

 **19th Annual HIV CONFERENCE**
May 14-15, 2010 • Orlando, FL

HIV New Developments

Iván Meléndez-Rivera, MD
Fellow American Academy of Family Physicians
American Academy of HIV Medicine Specialist
Faculty Ponce School of Medicine, Ponce PR
Faculty Florida/Caribbean AETC



Disclosure of Financial Relationships

This speaker has the following significant financial relationships with commercial entities to disclose:

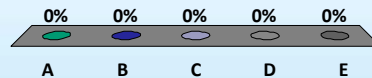
- Abbott
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Genentech
- Gilead Sciences
- Glaxo SmithKline
- Merck Sharp & Dohme
- Monogram Bioscience
- Napo Pharmaceutical
- Pfizer
- Salix Pharmaceutical
- Tibotec
- ViiV

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

 **19th Annual HIV CONFERENCE** May 14-15, 2010
Orlando, FL

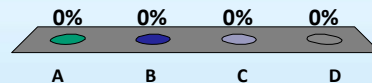
Intensification with which of the following agents will increase the CD4 level?

- A. Raltegravir**
- B. Maraviroc**
- C. Raltegravir or Maraviroc**
- D. A and B**
- E. None of the above**



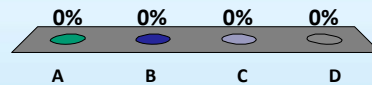
Which of the following investigational NRTI's has activity when M184V mutation is present?

- A. Apricitabine**
- B. Elvucitabine**
- C. Racivir**
- D. All of the above**



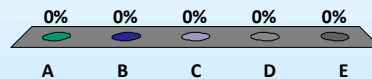
The investigational NNRTI's Rilpivirine shows better results in studies vs Efavirenz in all of the followings except?

- A. Lipid profile
- B. K103 mutation does not decrease susceptibility
- C. Teratogenicity
- D. Abnormal dreams



The components of the investigational one tablet, triple therapy once a day "Quad" include all of the following except?:

- A. Ritonavir
- B. Elvitegravir
- C. Tenofovir
- D. Emtricitabine
- E. G9350



Learning Objectives

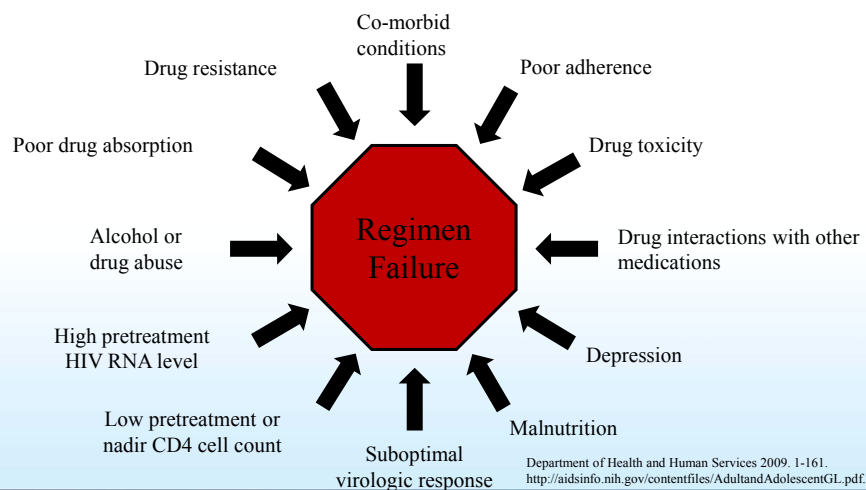
- Identify the clinical role of these new antiviral classes in optimizing the treatment of specific types of HIV patients
- *This session will discuss new HIV therapeutics in development within old and new classes which are progressing toward release.*
 - *Mechanism of action*
 - *Side effect profiles from earlier clinical trials*
 - *Expected placement within the realm of HIV care*



19th Annual HIV CONFERENCE

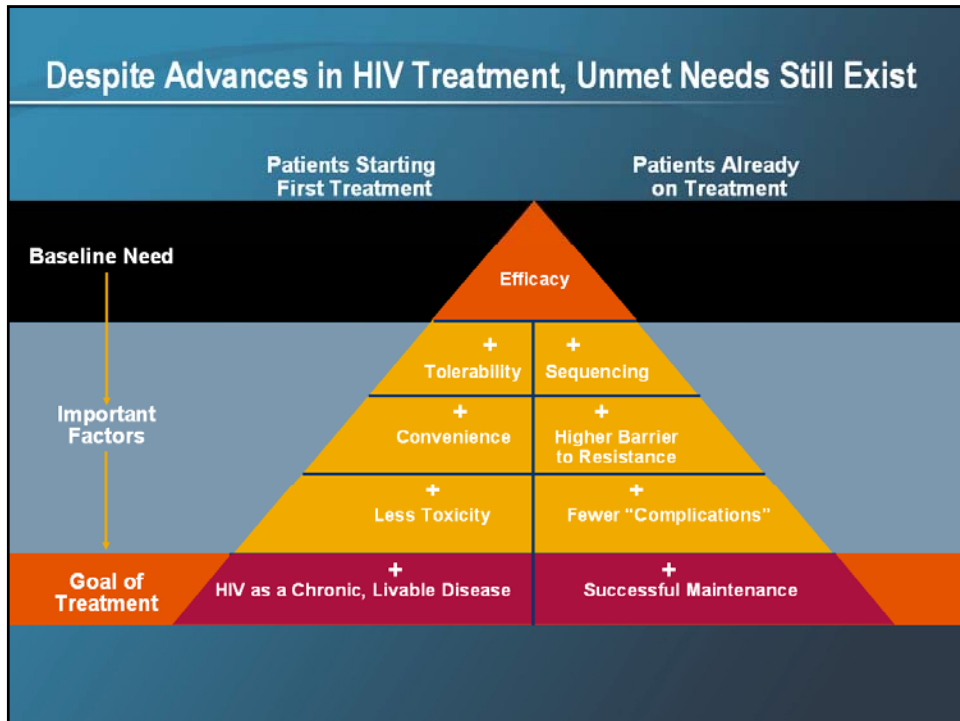
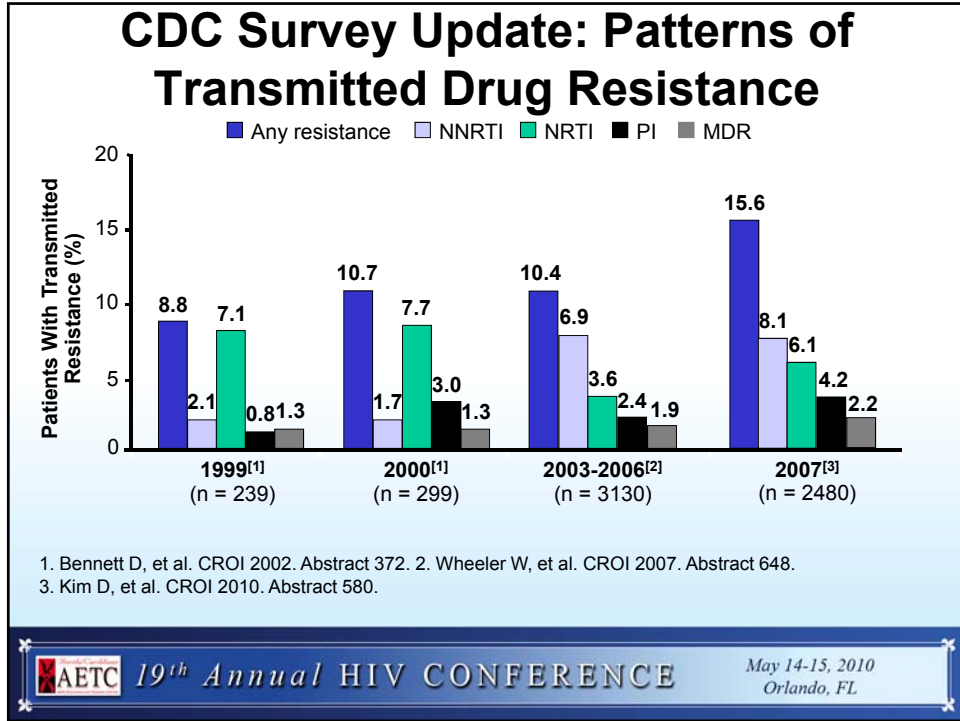
May 14-15, 2010
Orlando, FL

Multiple Factors Can Necessitate Regimen Modification



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

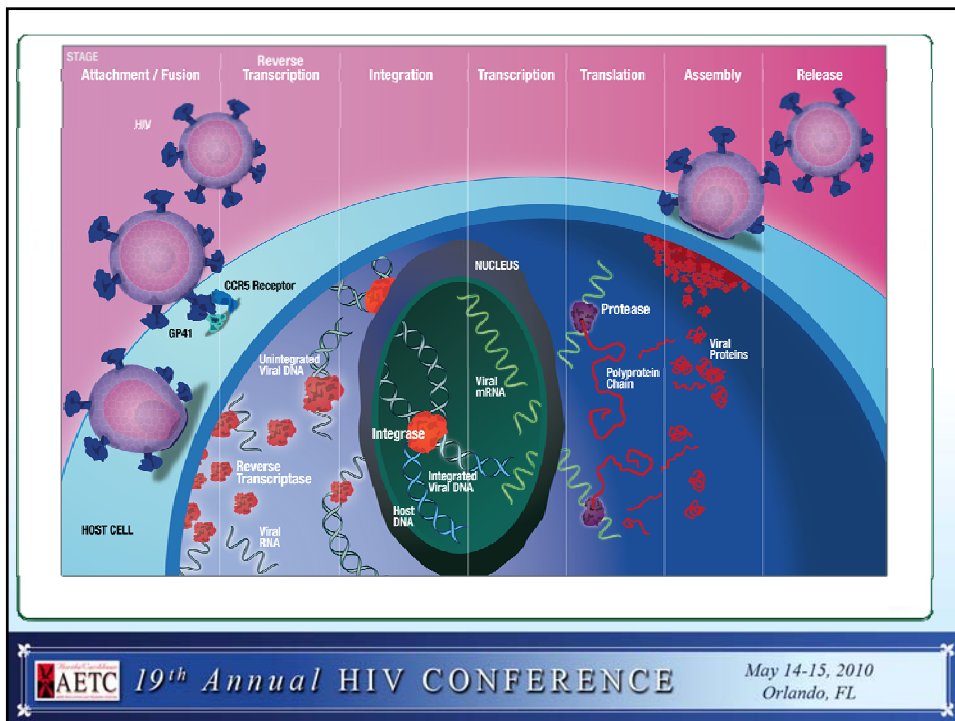


NEW IN KNOW MEDICATIONS



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Frequency of studies in specific ARVs (open or closed)

ClinicalTrials.gov - 849 open investigational studies.

- Maraviroc – 65
- Darunavir – 76
- Raltegravir - 145 studies
- Lopinavir – 238
- Efavirenz – 245
- Tenofovir - 268



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

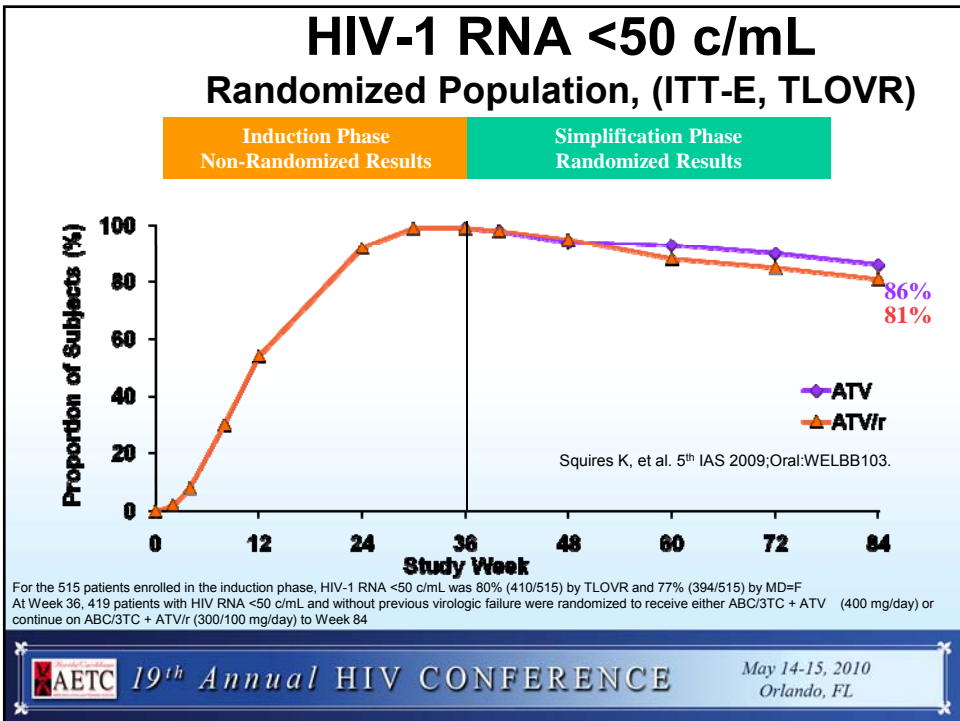
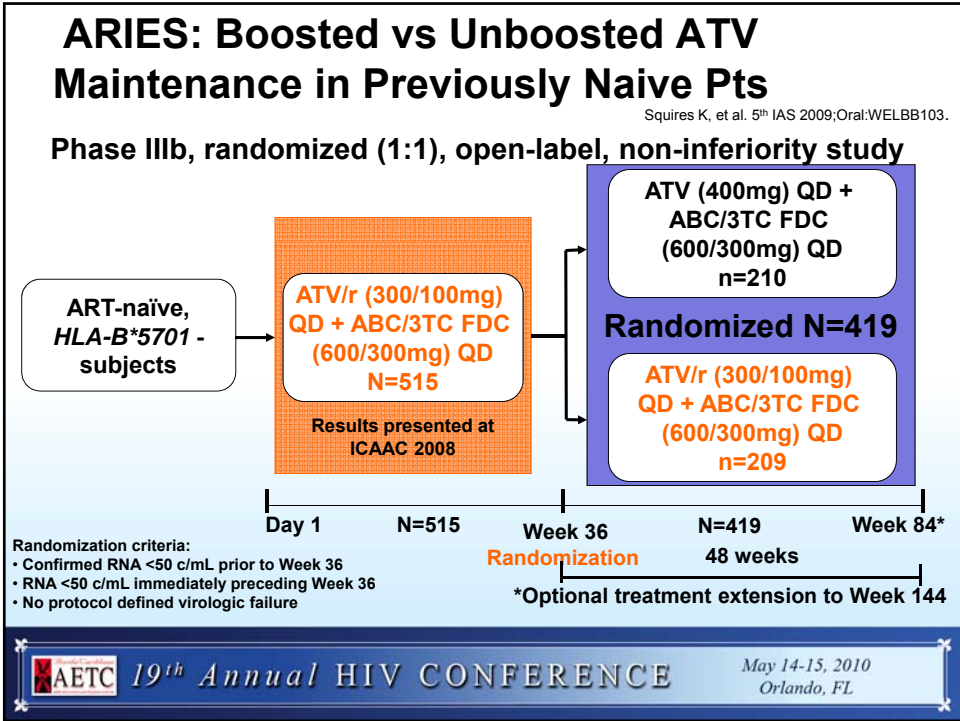
ARIES

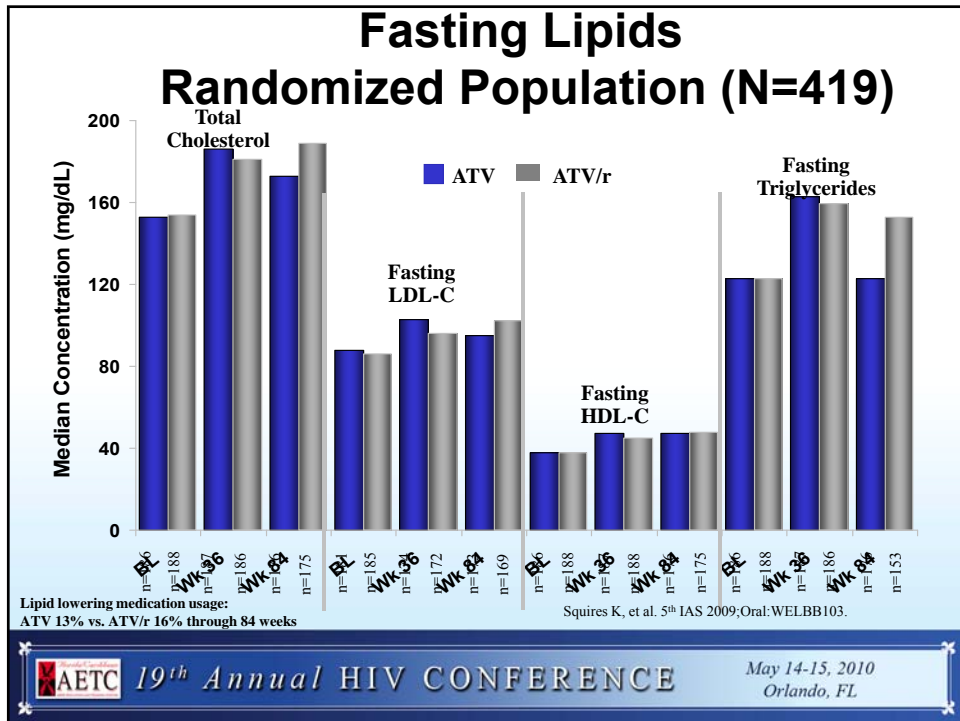
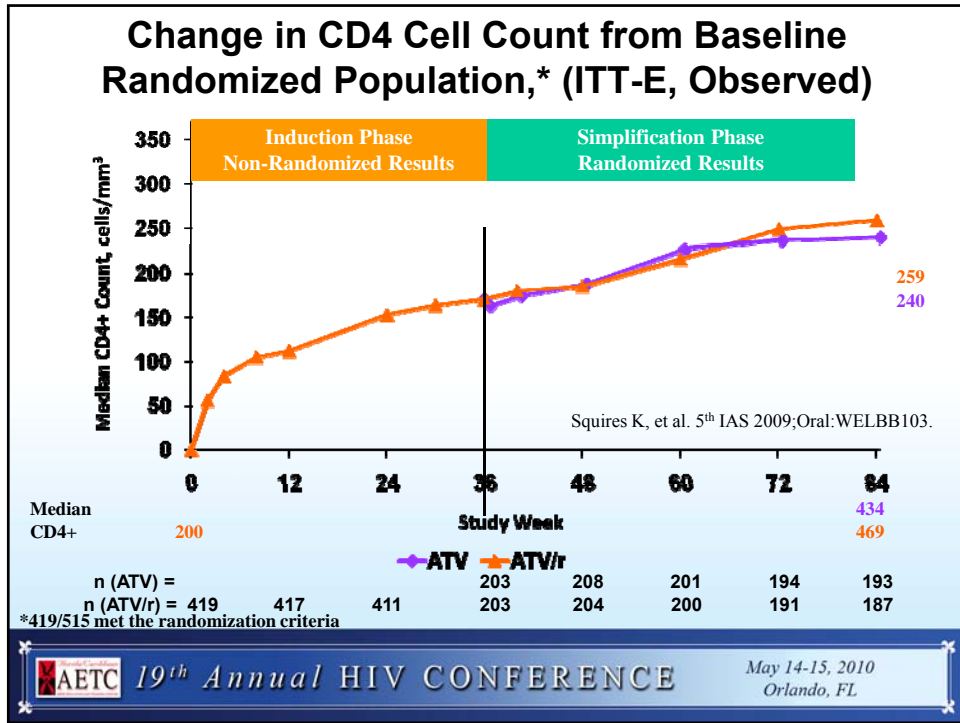
SIMPLIFICATION




19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL





MONET & MONOI
SIMPLIFICATION

 **19th Annual HIV CONFERENCE** May 14-15, 2010
Orlando, FL

**MONET Trial: Simplification to DRV/RTV
Monotherapy in Suppressed Pts**


Wk 48 primary endpoint Wk 96 planned follow-up

HIV-infected pts taking 2 NRTIs + either NNRTI or boosted PI at screening; no previous DRV use; HIV-1 RNA < 50 c/mL for at least 6 mos; no history of virologic failure (N = 256)

DRV/RTV 800/100 mg QD + 2 NRTIs* (n = 129)

DRV/RTV 800/100 mg QD (n = 127)

*N = 121 Mean duration of therapy longer in monotherapy group: 7.4 vs 6.4 yrs in the DRV/RTV + 2 NRTIs arm
Arribas JR, et al. IAS 2009. Abstract TUAB106LB

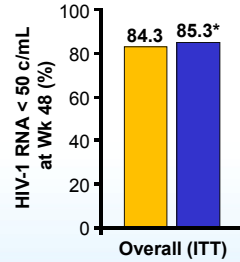
 **19th Annual HIV CONFERENCE** May 14-15, 2010
Orlando, FL

MONET Trial: 48-Wk Efficacy Results (ITT, TLOVR, Switch = Failure)

- DRV/RTV monotherapy noninferior to DRV/RTV HAART at Wk 48
- 1 pt with virologic failure in each arm developed primary PI and/or multiclass mutations

Drug Resistance, n	DRV Mono (n = 127)	DRV + 2 NRTIs (n = 129)
Pts with 1 genotype	13	22
No primary PI, DRV, or NRTI mutations	12	21
M184V	1	0
Primary PI mutations	1	1
DRV RAMs	0	1

■ DRV/RTV mono arm (n = 127)
■ DRV/RTV + 2 NRTIs arm (n = 129)



*Noninferiority definition: Δ lower limit < 12%; lower limit 95% CI: -1.0% to -9.9%

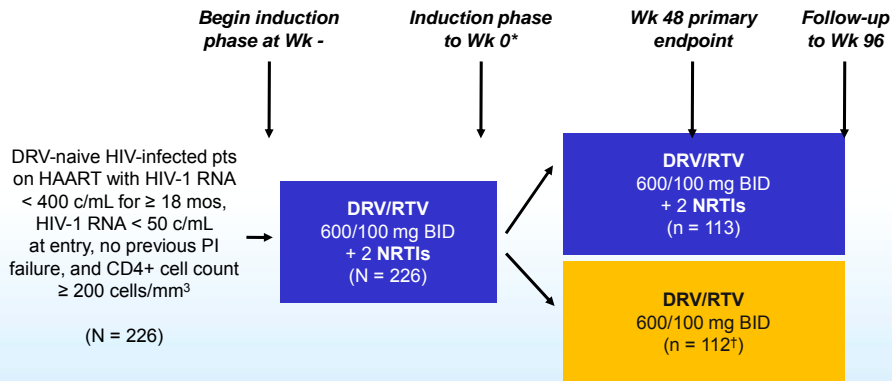
- Adverse events similar between groups

Arribas JR, et al. IAS 2009. Abstract TUAB106LB.

19th Annual HIV CONFERENCE

May 14-15, 2010
 Orlando, FL

MONOI Study: DRV/RTV Monotherapy vs Triple Therapy in Suppressed Pts



*Pts eligible for randomization into maintenance phase if HIV-1 RNA < 50 c/mL at Wk 8.

†1 pt not eligible for randomization; ITT-E population = 225.

Katlama C, et al. IAS 2009. Abstract WELBB102

19th Annual HIV CONFERENCE

May 14-15, 2010
 Orlando, FL

MONOI: 48 Wk Outcomes With DRV/RTV Monotherapy vs Triple Therapy

- **DRV/RTV monotherapy met criteria for noninferior virologic efficacy vs DRV/RTV + 2 NRTIs at Wk 48 in PP analysis, but not in ITT-E analysis**
 - PP population = all pts from ITT population except pts who d/c tx without virologic failure or SAE (n = 10) or pts withdrawn without virologic failure or SAE (n = 6)
- **Virologic failure in 3 pts (2.7%) on monotherapy vs 0 on standard therapy**
 - Low DRV drug levels noted in 1 pt
 - No DRV RAMs in any pt with virologic failure
 - All 3 pts regained HIV-1 RNA < 50 c/mL on reintroduction of 2 NRTIs

Virologic Response at Wk 48, %*	DRV/RTV	DRV/RTV + 2 NRTIs	Δ	Lower Limit of 90% CI
PP analysis (n = 204)	94.1	99.0	-4.9	-9.0
ITT-E analysis (n = 225)	87.5	92.0	-4.5	-11.0

Virologic failure defined as consecutive HIV-1 RNA > 400 c/mL or treatment modification or discontinuation

- **Viremia detected in CSF in 2 of 3 pts with serious CNS disorders on monotherapy arm**
 - Each pt had HIV-1 RNA < 200 c/mL in CSF following reintroduction of NRTIs

Katlama C, et al. IAS 2009. Abstract WELBB102


19th Annual HIV CONFERENCE
May 14-15, 2010
Orlando, FL

Maraviroc & Raltegravir INTENSIFICATION


19th Annual HIV CONFERENCE
May 14-15, 2010
Orlando, FL

Intensification of Stable HAART in Pts With Suboptimal CD4+ Cell Counts

- **ACTG 5256: Maraviroc added for 24 wks in 32 pts with HIV-1 RNA < 50 copies/mL for \geq 48 wks on stable HAART but CD4+ cell count < 250 cells/mm³[1]**
 - Maraviroc intensification not associated with clinically significant CD4+ gain
 - Median CD4+ count increase at Wk 22/24: +12 cells/mm³ (90% CI: 1-22)
 - Decrease in CD4+/CD8+ activation and improvements in markers of apoptosis, but not correlated with change in CD4+ cell count
- **Raltegravir intensification also not associated with significant CD4+ cell count increases in suppressed pts with low CD4+ cell counts[2]**

1. Wilkin TJ, et al. CROI 2010. Abstract 285. 2. Hatano H, et al. CROI 2010. Abstract 101LB.



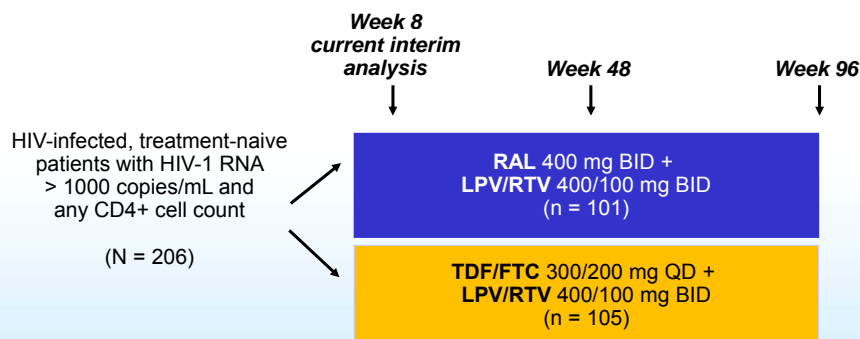
Progress

UNUSUAL COMBINATIONS



PROGRESS: RAL vs TDF/FTC, Both + LPV/RTV in Tx-Naive Pts (Interim Analysis)

- Randomized, open-label, phase III trial



Podsadecki T, et al. British HIV Association 2009. Abstract P31



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

PROGRESS: Virologic and Immunologic Outcomes Through Week 8

- More rapid HIV-1 RNA decline with RAL vs TDF/FTC
- Treatment-associated adverse events similar in both arms

Outcome	RAL + LPV/RTV	TDF/FTC + LPV/RTV
HIV-1 RNA < 40 copies/mL, %		
▪ Week 2	37	9
▪ Week 4	65	19
▪ Week 8	81	43
Mean CD4+ cell count increase, cells/mm ³		
▪ Week 4	113	97
▪ Week 8	125	108

Podsadecki T, et al. British HIV Association 2009. Abstract P31



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

NEW MEDS IN ALREADY KNOWN CLASSES



19th Annual HIV CONFERENCE

*May 14-15, 2010
Orlando, FL*

NRTI's

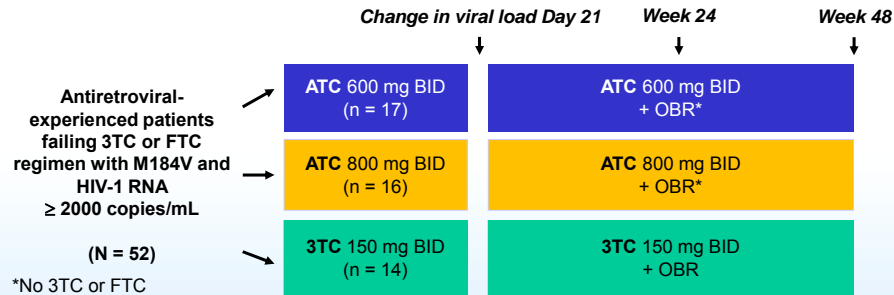
- **Apricitabine**
- **Elvucitabine**
- **Racivir**



19th Annual HIV CONFERENCE

*May 14-15, 2010
Orlando, FL*

AVX-201: Apricitabine vs 3TC in Tx-Experienced Patients With M184V



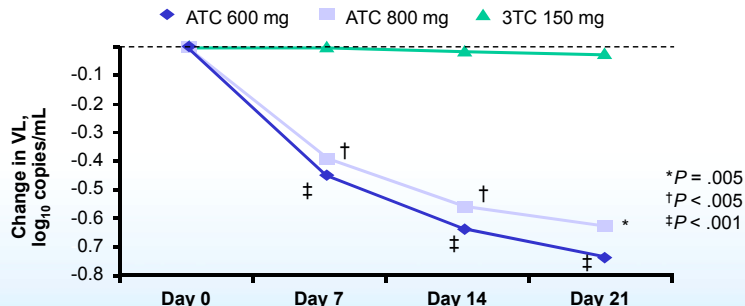
- All had M184V
- 48% had ≥ 3 TAMs

Cahn P, et al. IAS 2007. Abstract WESS203

19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

AVX-201: Activity of Apricitabine as De Facto Monotherapy



- 800-mg dose of ATC associated with HIV-1 RNA decrease of 0.75 log₁₀ in patients with ≥ 3 TAMs
- All patients maintained the M184V mutation

Cahn P, et al. IAS 2007. Abstract WESS203

19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Elvucitabine (ACH-126,443),(Beta-L-Fd4C) Achillion Pharmaceuticals Phase 2

- **Dose: 10mg p.o. daily**
- **Half life: >100 hours**
- **Preclinical studies: 4x potent in vitro (vs) Epivir (3TC) against wild-type HIV**
- **Greater potency in vitro against HIV with resistance to most NRTIs:**
 - Epivir (3TC)
 - Retrovir (AZT)
 - Zerit (d4T)
 - Viread (tenofovir).
- **SE: RBC reduction**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Racivir , RCV, Pharmasset, Phase 2

- **Oral, once-daily cytidine nucleoside analog 600mg**
- **Treatment-experienced patients with M184V previously on lamivudine therapy.**
- **Goal: Benefit of Racivir in patients with M184V replacing lamivudine with Racivir in existing therapies.**
- **Racivir demonstrated antiviral activity:**
 - M184V mutation present
 - <3 TAM.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

NNRTI's

- **Rilpivirine (TMC-278)**
- **Lersivirine (UK-453,061)**
- **GSK2248761**
- **RDEA806**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Rilpivirine

- **Rilpivirine (TMC-278), NNRTI, Tibotec, Phase 3 Tablet**
 - Long-acting rilpivirine IM injection, Tibotec, Phase 1)
- **For Naïve pt (no K103N mutation)**
- **Median CD4 ↑ with rilpivirine 138.0-149.0 cells/mm³ by week 96.**
- **The most commonly reported grade 2-4 occurred less frequently with rilpivirine than with efavirenz.**
 - nausea, dizziness, abnormal dreams, dyspepsia, asthenia, rash, somnolence and vertigo



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Rilpivirine

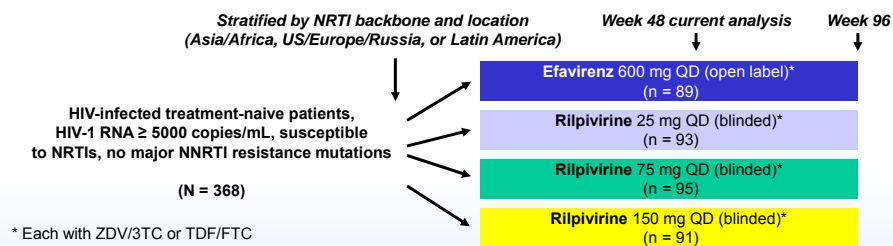
- Rilpivirine demonstrated potent and sustained efficacy comparable with efavirenz in treatment-naive patients over 96 weeks.
- Rilpivirine was well tolerated at all doses, "with lower incidences of neurological and psychiatric adverse events, rash, and lower lipid elevations than those with efavirenz.
- There have not yet been studies demonstrating which other drugs may interact with rilpivirine.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

TMC278-C204: Rilpivirine vs Efavirenz in Treatment-Naive Patients



Results at 48 Weeks	Rilpivirine 25 mg (n = 93)	Rilpivirine 75 mg (n = 95)	Rilpivirine 150 mg (n = 91)	Efavirenz 600 mg (n = 89)
VL < 50 copies/mL, %	81	80	77	81
Mean Δ in CD4+ count, cells/mm ³ (SD)	125 (112)	148 (148)	143 (140)	127 (104)

1. Pozniak A, et al. IAS 2007. Abstract WEPEA105. 2. Pozniak A, et al. CROI 2007. Abstract 144LB.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

TMC278-C204: Any Cause Psychiatric AEs and Metabolic Parameters

Patient Outcome	Rilpivirine			EFV 600 mg (n = 89)
	25 mg (n = 93)	75 mg (n = 95)	150 mg (n = 91)	
AE, regardless of causality, %^[1]				
Any psychiatric disorder	14	13	13	16
▪ Insomnia	7	5	6	5
▪ Depression	4	6	3	2
▪ Abnormal dreams/nightmares	1	6	0	10
Mean lipid change from baseline^[2]				
TC, mg/dL (SD)	8 (27)	3 (35)	5 (28)	31 (30)
LDL-C, mg/dL (SD)	3 (24)	1 (28)	-1 (24)	15 (23)
HDL-C, mg/dL (SD)	5 (8)	6 (9)	5 (10)	12 (10)
TC-to-HDL-C ratio	-0.4 (1.0)	-0.6 (1.0)	-0.4 (0.9)	-0.3 (0.9)
TG, mg/dL (SD)	-5 (76)	-19 (76)	-5 (85)	18 (66)

1. Pozniak A, et al. IAS 2007. Abstract WEPEA105.
2. Ruxrungtham K, et al. IAS 2007. Abstract TUAB105.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Lersivirine

- **UK-453,061 (lersivirine) , NNRTI, Pfizer, ViiV, Phase 2**
- **For pt with K103N mutation**
- **All doses (500 mg BID, 750 mg QD) well tolerated**
- **Less CYP3A4 induction by UK-453,061 than efavirenz. (possible less drug interaction)**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Lersivirine Drug Interactions

Drug	Interaction Results
tenofovir disoproxil fumarate + emtricitabine	↑ TDF levels
Lopinavir/r	↓ Lersivirine due to induction of glucuronidation pathway
atazanavir ± ritonavir	↔ Lersivirine

G Langdon,¹ J Davis,¹ G Layton,¹ HW Choo,² M-N Ndongo,³ A Milton,⁴ M Vourvahi⁴ UK-453,061 is a next-generation NNRTI showing potent antiviral activity against both wild-type and clinically relevant drug-resistant viruses; www.retroconference.org/2008/PDFs/763.pdf



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

GSK2248761

- **NNRTI, ViiV [Idenix], Phase 2**
- **Phase 1: showed efficacy and well-tolerated at 200mg, 400mg, and 800mg.**
- **At 800mg, median Δ from baseline to day 8 are:**
 - HIV-1 RNA -1.95 log₁₀ copies
 - CD4+ T-cell count ↑ by 52 cells/mm³.
- **Further evaluation to assess long-term safety and response durability**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

RDEA806

- **RDEA806, NNRTI, Ardea, Phase 2a**
- **Once a day**
- **High barrier to resistance against the common mutations that develop with efavirenz and nevirapine.**
- **Neither inhibitor nor inducer of CYP450**
- **No reproductive toxicity in animal studies**
- **No apparent effect on lipids**
- **SE: reductions in uric acid levels**

Moyle G, Boffito M, Manhard K, et al. Antiviral activity of RDEA806, a novel HIV non-nucleoside reverse transcriptase inhibitor, in treatment of naive HIV patients. Program and abstracts of the 17th International AIDS Conference; August 3-8, 2008; Mexico City, Mexico. Abstract THAB0403



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

PI's

- **TMC310911, protease inhibitor, Tibotec, Phase 2a**
 - No information available



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Viral Entry Inhibitors Monoclonal Antibodies

Ibalizumab (TNX-355) Tanox Inc

- **Non immunosuppressive, humanized IgG4, anti-CD4, domain 2 monoclonal antibody that prevents HIV entry into human cells.**
 - Responsible for the shape changes that occur after gp120 binds to the receptor.
- **IV administration once every other week.**
- **Dose depends on body weight**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Viral Entry Inhibitors Monoclonal Antibodies

- **In a phase 2 study, Tx-experienced patients who received intravenous infusions of TNX-355 plus OBT for 48 weeks achieved greater viral load suppression and larger CD4 cell increases than those who received a placebo, with no serious side-effects.**
- **No Cross resistance with T20**



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Integrase Inhibitor

- **Elvitegravir, Gilead, Phase 3**
- **EVG/FTC/TDF/ GS-9350 (Quad), Gilead, Phase 3**
- **GSK1349572, Integrase inhibitor, Shionogi/GSK, Phase 2**

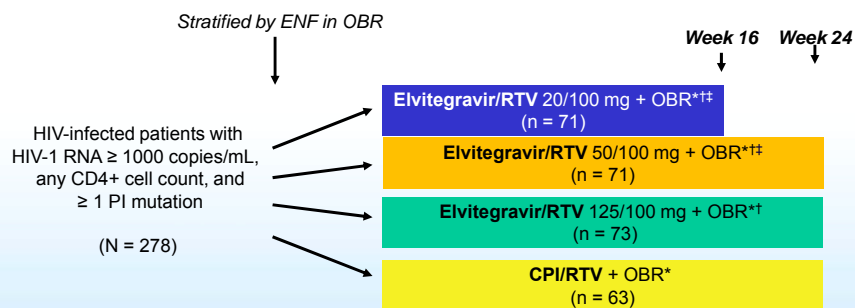


19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Elvitegravir in Treatment-Experienced Patients

- **Randomized, active-control, partially blinded (dose of elvitegravir) phase IIb dose-finding study**
 - Primary endpoint: time-weighted average change from baseline in HIV-1 RNA through 24 weeks (DAVG₂₄)



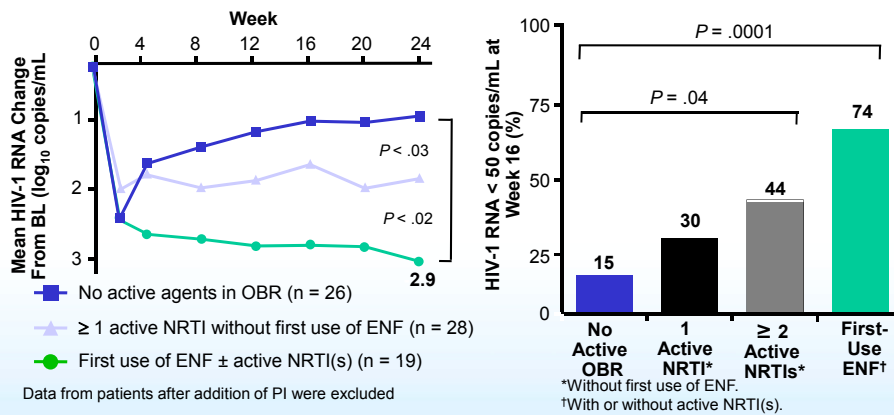
OBR = NRTIs \pm ENF (NNRTIs excluded). [†]TPV and DRV permitted after Week 8. ^{*}Discontinued by DMSB. Zolopa A, et al. ICAAC 2007. Abstract H-714.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Elvitegravir 125/100 mg: Virologic Response by Active Agents in OBR



Zolopa A, et al. ICAAC 2007. Abstract 714.



Early Clinical Evaluation of Elvitegravir With Investigational Booster, GS-9350

- GS-9350: increased systemic exposure of CYP3A substrates to similar extent as ritonavir
 - Greater specificity for CYP3A, less induction of other metabolizing enzymes and transporters such as P-glycoprotein
 - Safe and well tolerated, boosting of elvitegravir similar to ritonavir
 - Coformulated in once-daily “quad” tablet with elvitegravir and tenofovir/emtricitabine
 - Efficacy and safety under investigation in phase IIb trial

Mathias A, et al. CROI 2009. Abstract 40.

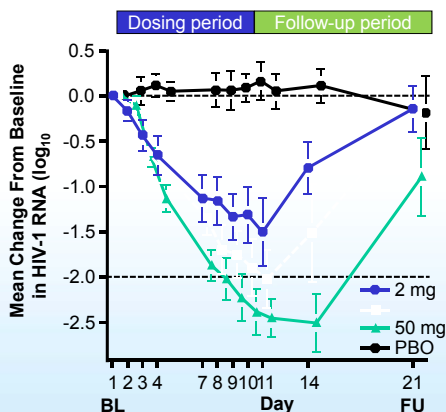


S/GSK1349572: Monotherapy With New INSTI in INSTI-Naive Pts

- Randomized, placebo-controlled, double-blind, 10-day monotherapy trial in INSTI-naive pts (either ARV naive or experienced) with CD4+ cell count ≥ 100 cells/mm³, HIV-1 RNA ≥ 5000 c/mL, and no HIV treatment for 12 wks^[1]
- 3 cohorts of approximately 10 subjects (8 active, 2 PBO)
 - S/GSK1349572 given at 2 mg, 10 mg, 50 mg, each QD
- S/GSK1349572 highly effective in reducing HIV-1 RNA: 2.5 log₁₀ copies/mL at Day 10 with 50-mg dose
- Exposure-response curve supports QD dosing with no boosting^[2]

Response	2 mg QD (n = 9)	10 mg QD (n = 9)	50 mg QD (n = 10)
VL < 50 c/mL, n	1	0	7

1. Lalezari J, et al. IAS 2009. Abstract TUAB105.
2. Song J, et al. IAS 2009. Abstract WEPEB250. Graphic used with permission.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

GSK1349572, Integrase inhibitor, Shionogi/GSK, Phase 2

- In vitro data demonstrates activity against resistance virus observed on raltegravir (RAL) and elvitegravir (ELV) .
- Combination with atazanavir (ATV) or ATV/ritonavir (RTV) do not require dose adjustment
- SE: Nauseas; ocular icterus; Increased bilirubin was observed only during concomitant ATV dosing



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

CCR5 inhibitors

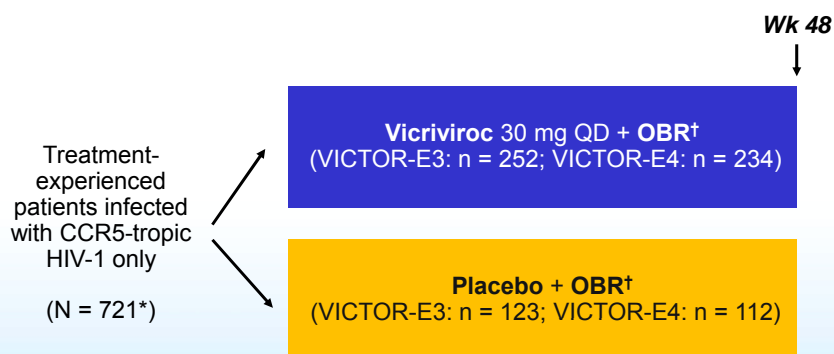
- Vicriviroc, CCR5 inhibitor, Merck, Phase 3
- PRO 140 Progenics
- (INCB9741) Incyte Pharmaceuticals.
- TBR-652



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

VICTOR-E3 and -E4: Vicriviroc vs Placebo + OBR in Tx-Exp CCR5-Tropic Patients



Modified ITT population includes patients with CCR5-only tropism at baseline, confirmed retrospectively using enhanced sensitivity phenotypic tropism assay.

[†]OBR selected by investigator: must contain ≥ 2 fully active drugs; must include ritonavir-boosted PI; etravirine only permitted NNRTI; raltegravir and darunavir permitted.

Gathe J, et al. CROI 2010. Abstract 54LB



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

VICTOR-E3 and -E4: HIV-1 RNA < 50 c/mL Overall and by OSS

HIV-1 RNA < 50 copies/mL at Wk 48, %	Vicriviroc 30 mg QD + OBR (n = 486)	Placebo+ OBR (n = 235)	Odds Ratio	P Value
Overall	64	62	--	--
By OSS				
≤ 2	70 (n = 176)	55 (n = 85)	1.9	.02
≥ 3	61 (n = 293)	65 (n = 145)	--	--

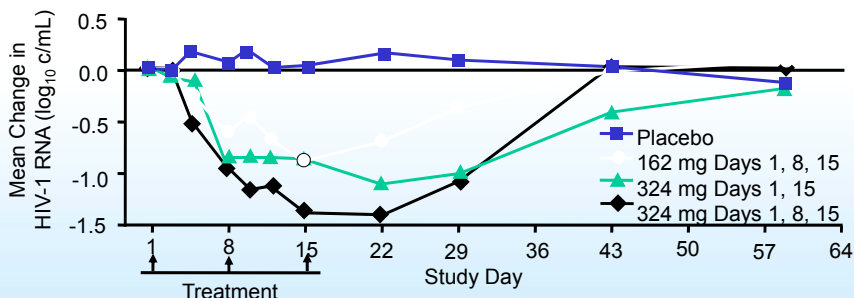
- CD4+ count increased 138 ± 7.3 cells/mm³ with vicriviroc vs 29 ± 9.4 cells/mm³ with placebo
- Diarrhea, nausea, headache most frequently reported AEs, with no significant differences between arms (malignancy incidence 1% in both treatment arms)
- 7 deaths in vicriviroc arm vs 0 in placebo arm (not judged related to study drugs)

Gathe J, et al. CROI 2010. Abstract 54LB.

AETC 19th Annual HIV CONFERENCE May 14-15, 2010
Orlando, FL

Weekly or Biweekly SC Dosing of PRO 140 Associated With VL Reductions

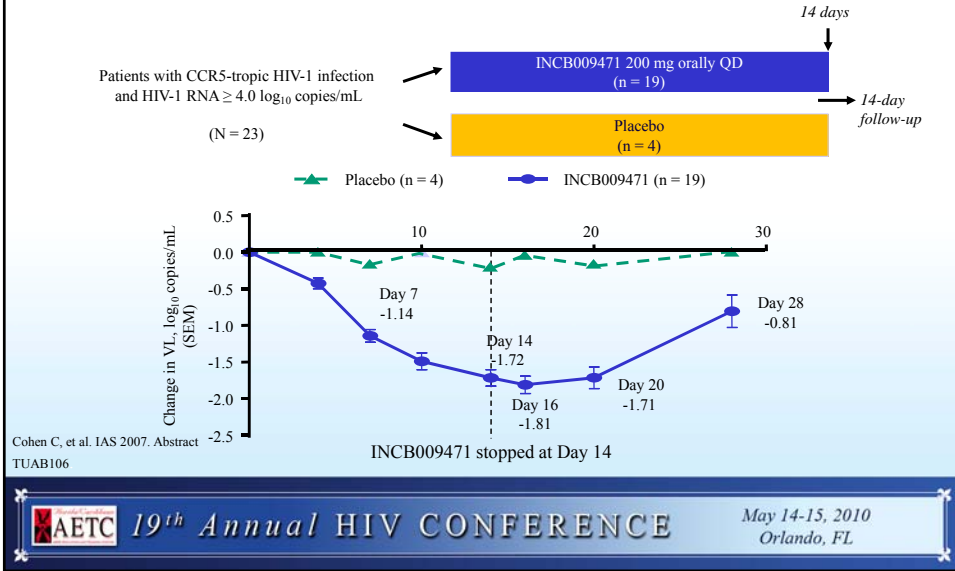
- PRO 140: investigational, humanized CCR5 monoclonal antibody**
 - 324 mg SC infusion dosed weekly for 3 weeks associated with mean reduction in HIV-1 RNA of 1.65 log₁₀ copies/mL
- SC PRO 140 well tolerated with mild injection-site reactions that resolved within 1-2 days**



Thompson M, et al. CROI 2009. Abstract 571a.

AETC 19th Annual HIV CONFERENCE May 14-15, 2010
Orlando, FL

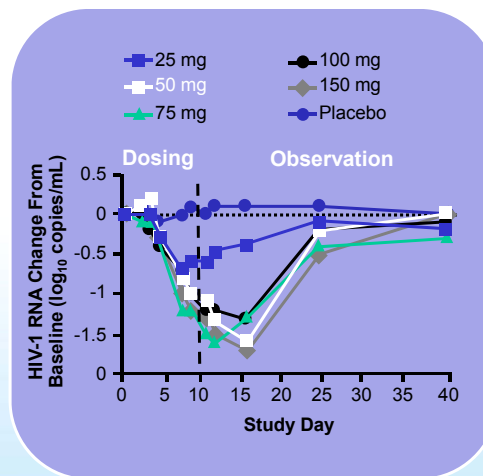
INCB009471: 14-Day Monotherapy Trial of Investigational CCR5 Inhibitor



Novel CCR5 Antagonist TBR-652: Potent Antiviral Activity in CCR5-Tropic HIV Pts

- **TBR-652, QD oral CCR5 antagonist**
 - Also inhibits CCR2 through MCP-1 ligand
 - CCR2 associated with several inflammation-related diseases
- **No serious adverse events or deaths reported in any arm**
- **TBR-652 50 mg, 100 mg, and 150 mg significantly increased MCP-1 concentrations from baseline to Day 10 compared with placebo ($P \leq .02$)**

Palleja S, et al. CROI 2010. Abstract 53. Reproduced with permission.



NEW CLASSES



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Booster

- **Cobicistat GS-9350 booster, Gilead, Phase 3**
- **SPI-452, Phase 2**

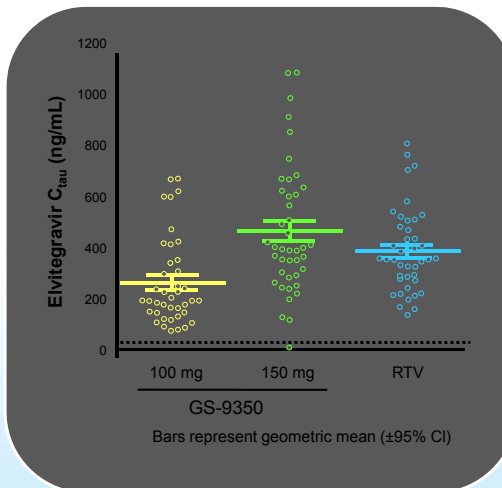


19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

GS-9350 Cobicistat : PK Enhancement Without Ritonavir

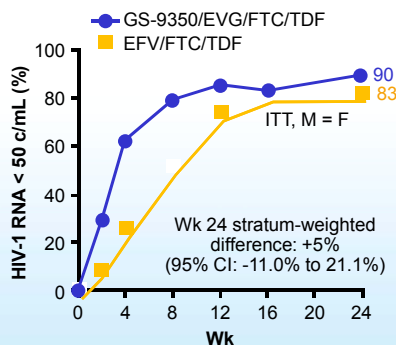
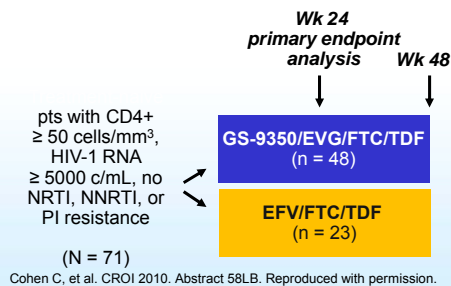
- **GS-9350: Potent, specific inhibitor of CYP3A with no anti-HIV activity**
- **Boosting of EVG similar to RTV**
 - GS-9350 (150 mg) maintained EVG trough concentrations 11-fold above the protein binding-adjusted IC95 (44.5 ng/mL)
- **Promising tolerability profile with minimal impact on adipocytes or insulin resistance**
- **FDC of GS-9350 + EVG + TDF/FTC being explored**
Kearney B, et al. 16th CROI; 2009; Montreal. Abstract 40



GS-9350–Boosted Elvitegravir + FTC/TDF Noninferior to EFV/FTC/TDF in Naive Pts

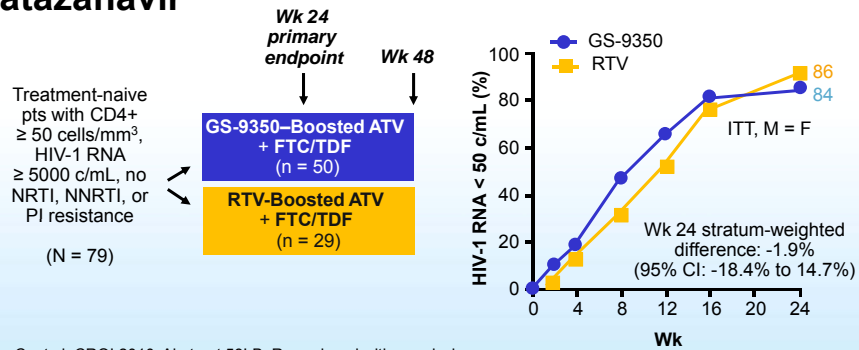
- **Cobicistat (GS-9350): investigational CYP3A inhibitor (boosting agent)**

- Elvitegravir: investigational integrase inhibitor



GS-9350–Boosted ATV Virologic Efficacy Similar to ATV/RTV in Naive Pts

- Phase II study comparing cobicistat (GS-9350) vs ritonavir as boosting agent for atazanavir



Cohen C, et al. CROI 2010. Abstract 58LB. Reproduced with permission.

19th Annual HIV CONFERENCE
May 14-15, 2010
Orlando, FL

GS-9350: AEs When Combined With EVG/FTC/TDF or ATV + FTC/TDF

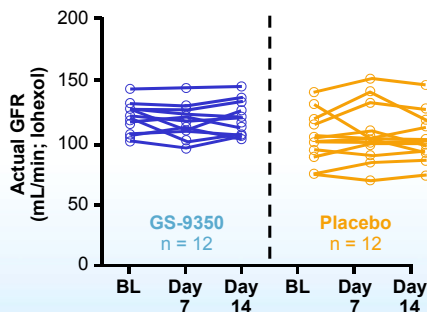
AEs, n (%)	GS-9350/ EVG/FTC/TDF (n = 48)	EFV/FTC/TDF (n = 23)	GS-9350 + ATV + FTC/TDF (n = 50)	RTV + ATV + FTC/TDF (n = 29)
Grade 1-4 AEs related to randomized drug	17 (35)	13 (57)	10 (20)	7 (24)
Abnormal dreams, nightmares	5 (10)	8 (35)	0	0
Dizziness	0	3 (13)	0	0
Fatigue	4 (8)	3 (13)	1 (2)	2 (7)
Somnolence	2 (4)	2 (9)	0	0
Diarrhea	4 (8)	1 (4)	3 (6)	3 (10)
Nausea	2 (4)	1 (4)	5 (10)	1 (3)
Bilirubin, total	0	0	40/49 (82)	25 (86)
Creatinine (grade 1)	1 (2)	0	6 (12)	0
Δ mean serum creatinine from BL to Wk 24, mg/dL	+ 0.14	+ 0.04	+ 0.18	+ 0.14
Δ mean eGFR from BL to Wk 24, mL/min	- 18	- 7	- 15	- 14

Cohen C, et al. CROI 2010. Abstract 58LB

19th Annual HIV CONFERENCE
May 14-15, 2010
Orlando, FL

GS-9350 Appears to Alter Estimated GFR, Not Actual GFR

- Most creatinine excretion occurs by filtration, but 10-15% excreted by active tubular secretion
- Lower estimated GFR for GS-9350 appears due to inhibition of tubular secretion
 - Separate study of 7-day GS-9350 150 mg monotherapy vs placebo in healthy volunteers demonstrated no impact of GS-9350 on actual GFR (measured by iohexol clearance) despite lower estimated GFR (Cockcroft-Gault) with GS-9350 vs placebo



Cohen C, et al. CROI 2010. Abstract 58LB. Reproduced with permission

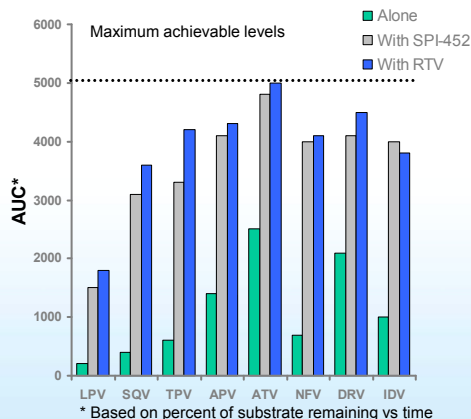
AETC 19th Annual HIV CONFERENCE May 14-15, 2010
Orlando, FL

SPI-452: PK Enhancement Without Ritonavir

- **SPI-452: Potent CYP3A inhibitor in preclinical evaluation**
- **PI boosting similar to RTV**
 - DRV ↑37 fold, ATV ↑12 fold, and levels remain significantly increased 24 hours after last dose
- **Moderate tolerability issues with headache and nausea, diarrhea**
- **Solubility issues are a concern, as current formulation is a liquid**

Gulnik S, et al. 16th CROI; 2009; Montreal. Abstract 41.

PI Enhancement in Human Liver Microsomes



AETC 19th Annual HIV CONFERENCE May 14-15, 2010
Orlando, FL

Maturation Inhibitor

- Bevirimat
- PA1050040

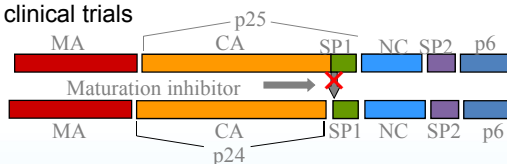


19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Maturation Inhibitors

- **Bevirimat (BVM, formerly PA-457) first in class maturation inhibitor-**
 - Maturation inhibitors inhibit the conversion of p25 (CA-SP1) to p24 (CA), yielding non infectious virions.
 - BVM is currently in Phase 2B clinical trials



- **PA1050040 a 2nd generation maturation inhibitor**
 - > Retain BVM's attractive profile
 - Once daily oral administration
 - No drug interactions
 - Safe and well tolerated
 - > A distinct resistance profile
 - > Reduced serum protein binding



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Bevirimat (MPC-4326) maturation inhibitor, Myriad, Phase 2

- Bevirimat is a derivative of a Chinese herb called *Syzygium claviflorum*
- Blocks viral maturation by inhibiting the final step in the processing of the HIV Gag protein
- Potent anti-viral activity against HIV-1 isolates resistant to many of the approved HIV medications and acts synergistically with protease inhibitors *in vitro*.
- There is no evidence of antagonism between MPC-4326 and other HIV therapies
- Clinically relevant reductions in viral load in both anti-retroviral treatment experienced and treatment naïve patients



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Bevirimat (MPC-4326) maturation inhibitor, Myriad, Phase 2

- Epidemiological data suggest 60% or greater of patients with HIV are infected with viral strains that are free of Gag polymorphisms
- Low probability for certain types of drug-drug interactions
- Resistance: High prevalence of Bevirimat resistance among wild-type clade B viruses (>30%),
 - Unlikely to prove useful for many treatment-naïve patients.
 - PI resistance is associated with diminished activity of bevirimat
 - Resistance testing that incorporates the gag region of the HIV genome will be an essential step in selecting appropriate patients for bevirimat.
- Multiple PI mutations can affect susceptibility



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

PA1050040, a 2nd generation maturation inhibitor

- PA1050040 is a chemical analog of BVM
- Inhibits virus replication by the same mechanism of action
- Potent inhibitor of primary and prototypic HIV-1 isolates with an IC₅₀ ~15 nM
- Wild-type activity against HIV isolates resistant to all four classes of approved drugs
- Wild-type activity against the BVM-resistant isolate, L363M
- Reduced protein binding, free fraction ~8-15 fold greater than BVM in serum shift assays
- Favorable pre-clinical pharmacokinetic and metabolic profile
- Entered Phase I single dose clinical trial



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Attachment Inhibitor

- **BMS-663068, prodrug for HIV attachment inhibitor BMS-626529, BMS, phase 2**
 - No data published.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

NEW TESTS



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Genotypic Assays for Integrase Inhibitor Resistance Detection

- Technology used to develop genotype assays for PIs, NRTIs, and NNRTIs adapted to develop genotypic tests for integrase inhibitors
- Variety of genotypic assays for integrase inhibitor resistance in use at many major laboratories worldwide^[1-3]

1. Van Laethem K, et al. J Virol Methods. 2008;153:176-181. 2. Eshleman SH, et al. AIDS Res Hum Retroviruses. 2009;25:343-345. 3. Paar C, et al. J Clin Microbiol. 2008;46:4087-4090.

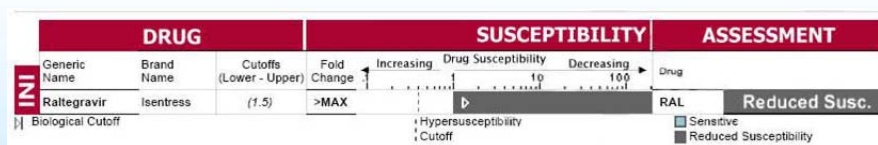


19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Integrase Assay Accurately Determines Raltegravir Susceptibility

- **Phenotypic integrase resistance assay now commercially available**
 - Amplification threshold: HIV-1 RNA > 500 copies/mL
 - Biological cutoff for raltegravir is FC > 1.5
 - Clinical cutoff not yet determined
 - Report does not detail genotypic mutations
- **High assay accuracy demonstrated by IC₅₀ fold change values reported for site-directed mutants**



Fransen S, et al. ICAAC/IDSA 2008. Abstract 1214.



Clinical Use of Integrase Inhibitor Resistance Detection Assays


- **Indications for antiretroviral agent resistance testing**
 - Determine susceptibility to other agents in class after failure of 1 agent
 - Detect transmitted drug resistance before first use
- **Raltegravir currently the only approved integrase inhibitor, so susceptibility to other agents in class not yet clinically relevant**
 - Will be applicable if elvitegravir or other agents become available
 - Some experts test for integrase resistance at failure (for future reference) or store a sample for future testing
- **Absence of transmitted integrase inhibitor resistance indicates resistance testing prior to initial use also not yet warranted**
 - Surveillance programs needed to monitor for emergence of transmitted integrase inhibitor resistance

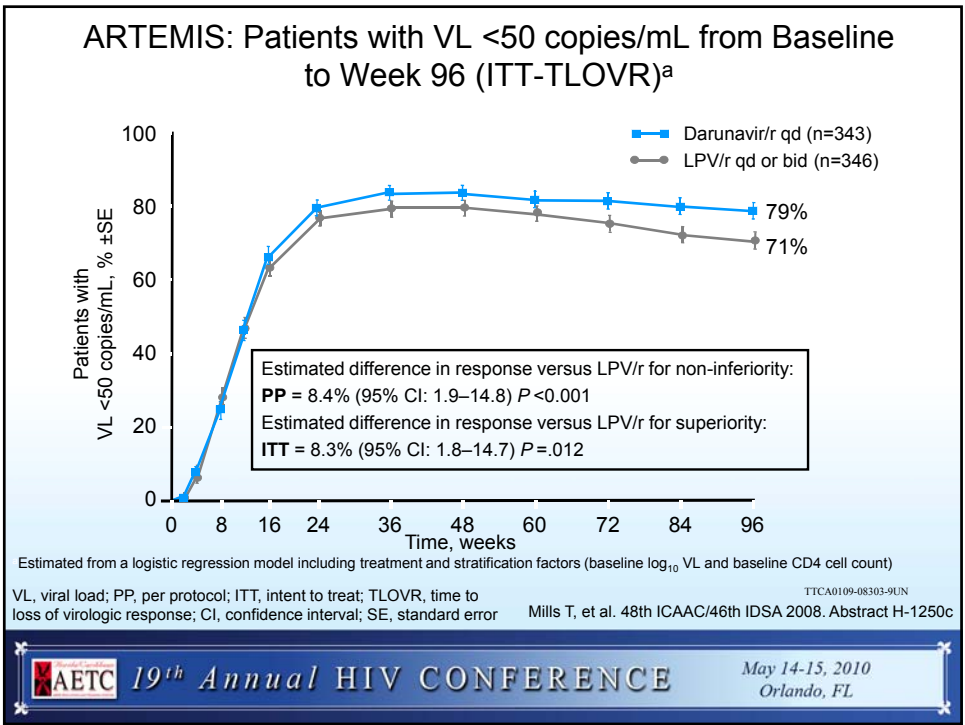


HIV RNA Endpoints Cross-Sectional “Snapshot”

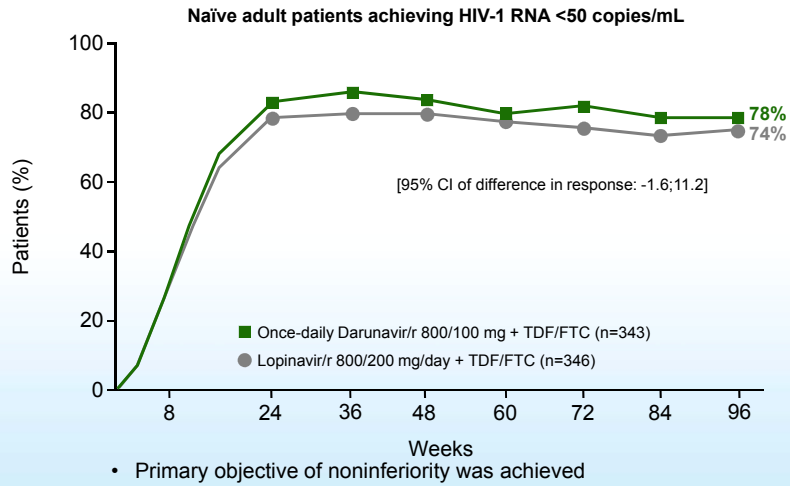
- **New way to measure Efficacy (<50 copies/ml) required by FDA**
- **Above/Below threshold at week x**
- **Not affected by transitional changes in HIV levels.**
- **Uses the last available measurement of viral load within Weeks 90-102 in a 96 week analysis**
 - More similarity to real life.
 - No penalty from leaving the study early
 - No penalty from “Blips”

http://www.fda.gov/ohrms/DOCKETS/ac/01/slides/3678s1_08_degruttola.ppt


19th Annual HIV CONFERENCE
May 14-15, 2010
Orlando, FL



Durable Virologic Response (<50 copies/mL) at 96-Week Window (Snapshot Analysis)



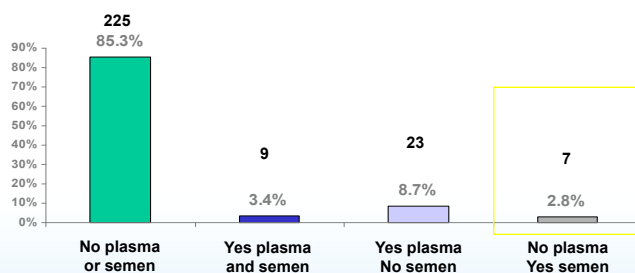
 **19th Annual HIV CONFERENCE** May 14-15, 2010
Orlando, FL

NEW ON PREVENTION

 **19th Annual HIV CONFERENCE** May 14-15, 2010
Orlando, FL

Persistent HIV RNA Shedding in Semen Despite Virologic Suppression

- N=264 pair of semen/blood samples from 145 HIV+ men (2002-2008)¹
 - 5% of patients on HAART had detectable HIV RNA in semen



- Longitudinal studies on semen and blood HIV RNA post HAART²
 - 25 men initiating therapy and undetectable VL by week 16
 - 12/25 (48%) with isolated HIV shedding
 - 4/25 (16%) with high level viral shedding (>5,000 copies/mL)
 - Semen isolates infectious without drug-resistant mutations
 - 4/13 (31%) men with HIV in semen despite prolonged viral suppression
 - Median 10.5 years

1. Marcelin A et al. 16th CROI; 2009; Montreal. Abstract 51.
2. Sheth P et al. 16th CROI; 2009; Montreal. Abstract 50.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

PrEP With Microbicides and Gels

- 0.5% PRO 2000, phase 2B.
- N=3,087 woman from Africa and US¹
 - 4 arms: PRO 2000, Buffered gel, Placebo gel, Control
 - PRO 2000 was ~33% effective in preventing HIV when compared to Placebo gel

	No. HIV Infections	Women-Yr F-Up	Incidence Rate (95% CI)
PRO 2000	36	1332	2.7 (1.9 – 3.7)
Buffer Gel	54	1304	4.1 (3.1 – 5.4)
Placebo Gel	51	1305	3.9 (2.9 – 5.1)
No Gel	53	1318	4.0 (3.0 – 5.3)

ITT Analysis	Hazard Ratio vs Placebo	Hazard Ratio vs Bf Gel
PRO 2000	0.70 (0.46 – 1.08), P=.10	0.67 (0.44 – 1.02), P=.06

- Other products in early phases of development
 - Dapivirine², dapivirine/maraviroc³, UC781⁴

1. Abdool Karim S, et al. 16th CROI; 2009; Montreal. Abstract 48LB., 2. Nel A, et al. 16th CROI; 2009; Montreal. Abstract 1065., 3. Faheem A, et al. 16th CROI; 2009; Montreal. Abstract 1069., 4. Anton P, et al. 16th CROI; 2009; Montreal. Abstract 1066-7.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Life Expectancy and Mortality in HIV-Infected Patients

- **ART-CC: Depending on when ARV therapy is started, life expectancy is 10-30 yrs less than that in uninfected pts**
 - Life expectancy for pts at age 20 was 32 yrs for pts with CD4+ < 100 cells/mm³ and 50 yrs for pts for CD4+ > 200 cells/mm³[1]
- **AQUITAINE cohort: Pts with CD4+ ≥ 500 for 6 yrs after combination ARV therapy attained mortality similar to general population[2]**
 - COHERE cohort: HIV-infected men, but not women, reached mortality rates similar to uninfected population after 3 yrs of CD4+ ≥ 500 cells/mm³[3]
- **ATHENA cohort: For asymptomatic HIV-infected pts diagnosed from 1998-2007 who remained ARV naive and without AIDS at Wk 24 after diagnosis, modeled life expectancy similar to age- and sex-matched uninfected controls in Netherlands[4]**
 - 52.7 vs 53.1 yrs, respectively

1. Antiretroviral Cohort Collaboration. Lancet. 2008;372:293-299. 2. Lewden C, et al. J Acquir Immune Defic Syndr. 2007;46:72-77. 3. Lewden C, et al. CROI 2010. Abstract 527. 4. Van Sighem A, et al. CROI 2010. Abstract 526.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

EARLY OR INTERESTING/ ODD INVESTIGATIONAL TREATMENTS:



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Early or Interesting/ Odd Investigational Treatments:

- Neurokinin-1 receptor antagonists like aprepitant to decrease the expression of CCR5, Phase 1
- Anti-HIV V3 Monoclonal Antibody KD-247, The Chemo-Sero-Therapeutic Research Institute, Phase 1
- TXA127 (Lymphocyte growth factor) to increase T-lymphocyte counts, US Biotest, Inc., Phase 1
- Chloroquine for Reducing Immune Activation, NIAID, Phase 2



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Early or Interesting/ Odd Investigational Treatments :

- Mycophenol mofetil to treat immune hyperactivation
- Valacyclovir
- Anthelmintics to slow progression
- KP-1461, Koronis
- HE2000 (DHEA-like hormone), Hollis-Eden, Phase 1

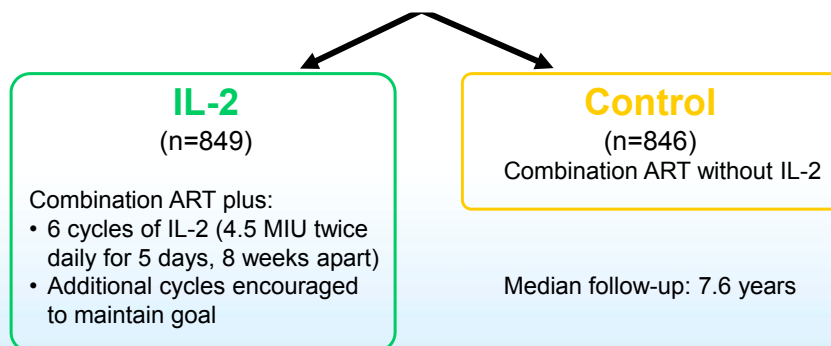


19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

SILCAAT: Study Design

Patients taking combination ART with CD4+ 50-299 cells/mm³



Levy Y, et al. 16th CROI; 2009; Montreal. Abstract 90bLB.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

SILCAAT: Primary Endpoint Opportunistic Disease or Death

IL-2		Control		HR (95% CI)	P value
No.	Rate	No.	Rate		
109	1.92	118	2.12	0.91 (0.70-1.18)	.47

(Predicted HR based on CD4+ difference = 0.74)

Average Difference in CD4 counts over study period: 59 cells/mm³ (P < .001)

Time spent	IL-2	Control
<200 cells	23%	29%
>350 cells	38%	28%

Levy Y, et al. 16th CROI; 2009; Montreal. Abstract 90bLB.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Summary

- There is an important clinical role of new antiviral classes in optimizing the treatment of specific types of HIV patients
- Goal of successful ART for treatment-experienced patients is to achieve and maintain undetectable VL
- Achieving goal requires full assessment of patient's treatment history, drug resistance, and tropism
- This goal is achievable in most patients with available new agents from existing classes combined with agents from new classes
- There are numerous possibilities for constructing successful new regimens with new experimental medications.



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Questions?



19th Annual HIV CONFERENCE

May 14-15, 2010
Orlando, FL

Disclosure of Financial Relationships

This speaker has the following significant financial relationships with commercial entities to disclose:

- **Abbott**
- **Boehringer Ingelheim**
- **Bristol-Myers Squibb**
- **Genentech**
- **Gilead Sciences**
- **Glaxo SmithKline**
- **Merck Sharp & Dohme**
- **Monogram Bioscience**
- **Napo Pharmaceutical**
- **Pfizer**
- **Salix Pharmaceutical**
- **Tibotec**
- **ViiV**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

