NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Antiretroviral Switch Studies

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Antiretroviral Switch Studies

1. To raltegravir (Isentress): **SWITCHMRK, SPIRAL**
2. To tenofovir/emtricitabine (Truvada): **SWIFT**
3. To tenofovir/emtricitabine/rilpivirine (Complera): **SPIRIT**
4. To atazanavir (Reyataz): **ATAZIP, SWAN, SLOAT**
5. From tenofovir/emtricitabine/efavirenz (Atripla)

Why Switch?

- To reduce side effects (acute or chronic)
- To decrease pill burden, simplify regimen
- Key = must maintain virological control
- Are switch studies *ethical*?

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PLoS MEDICINE

Essay

The Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior?

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Switch to Raltegravir: SWITCHMRK, SPIRAL

SWITCHMRK 1 & 2: Boosted PI to Raltegravir

Study Design

- N = 707 HIV-infected adults
- Virologically suppressed on lopinavir/ritonavir (Kaletra) + ≥2 NRTI's for ≥3 months
- Multicenter, double-blind, double-dummy, phase 3 RCT's
- Goal: improve lipids and other side effects
- Endpoints: change in lipids at week 12, VL <50 at week 24

352: Continue lopinavir/ritonavir (Kaletra)

350: Switch to raltegravir (Isentress)

24 Weeks

Source: Eron JJ et al. Lancet 2010 Jan 30; 375:396.

SWITCHMRK 1& 2 Combined Results

	Total cholesterol	LDL	Triglycerides	HIV RNA <50 copies
Lopinavir/ ritonavir (Kaletra)	+1.0%	+2.6%	+6.2%	**90.6%**
Raltegravir (Isentress)	**-12.6%**	**-15.0%**	**-42.2%**	84.4%

- *What did we learn?* Raltegravir is not for everyone! Increased risk of virological failure when switching from a PI, particularly if prior ART failure or NRTI resistance

Source: Eron JJ et al. Lancet 2010 Jan 30; 375:396.

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SPIRAL: Another PI to Raltegravir Switch
With Remarkably Different Results

- **Conclusion:**
  - Switch to raltegravir non-inferior, also improves lipids[1] and bone mineral density[2]
- **What accounts for the difference?**
  - Smaller study (273 participants), 48 weeks, open label
  - Participants VL suppressed for ≥6 months (median 6 years)
  - Other boosted PI's included (lopinavir 44%, atazanavir 35%)
  - NRTI backbones not equivalent?
  - Prior virological failure: SPIRAL 38%, SWITCHMRK 34%

Sources:

1. Martinez E et al. AIDS. 2010;24:1697-1707.
2. Curran A et al. AIDS. 2012 Feb 20;26(4):475-81

Switching Boosted PI to Raltegravir

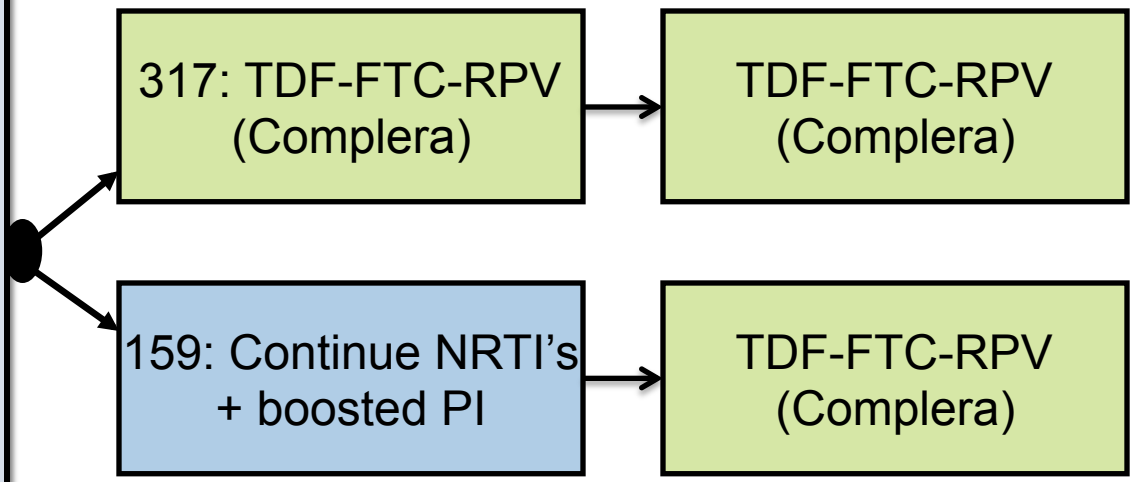
- **Summary**:
  - Requires caution and likely should be avoided if history of multiple prior regimens, poor adherence, or prior virological failure
  - If suppressed on boosted PI for a long time without that history, more likely the switch will be ok
  - Switch leads to improvement in metabolic parameters

Switch to Complera: SPIRIT

SPIRIT: Switch to Tenofovir-Emtricitabine-Rilpivirine (Complera)

Study Design

- N = 476 HIV+ adults
- HIV RNA <50 on 2 NRTI's + boosted PI x ≥6 months
- On 1st or 2nd regimen with no h/o NNRTI use or resistance to study drugs
- 1º endpoint: HIV RNA <50 at 24 weeks
- 2º endpoints: tolerability, lipids at 24 & 48 wks



Source: Palella F et al. ACT HIV Conference, March 2013.

SPIRIT Results

	Total cholesterol	LDL	Triglycerides	HIV RNA <50 copies
Boosted PI	-1	0	+3	89.9%
Complera	**-25**	**-16**	**-53**	93.7%

- PI: 30% lopinavir, 30% atazanavir, 20% darunavir
- *What did we learn?* For select patients, a switch to Complera may be safe and may improve lipid parameters

Source: Palella F et al. ACT HIV Conference, March 2013.

To Tenofovir/Emtricitabine (Truvada): SWIFT

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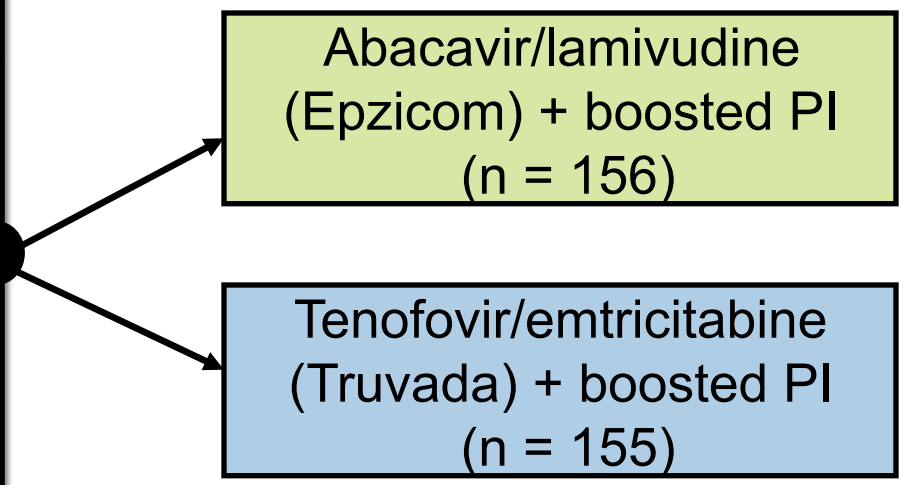
Study Design

- N = 311 HIV-infected adults
- On abacavir/lamivudine (Epzicom) + boosted PI with HIV RNA <50
- Prospective, randomized, double-blind, multicenter trial
- 1^{o} endpoint: Proportion with HIV RNA <200 at 48 weeks
- 2^{o} endpoints: virological failure, safety and tolerability, lipid changes, renal changes



Source: Campo R et al. Clin Infect Dis. 2013 Jun;56(11):1637-45.

SWIFT Results

	HIV RNA <200	Virological failure	Discontinued due to AE	Renal AE	Lipid Change
Tenofovir-emtricitabine (Truvada)	86.4%	**1.9%**	4.5%	4.5%	**TC -21, LDL -7, HDL -18**
Abacavir-lamivudine (Epzicom)	83.3%	7.9%	**1.9%**	5.1%	TC -3, LDL -1, HDL -9

- *What did we learn*? Confirms results of A5202 and ASSERT: less virological failure with Truvada
- Biggest limitation: few participants taking boosted darunavir

Source: Campo R et al. Clin Infect Dis. 2013 Jun;56(11):1637-45.

To Atazanavir (Reyataz): ATAZIP, SWAN, SLOAT

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- **ATAZIP & SLOAT**:
  - Lopinavir/ritonavir (Kaletra) to atazanavir (Reyataz) + ritonavir (Norvir) maintains VL <50 and improves lipids through 48 weeks
- **SWAN:**
  - Boosted PI (70% lopinavir/ritonavir) to atazanavir + ritonavir in maintains VL <50 and improves lipids through 48 weeks

Sources:

1. Mallolas J et al. J Acquir Immune Defic Syndr. 2009 May 1;51(1):29-36.
2. Soriano V et al. J Antimicrob Chemother. 2008 Jan;61(1):200-5.
3. Gatell et al. Clin Infect Dis. 2007 Jun 1;44(11):1484-92.

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Switching From Efavirenz

- **Efavirenz to rilpivirine:**
  - 50 participants (46 men), suppressed on tenofovir-emtricitabine-efavirenz (Atripla) for ≥8 weeks
  - All remained suppressed at 12 weeks despite lower rilpivirine levels
- **Efavirenz to raltegavir:**
  - 40 participants (38 men), suppressed on tenofovir-emtricitabine-efavirenz (Atripla)
  - All remained suppressed, plus improved CNS symptoms and sleep (by 4 weeks) and lipids (by 12 weeks)

Sources:

1. C Cohen, A Mills, E DeJesus, et al. 13th European AIDS Conference (EACS 2011). Belgrade, October 12-15, 2011. Abstract LBPS10/4
2. Yapa HM, Waters L, Rowlands J, et al. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, June 30-July 3, 2013, Kuala Lumpur. Abstract MOPE090.

Ongoing and Future Studies

- Switch studies to tenofovir/emtricitabine/cobicistat/ elvitegravir (Stribild)
- MARCH: switch to maraviroc (Selzentry)
- Switch studies to dolutegravir