Stribild. Another building block in the fight against HIV

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10 October 2013

Case of NB

- NB 15yo female comes to Oak Tree Clinic at Children & Women's Hospital on 10 July 2013
- C/C: New rash on arms and face
- Restarted antiretrovirals (ARV) on 3 June

Case of NB

- Perinatally infected since birth, otherwise healthy
- on ARV at birth until 3yo
- attempted to restart ARV twice (Oct 2010 and April 2011) but side effects from regimens made therapy intolerable
- annual blood work on 15 April 2013

  VL 15,314 copies/mL and CD4 330 (17%)
- restarted ARV with Kivexa (abacavir and lamivudine), atazanavir, ritonavir, raltegravir

Case of NB

3 June	Started ARV
5 June	New diffuse itch on both arms
6 June - 7 July	Scleral icterus developed and itchiness persisted despite diphenhydramine topical creams
8 July	Maculopapular rash started on anus that spread to both arms and shoulders with a little on her face
9 July	Called Oak Tree when rash did not go away and told to come in 10July

Case of NB

- Drug Rash?
- No other medications
- No known drug allergies
- HLA negative
- Previous ARV trials
  - Kivexa/ Tenofovir/ Kaletra (lopinavir and ritonavir)
  - Kivexa/ Tenofovir/ Atazanavir/ Ritonavir
- Current ARV regimen
  - Kivexa/ Raltegravir/ Atazanavir/ Ritonavir

Rating scheme for recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Optional recommendation	I: ≥ 1 randomized trials <u>in children</u> with clinical outcomes and/or validated laboratory endpoints I*: ≥ 1 randomized trials <u>in adults</u> with clinical outcomes and/or validated lab endpoints with data <u>in children</u> from ≥ 1 well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes II: ≥ 1 well-designed, nonrandomized trials or observational cohort studies <u>in children</u> with long-term clinical outcomes II*: ≥ 1 well-designed nonrandomized trials or observational cohort studies <u>in adults</u> with long-term clinical outcomes with data <u>in children</u> from ≥ 1 smaller nonrandomized trials or cohort studies with clinical outcome data III: Expert opinion

Pediatric HIV Guidelines

- When to start ARV
  - if <12 weeks old (AI)
  - if 12 weeks - 12 months old (AII)
  - if 1 - 3yo, CD4 <1000cells/mm3 or CD4% <25% (AII)
  - if 3 - 5yo, CD4 < 750cells/mm3 or CD4% <25% (AII)
  - if ≥ 5yo, CD4 ≤ 500cells/mm3 (AI* for <350, BII* for 350-500)
  - If AIDS or significant HIV-related symptoms regardless of CD4 percentage/count or HIV RNA level (AI*)

Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children.http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf .

Goals of therapy

- Reduce HIV-related mortality and morbidity
- Preserve or normalize immune status (AI)
- Achieve maximal and durable viral suppression to below limits of quantification on ultrasensitive assays (AI)
- Prevent emergence of viral drug resistance
- Minimize and avoid adverse drug reactions
- Maintain normal physical growth and development
- Discuss and stress adherence at each visit and explore strategies to maintain or improve adherence (AIII)
- Prescribe simplest ARV regimen (once daily) when feasible (AI*)

Current ARVs

NRTI	Abacavir (ABC)	Protease Inhibitors	Atazanavir (ATV)
	Didanosine (ddI)		Cobicistat (COBI)
	Emtricitabine (FTC)		Darunavir (DRV)
	Lamivudine (3TC)		Fosamprenavir (FPV)
	Stavudine (d4T)		Indinavir (IDV)
	Tenofovir (TDF)		Lopinavir (LPV)
	Zidovudine (AZT)		Nelfinavir (NFV)
			Ritonavir (RTV, /r)
			Saquinavir (SQV)
			Tipranavir (TPV)
NNRTI	Efavirenz (EFV)	Fusion Inhibitor	Enfuvirtide (ENF)
	Etravirine (ETR)	CCR5 Antagonist	Maraviroc (MVC)
	Nevipraine (NVP)	Integrase Inhibitor	Raltegravir (RAL)
	Rilpivirine (RPV)		Elvitegravir (EVG)

What to start...

Preferred Regimens	
NNRTI based	- EFV/TDF/FTC (Atripla)
Boosted PI based	- ATV/r + TDF/FTC (Truvada) - DRV/r + TDF/FTC (Truvada)
INSTI based	- RAL + TDF/FTC (Truvada)
Alternative Regimens	
NNRTI based	- EFV + ABC/3TC (Kivexa) - RPV/TDF/ FTC (Complera) - RPV + ABC/3TC (Kivexa)
Boosted PI based	- ATV/r + ABC/3TC (Kivexa) - DRV/r + ABC/3TC (Kivexa) - FPV/r + (ABC/3TC or TDF/FTC) - LPV/r + (ABC/3TC or TDF/FTC)
INSTI based	- RAL + ABC/3TC - EVG/COBI/FTC/TDF (Stribild)

Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children.http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf .

Stribild

- Approved in Canada 28 Nov 2012; available in BC since May 2013
- Components:
  - Elvitegravir 150mg - daily integrase inhibitor
  - Cobicistat 150mg- CYP3A4 inhibitor - no HIV activity
  - Emtricitabine 200mg - NRTI
  - Tenofovir 300mg - NRTI
- Indications
  - Complete regimen for treatment of HIV-1 in ARV-naive adult ≥ 18yo

The new players...

- Elvitegravir (EVG)
  - Integrase strand transfer inhibitor selectively inhibiting strand-transfer step of integration process of viral DNA into host DNA
- Cobicistat (COBI)
  - CYP3A4 inhibitor to ↑ elvitegravir
  - Inhibits renal tubule secretion
  - Many drug interactions from CYP3A4 inhibition, w modest inhibition of CYP2D6 and limited P-gp

Metifiot M. Advances in Pharmacology 2013; 67: 75 - 105.

Pharmacokinetics

		EVG	COBI	FTC	TDF
A	W/ light meal (20% fat)	34%	--	--	24%
	W/ big meal (50% fat)	87%	--	--	23%
D	Plasma protein binding	98%	97%	< 4%	< 0.7%
M	Metabolism	CYP3A4 Glucuronidation	CYP3A4 CYP2D6	--	--
	Drug interactions	Antacids ↓ EVG CBZ, PHN ↓ EVG RIF, SJW ↓ EVG	Clarithro ↑ COBI CBZ, PHN ↓ COBI RIF, SJW ↓ COBI	--	Induces P-gp
E	Median t1/2 (hrs)	12.9	3.5	10	17
	Eliminated by	Feces	Feces	Renal	Renal

Literature search

P	HIV-1 infected meeting indications for treatment
I	Stribild (EVG/COBI/FTC/TDF)
C	Approved ARV regimen
O	Efficacy - Viral load suppression - CD4 change from baseline Safety: any adverse effects

Literature search

Databases	Cochrane, Google, Google Scholar, EMBASE, Medline, PubMed, Web of Science
Search terms	stribild, cobicistat, elvitegravir, HIV
Limits	English, Humans
Results	3 RCT 1 Open-Label

Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks

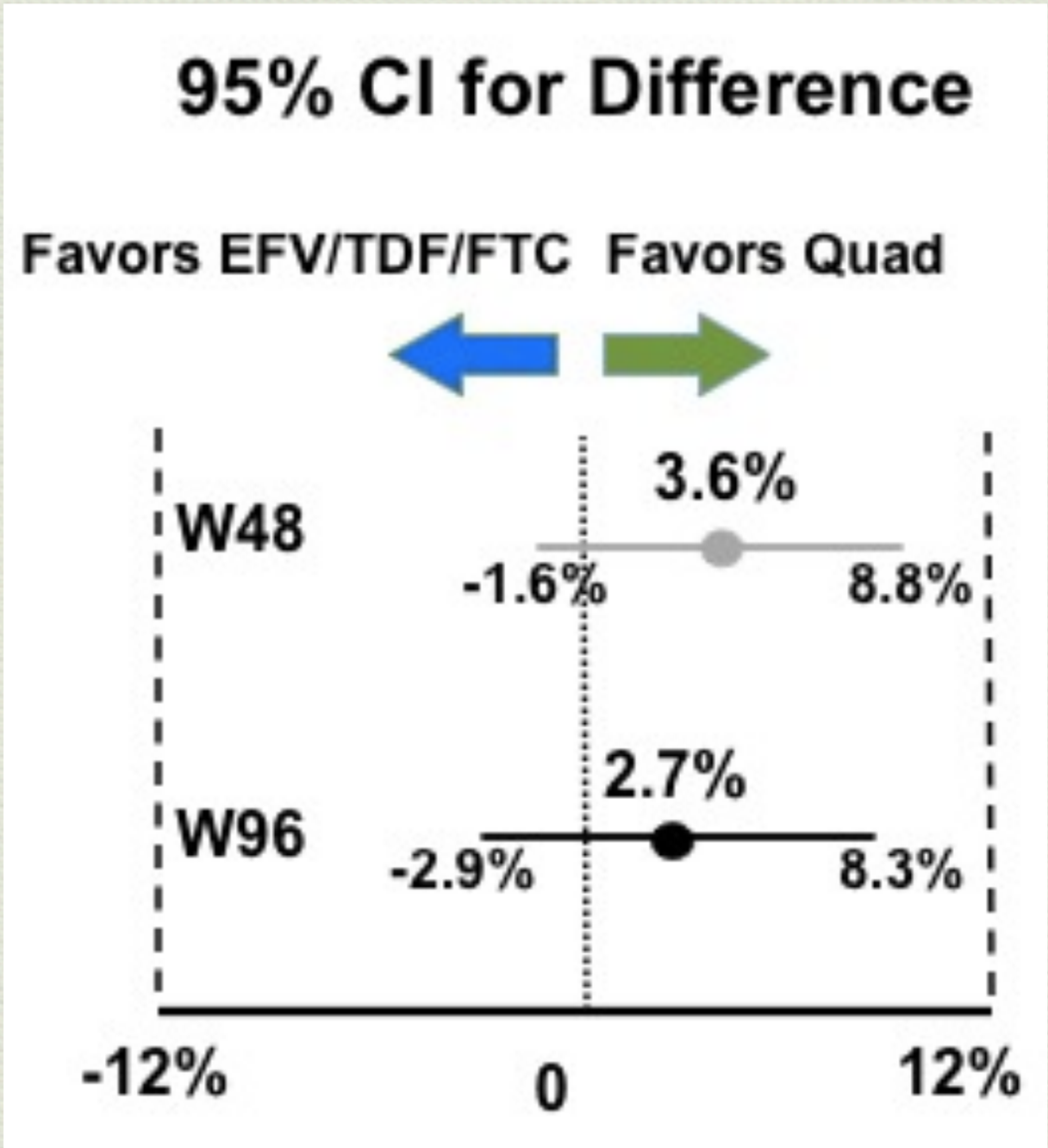
Paul E Sax, Edwin DeJesus, Anthony Mills, Andrew Zolopa, Calvin Cohen, David Wohl, Joel E Gallant, Hui C Liu, Lijie Zhong, Kitty Yale, Kirsten White, Brian P Kearney, Javier Szwarcberg, Erin Quirk, Andrew K Cheng, for the GS-US-236-0102 study team

Lancet 2012; 379:2439-48.

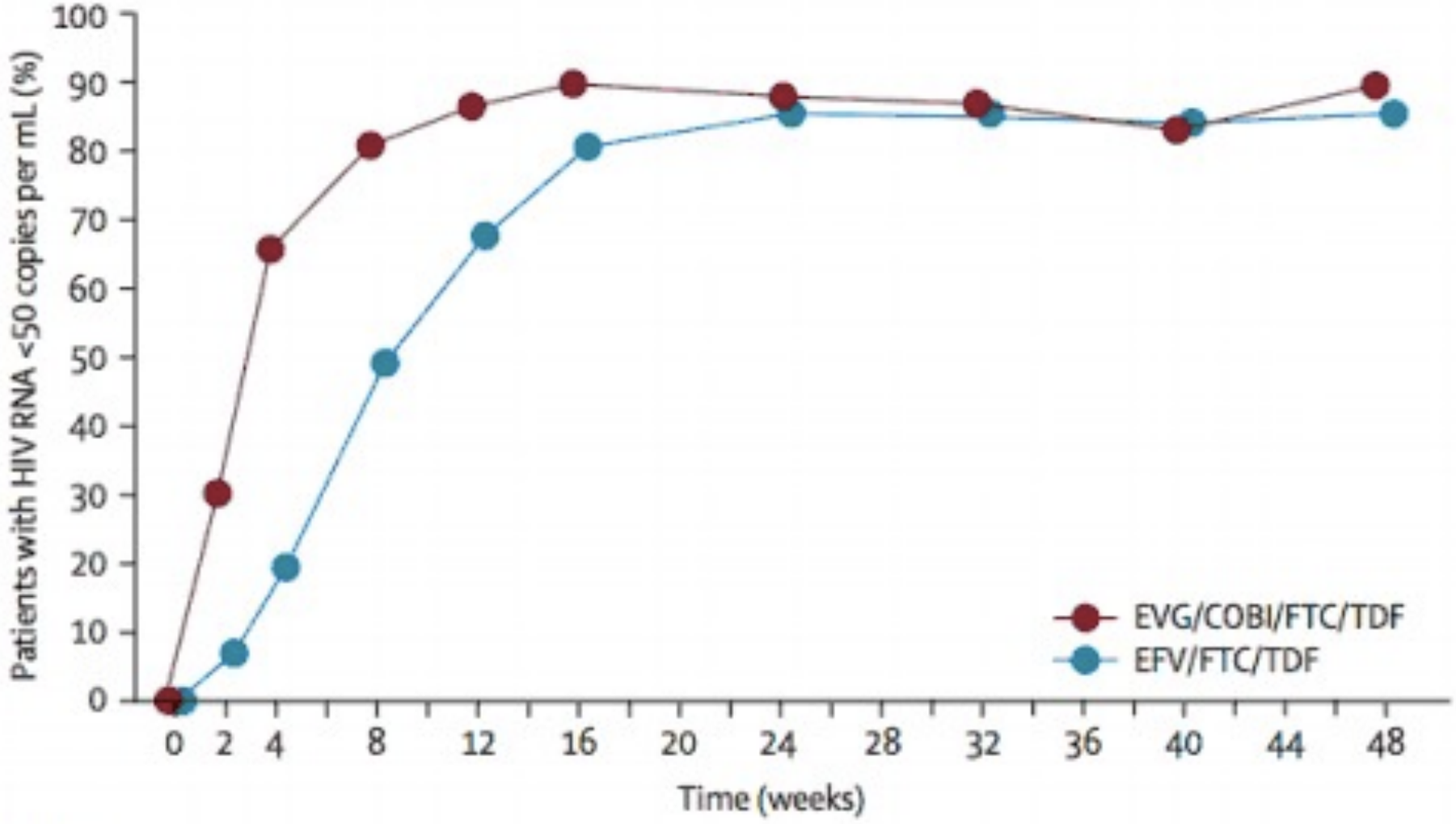
Sax et al 2012

D	Stratified R (1:1), DB, 130 N American sites; Sponsored by Gilead started Mar 2010			
P	n=700, median 37yo, 90% male, 75% white, median HIV RNA 56,230 cells/mm3, Median CD4 376 cells/μL **Incl**: Age ≥ 18yo, ARV naive, no baseline NRTI or NNRTI mutation, HIV RNA ≥ 5,000; negative pregnancy test, HgB ≥ 85, CrCl ≥ 70mL/min; **Excl**: new AIDS defining disorder or serious infection w/in 30d, on treatment for HepC			
I	Stribild with food (n=348)			
C	Atripla HS (n=352)			
O		Stribild	Atripla	Difference (95%CI)
	HIV RNA <50 copies/mL @ 48weeks ITT	87.6%	84.1%	3.6% (-1.6 - 8.8%)
	HIV RNA <50 copies/mL @ 48wks PP	94.9%	96%	-1% (-4.4 - 2.4%)
	Δ baseline CD4 (cells/mm3) @ 48wks	↑ 239	↑ 206	p = 0.009

Sax et al 2012



Sax et al 2012



Number of patients										
EVG/COBI/FTC/TDF	348	348	348	348	348	348	348	348	348	348
EFV/FTC/TDF	352	352	352	352	352	352	352	352	352	352

From ITT population

Sax et al 2012

	Stribild (n=348)	Atripla (n=352)
Median adherence	98%	98%
Adherence <95%	86 (25%)	89 (25%)
Adherence <90%	23 (7%)	36 (10%)
Subjects analyzed for resistance at week 96	14 (4%)	17 (5%)
Resistance at week 96	8 (2%)	8 (2%)

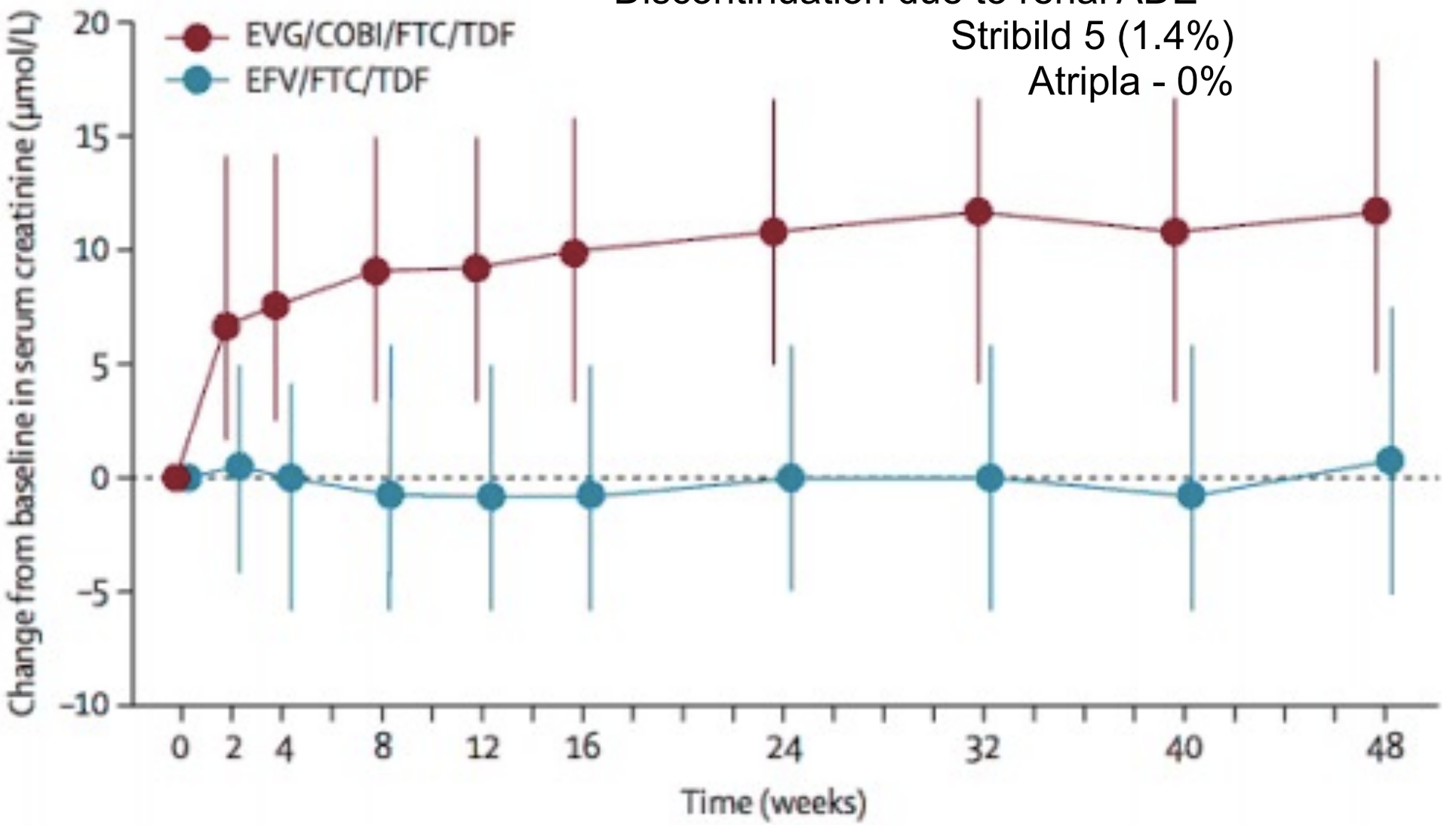
DeJesus E. Poster abstract IDSA 2012

Sax et al 2012

Treatment ADE in ≥ 10% of pt				
		Stribild (n=348)	Atripla (n=352)	
CNS	Abnormal dreams	15%	27%	p <0.001
	Headache	14%	10%	NSS
	Fatigue	12%	13%	
	Depression	9%	11%	
	Insomnia	9%	14%	p <0.031
	Dizziness	7%	24%	p < 0.001
GI	Diarrhea	23%	19%	NSS
	Nausea	21%	14%	p < 0.016
	Fasting cholesterol (mmol/L)	↑ 0.25	↑ 0.49	p <0.001
	LDL Δ (mmol/L)	↑ 0.26	↑ 0.44	p = 0.001
GU	GFR Δ (mL/min)	↓ 14.3	↓ 3.0	p <0.001
Derm	Rash	6%	12%	p = 0.009
	Discontinuation due to ADE	3.7%	5.1%	NSS

Sax et al 2012

Discontinuation due to renal ADE
Stribild 5 (1.4%)
Atripla - 0%



Number of patients										
EVG/COBI/FTC/TDF	348	341	345	341	337	335	328	323	320	320
EFV/FTC/TDF	352	340	340	336	327	323	317	313	309	307

Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial

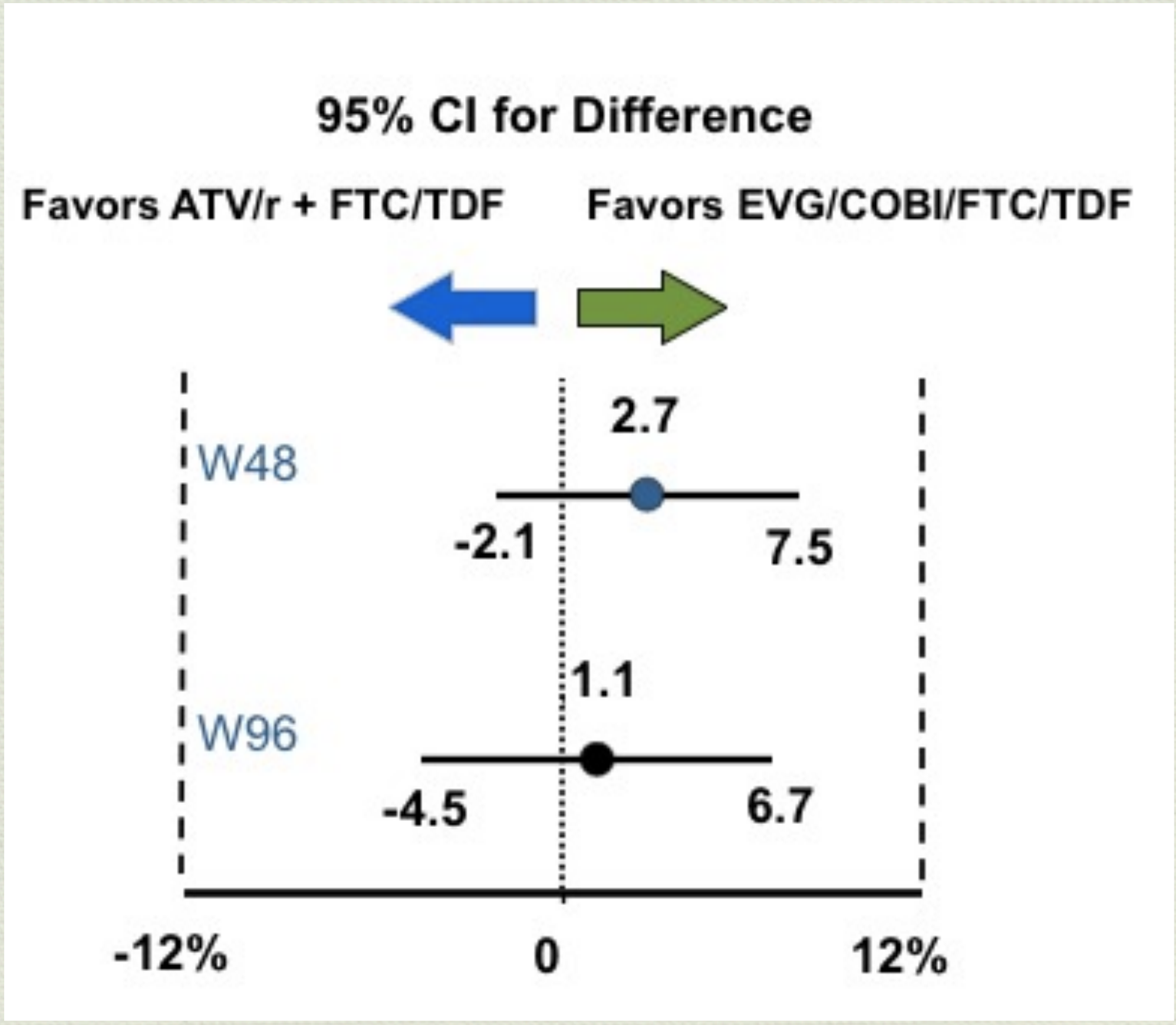
Edwin DeJesus, Jürgen K Rockstroh, Keith Henry, Jean-Michel Molina, Joseph Gathe, Srinivasan Ramanathan, Xuelian Wei, Kitty Yale, Javier Szwarcberg, Kirsten White, Andrew K Cheng, Brian P Kearney, for the GS-236-0103 Study Team

Lancet 2012; 379:2429-38.

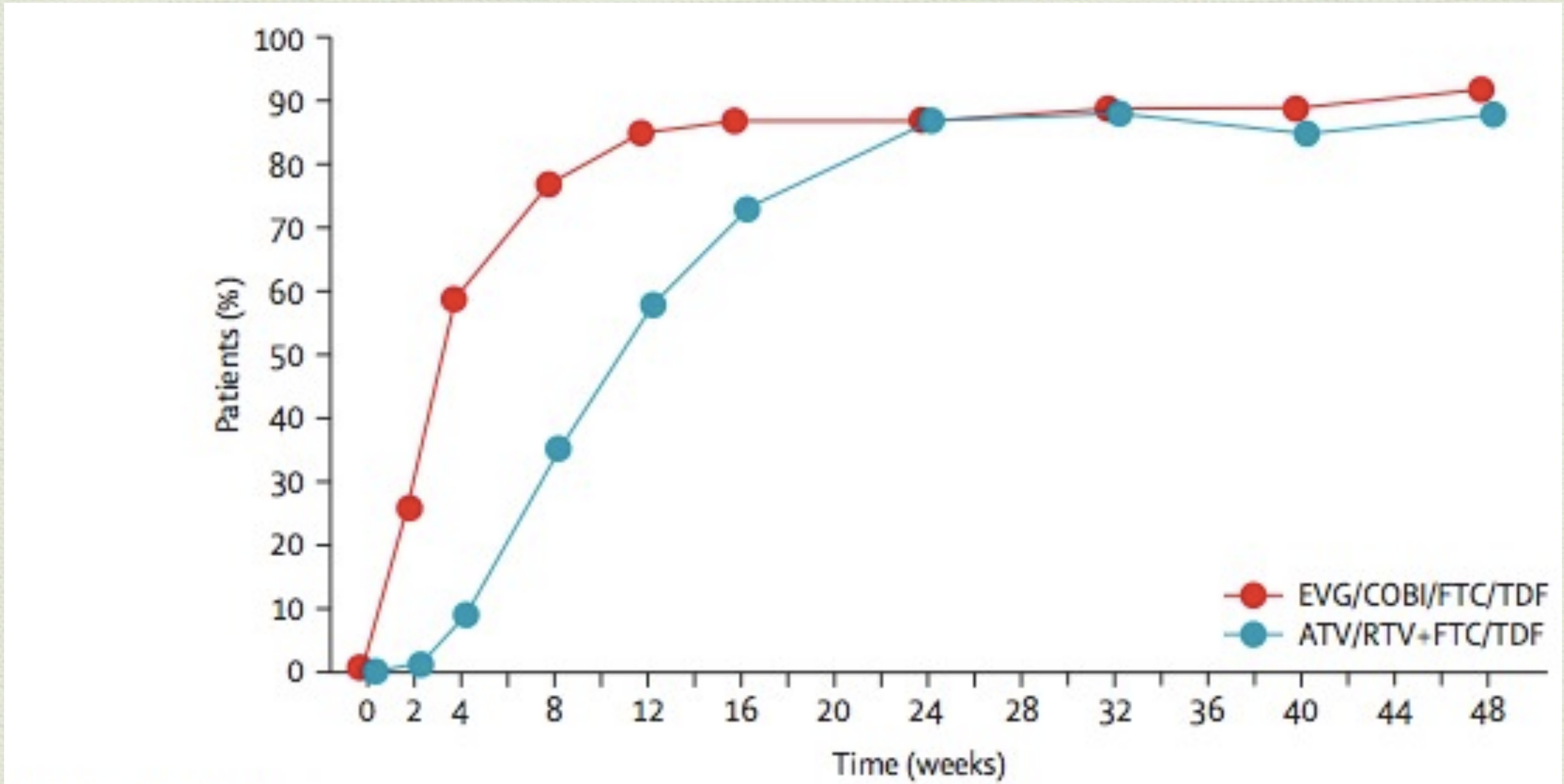
DeJesus et al 2012

D	R (1:1) , DB, double dummy, 146 international sites, non-inferiority, Funded by Gilead			
P	n=708, median age 38yo, 90% men, 75% white, median HIV RNA 63,000 copies/mL, median CD4 359 cells/µL **Incl:** Age ≥ 18yo, ARV naive, no baseline NRTI, NNRTI, or PI mutation, HIV RNA ≥ 5,000, any CD4 count, CrCl ≥ 770mL/min, negative pregnancy test **Excl:** New AIDS defining disorder or serious infection w/in 30d			
I	Stribild (n=353)			
C	ATV/r + TDF/FTC (n=355)			
O		Stribild	ATV/r +TDF/FTC	Difference (95% CI)
	HIV RNA <50 copies/mL @ 48wk: ITT	89.5%	86.8%	3% (-1.9 - 7.8%)
	HIV RNA <50 copies/mL @ 48wk: PP	97.5%	97.7%	- 0.1% (-2.6 - 2.4)
	∆ baseline CD4 (cells/mm3) @ 48wks	↑ 207	↑ 211	SD 160

DeJesus et al 2012



DeJesus et al 2012



Numbers of patients											
EVG/COB/FTC/TDF	353	353	353	353	353	353	353	353	353	353	
ATV/RTV+FTC/TDF	355	355	355	355	355	355	355	355	355	355	

DeJesus et al 2012

	Stribild (n=353)	ATV/r + FTC/TDF (n=355)
Subjects analyzed for resistance	12 (3%)	8 (2%)
Resistance to ARV	5* (1%)	0

*4 pt had primary integrase and NRTI resistance

DeJesus et al

Treatment ADE in ≥ 10% of pt				
		Stribild (n=353)	ATV/r - Truvada (n=355)	p-value
CNS	Headache	53 (15%)	44 (12%)	NSS
	Fatigue	50 (14%)	43 (13%)	
EENT	Ocular Icterus	2 (1%)	51 (14%)	p<0.001
RESP	URTI	54 (15%)	44 (12%)	
GI	Diarrhea	77 (22%)	97 (27%)	NSS
	Nausea	70 (20%)	69 (19%)	
	Δ in triglyceride (mmol/L)	+ 0.001	+ 0.003	0.006
GU	d/c 2o ↑ SCr or toxic nephropathy	2 (1%)	2 (1%)	NSS
	Median Δ in eGFR (mL/min)	-12.7 (-21.8 to -4.3)	-9.5 (-17.9 to 0.2)	<0.001
Discontinuations due to ADE		13 (3.7%)	18 (5.1%)	NSS

Back to NB

Sample Date	AZT	3TC	DDI	D4T	ABA	FTC	TDF	NEV	EFV	ETV	RPV
15-FEB-2001	Fail	Fail	Fail	Fail	Fail		Fail	Fail	Fail		
24-MAY-2001	.9	48.4	1.3	.8	1.7			39.8	24.9		
13-DEC-2001	.9	46.4	1.3	.7	1.6		.6	37.9	24.4		
30-JUL-2012	1.1	.9	.8	.9	.8	.8	.8	1.7	1.4	1.3	
15-APR-2013	.9	.9	.8	.9	.8	.8	.8	2.3	2.2	1.5	1.7

IND/r	NEL	SAQ/r	fAPV/r	LPV/r	ATV/r	TPV/r	DRV/r
Fail	Fail	Fail		Fail			
.8	1	.7					
.7	1	.6		.7			
.7	.8	.6	.7	.8	.7	.8	.6
.7	.8	.6	.6	.8	.7	.8	.6

Will try

Stribild (EVG/COBI/TDF/FTC)
+ ABC

Back to NB

	31 July 2012	15 April 2013	10 July 2013	19 Aug 2013
CD4	410 (19%)	330 (17%)	360 (28%)	830 (22%)
VL	31368	15314	244	50
Glucose random				4.3
SCr	40	43	43	45
Chol				4.22
TG				2.17
LDL				2.29
HDL				0.94
Ratio				4.5

Comparison

	Atripla	Complera	Stribild	ATV/r + Truvada
Pro	- PK "forgiving" for missed doses	- better tolerated to EFV - once daily - data for safety in pregnancy	- non-inferior to Atripla - better tolerated than EFV	- Resistant to mutations
Con	- CNS SE - Teratogenic - Resistance w interruption - Rash incidence - ↑ lipid effects	- only if VL <100,000 - resistance high if non-adherent - ↑ resistance w failure incl ETR cross resistance - req 500 calories of food - no PPI, caution H2RA	- COBI drug interaction - COBI effect on eGFR - caution H2RA	- scleral icterus stigmatizing - 3 pills - no PPI, caution H2RA
Cost (Cda $/d)	$41.40	$40.43	$45.52	$50.20

Questions?