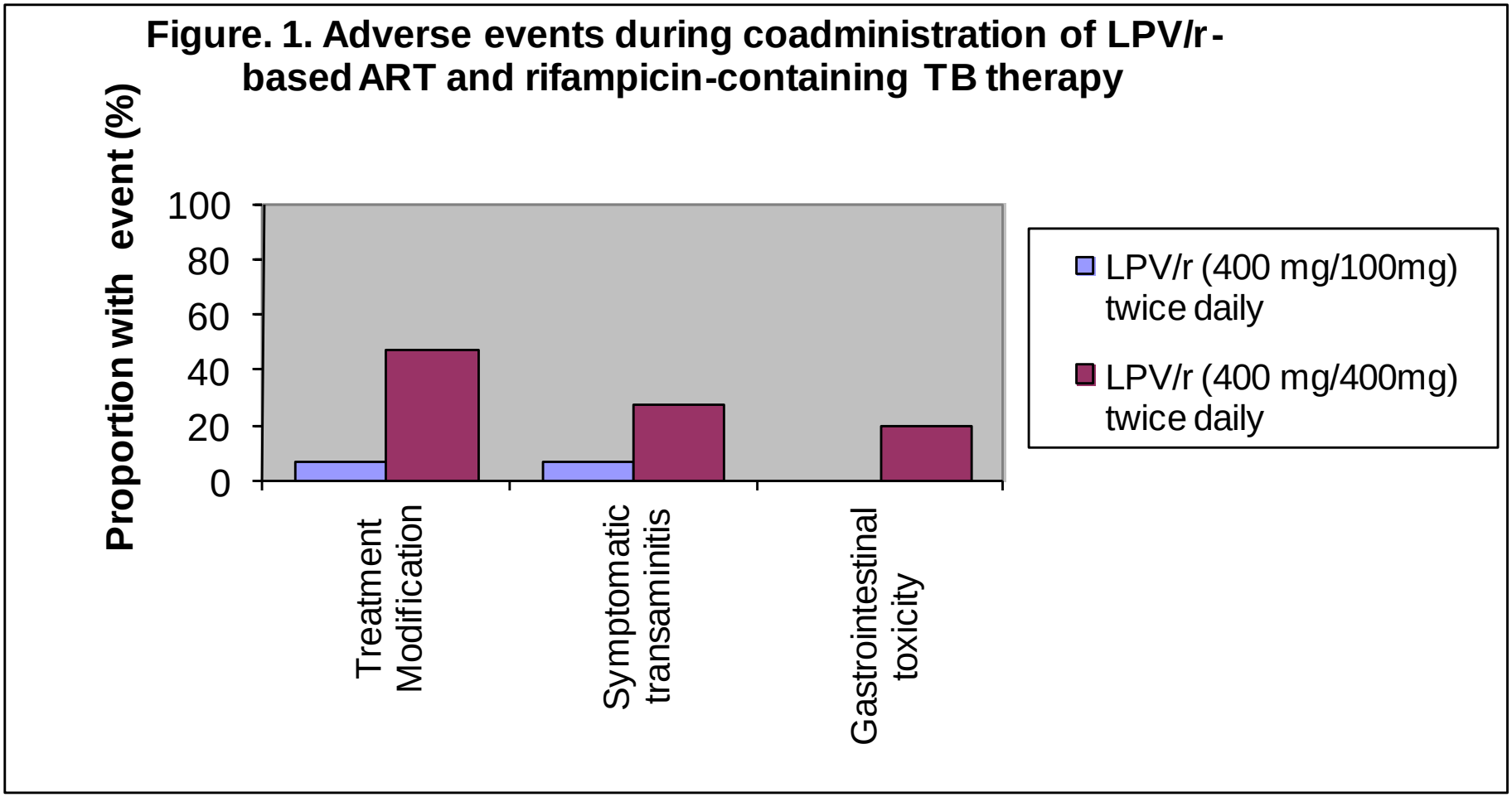
- **Involved providing supplemental dose of RTV 300 mg twice daily**

Although reasonably well tolerated in HIV-infected children, this strategy has been poorly well tolerated in adult volunteers and in HIV-infected patients in Europe.

McCord Hospital: Clinical outcomes associated with coadministered super-boosted LPV/r and rifampicin



McCord Hospital: Toxicity associated with coadministered super-boosted LPV/r and rifampicin



South African recommendation for HIV/ TB patients receiving LPV/r-based 2nd line ART

2010 SA HIV Guidelines: “Patients receiving lopinavir/ritonavir (Aluvia) should have their dose doubled slowly over 2 weeks to 800/200 mg twice a day (4 tabs bd)”

The total ritonavir dose with the new recommendation is 400 mg/day (LPV/r 4 tabs bd contains 400 mg RTV) versus 800 mg/day with prior strategy.

What is the evidence?

PI-containing ART in TB:

Double dose LPV/r 800/200mg (4 tabs) bid?

Decloedt and Maartens *et al* (SA) study of patients receiving TB therapy:

- 11 patients received double dose LPV/r (4 tabs/bd)
- 9 received additional RTV (+300 mg RTV /bd)

Results: LPV concentrations remain above 1mg/L in most patients

- 10/11 (91%) patients maintained an undetectable viral load

1/2 of patients developed at least one AE

- Grade 1 and 2 transaminitis common but no severe hepatotoxicity
- More patients in the additional RTV group developed AE vs double dose LPV/r group (5/7 compared to 5/11).
- 1 pt. defaulted additional RTV due to nausea , 1 pt. receiving double-dose LPV/r had "intolerable diarrhea" and LPV/r dose ↓ to 3 tabs bd

Authors recommend: Gradually increasing LPV/r to 4 tabs bd & monitor transaminases.

PLOS One 2012

Future options? Use of raltegravir in HIV/TB coinfection

Raltegravir 400 mg bid acceptable, maybe preferable

Prior data showed that when raltegravir is combined with rifampicin, trough RAL concentrations are reduced 61% and AUC drops 40%.

This effect partially compensated if RAL is increased to 800 mg bid.

But a randomized clinical trial showed that among patients who received rifampicin-based TB therapy followed after a median of 8 wks by TDF + 3TC + RAL 400 mg OR 800 mg BID the following 24 week outcomes were observed (n=~50 per group):

- RAL 400 mg bid: 24 wk suppression rate 76%, 0 AE with discontinuation
- RAL 800 mg bid: 24 wk suppression rate 78%, 3 AE with discontinuation

(**2 with severe hepatotoxicity including 1 fulminant failure → liver tranpt.)**

- Trend to ↑ integrase resistance in RAL 400 bid arm (4 pts.) vs 800 bid (1 pt.)
- Suggestion of ↑toxicity in the RAL 800 mg bid arm

Grinsztejn B et al IAC 2012

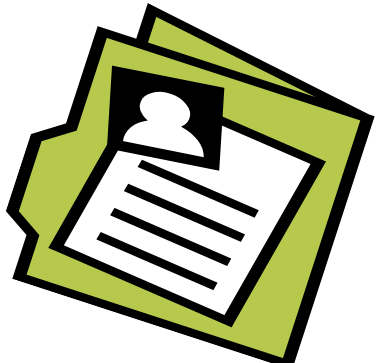
Case

Ongoing virologic failure with triple class resistance including high level resistance to LPV/r and atazanavir/r

- Oct 2011: CD4 count 240, VL 25,119

What is your next regimen?

1. No change: LPV/r + EFV + 3TC
2. DRV/r + TDF + 3TC
3. DRV/r + RAL + etravirine
4. Withdraw ART, monitor closely



Considerations for 3rd-line ART

1. A thorough history of prior regimens and outcomes, prior adverse effects, and resistance testing if available are key.

2. There should be 2, ideally 3, active new agents in salvage regimen.

3. Total pill burden an important consideration.

   Example: - DRV 600 mg (one 600 mg tab) + RTV 100mg twice daily with food = 4 pills/day
   - Etravirine 200 mg twice daily with food = 4 pills/day
   - Raltegravir 400 mg twice daily = 2 pills/day

4. Drug-drug interactions may be present

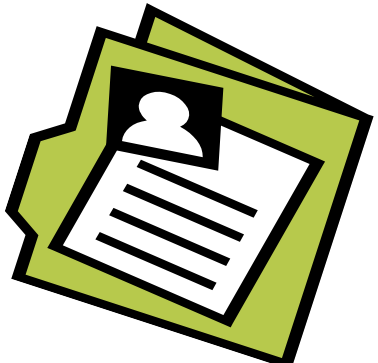
   Example: Rifampicin interaction with boosted PIs

Case

- Feb 2012, initiated DRV/r + TDF + 3TC

- Apr 2012: CD4 334 and VL <40
  - Pt tolerating regimen with no side effects
  - Metabolic profile:
    - Cholesterol 5.9 mmol/l (228 mg/dl)
    - Trig 3.2 mmol/l (283 mg/dl)
    - HBAIC 7.2

Lipodystrophy → unchanged



Darunavir/r

DRV/r dosing

Treatment experienced: 600/100 mg twice daily with food

Treatment naive: 800/100 mg once daily with food

(RTV must be given separately !)

Bioavailability: 82%, food increases AUC 30%

Interactions: Substrate and inhibitor of CYP 3A4.

Adverse effects

Rash 7%

GI intolerance (nausea, diarrhea) 20%

But better GI tolerability and lipid side effects compared LPV/r

Low rate of dyslipidemia and insulin resistance/hyperglycemia.

- Metabolic profile closer to atazanavir/r than LPV/r

SA HIV Clinician's Society

New recommendations for genotype resistance testing

- 2012 Recommendations:

Adults and children with virologic failure of NNRTI or PI-based ART	**Recommended**	**Adherence must be addressed at time of failure.**
Documented acute infection	**Recommended**	**Public health surveillance**
Infants/children <2 years of age exposed or possibly exposed to PMTCT	**Recommended**	**At the time of diagnosis**
Children ≥ 2 years of age who stopped NVP within 2 years.	**Recommended**	**At the time of diagnosis**
Pregnant women receiving triple therapy with two viral loads >1000 copies after ≥3 months of ART.	**Recommended**	**Adherence must be addressed at time of failure.**

Acknowledgments

McCord Hospital

Henry Sunpath
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Metabolic effects of Darunavir/r

Metabolic effects for DRV/r 800/100 mg daily compared with ATV/r 300/100 mg daily both in combination with TDF/FTC.

At week 48, 77% of DRV/r and 71% of ATV/r subjects achieved virologic response.

- Only small changes in lipid levels observed to 48 weeks with no clinically relevant difference between arms
- At week 48 minimal effect of both DRV/r and ATV/r on fasting glucose and insulin sensitivity with no difference between the arms
  - Impact of PIs on insulin sensitivity remains controversial
- Changes in adipose tissue were small and comparable between arms

Conclusion: *Metabolic profile of DRV/r when combined with 100mg of RTV is comparable to atazanavir/r.*

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