



**UPDATE FROM THE
CONFERENCE ON RETROVIRUSES
AND OPPORTUNISTIC INFECTIONS
SAN FRANCISCO, CA
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Texas/Oklahoma AIDS Education & Training Center
Curriculum Development Group

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TRANSMISSION AND PREVENTION

Mathematical Models of HIV Transmission

- Low infectivity: ~ 0.001 per heterosexual encounter
 - ~10 fold variability from person to person
- Slow rate: Doubling time 1-3 years
- Long duration: 5-15 years
- Reduction in Transmission rate by 7 fold would eliminate HIV infection
- HAART has the potential to decrease by 10 fold with good compliance



Strategies to Eliminate Transmission

■ Test and treat

- ARV within one year from diagnosis

- Women 20-35

- Men 25-40

- Test couples

 - Address barriers

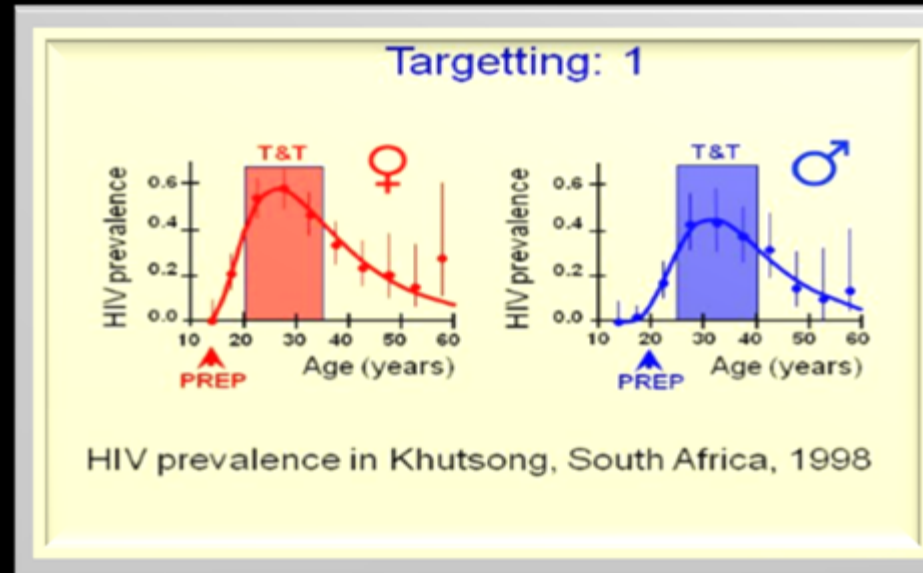
 - Focus on the affected couples

■ PreP for young people

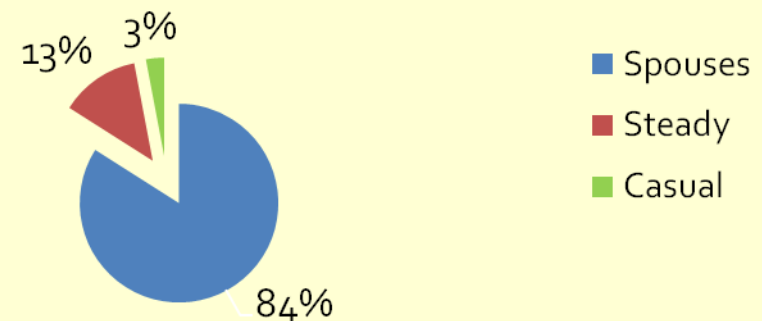
- Women 15-20

- Men 20-25

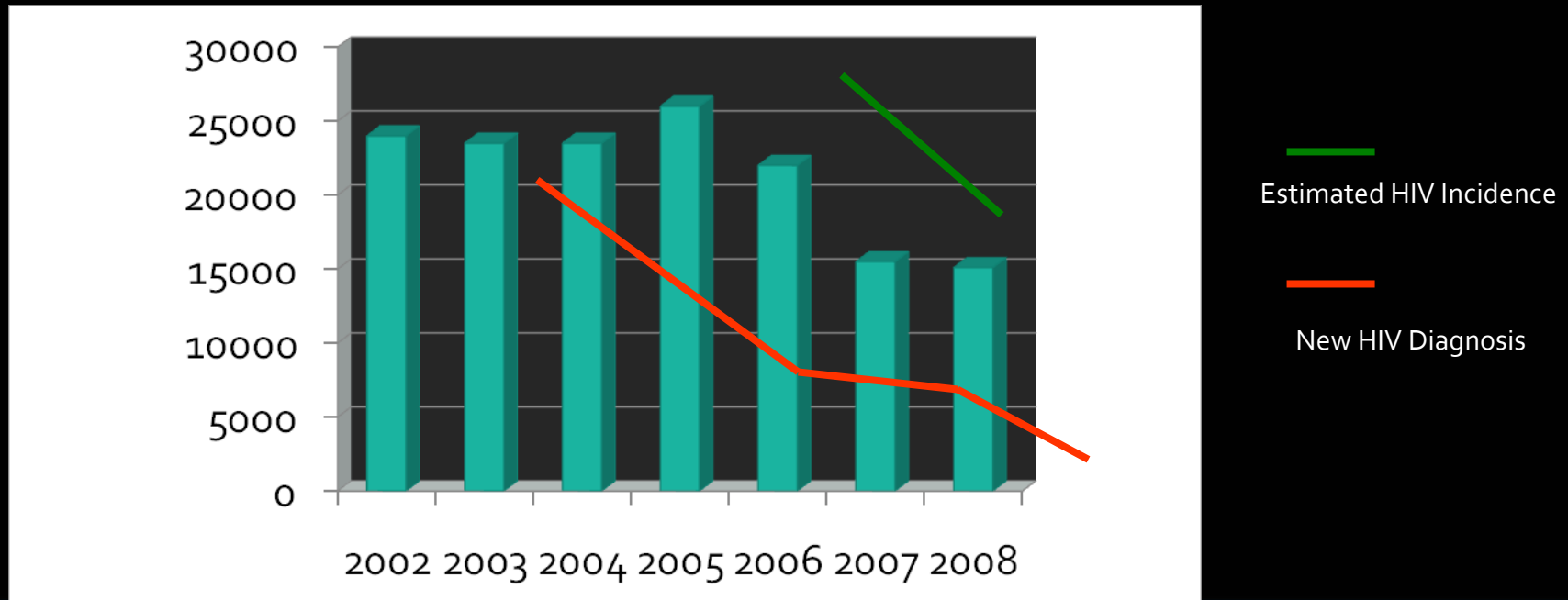
- Discordant couples



Unprotected Sex in Couples



Reduction of Transmission Associated With Testing and Linkage to Care



San Francisco established aggressive linkages to care from testing facilities

All patients have viral load testing on HIV diagnosis

Linkage to care has been associated with:

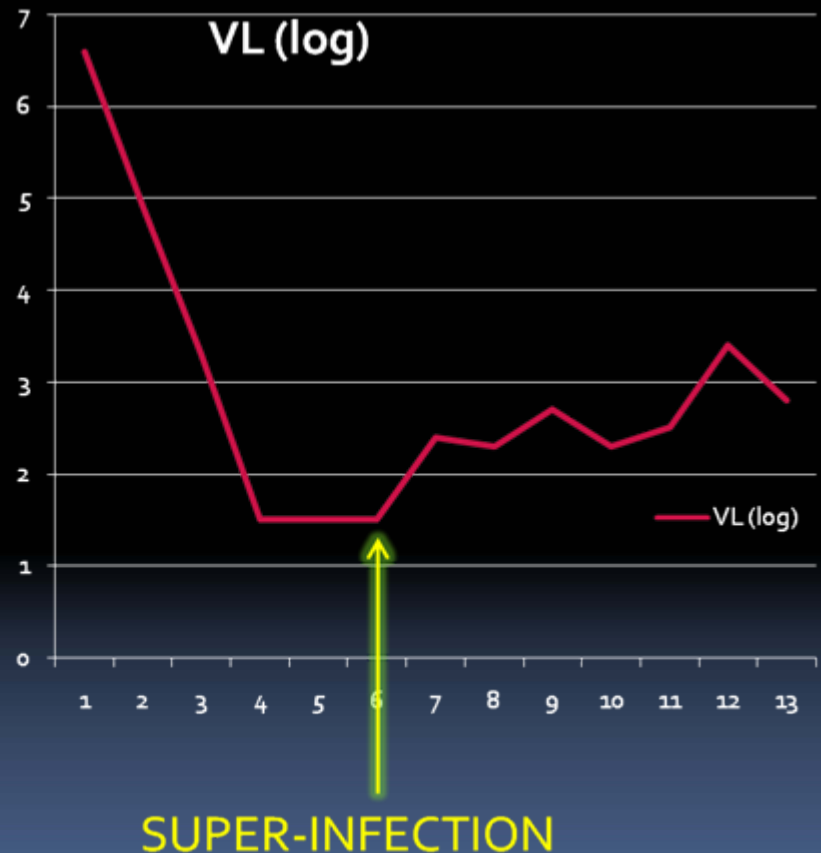
- Decreased HIV Incidence
- New HIV Diagnosis
- Average HIV Viral Load in the community

Superinfection with MDR Virus

Gay man having unprotected sex for two years with a single partner

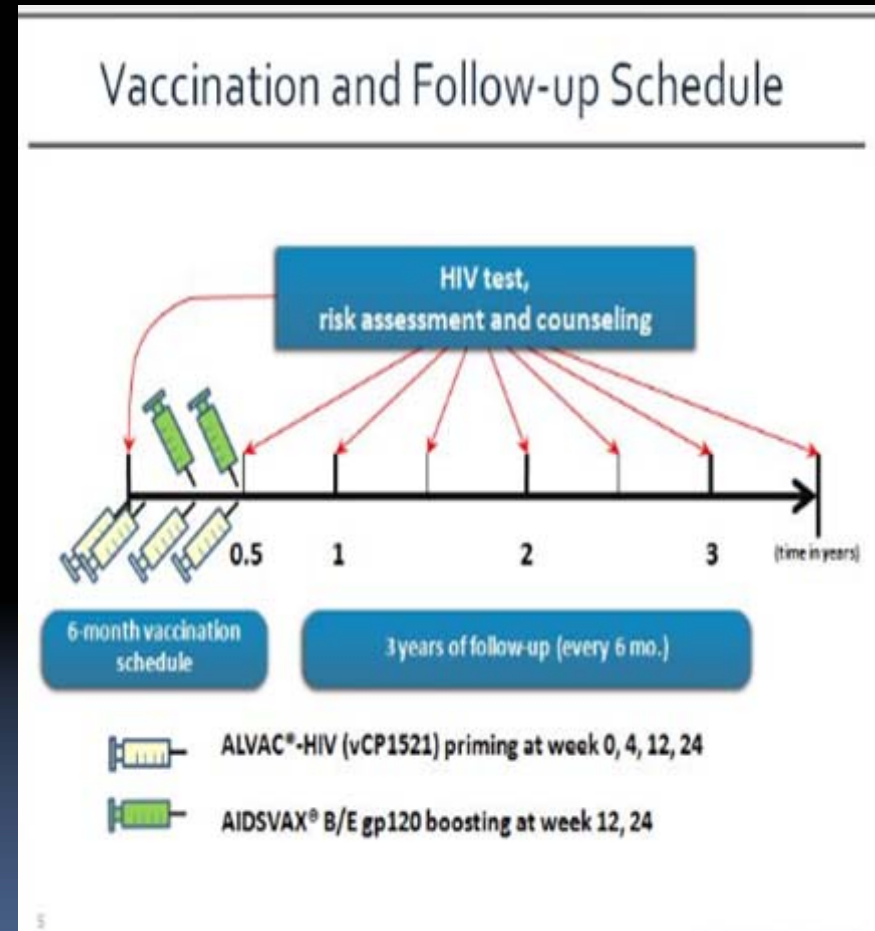
He became super-infected with his partners virus

His viral load increased and his virus showed mutations to the drugs to which his partners virus was resistant



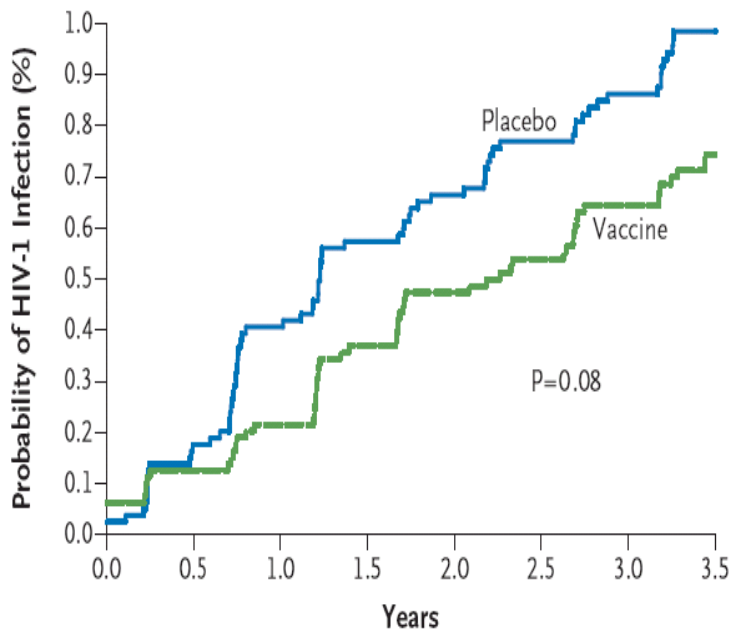
RV 144 Update: Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

- Community-based, randomized, multicenter, double blind, placebo-controlled efficacy trial in Thai heterosexual population.
- Vaccine strategy: 4 priming injections of ALVAC or placebo and 2 booster injections with AIDSVAX or placebo during first 6 months of the study.
- Patients monitored for HIV-1 infection and early HIV-1 viremia every 6 months for 3 years.
- 3 analyses performed: intention-to-treat, per protocol, and modified intention-to-treat.



RV 144 Update: Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

A Intention-to-Treat Analysis



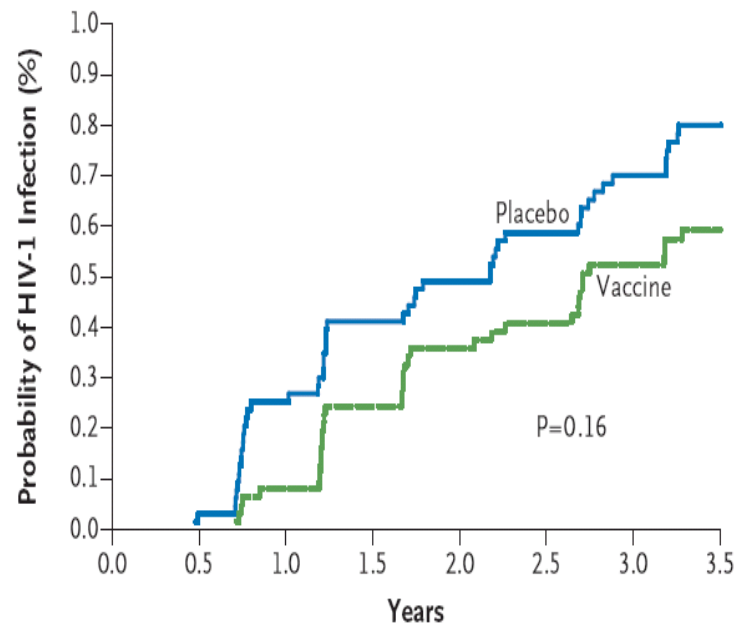
No. at Risk

Placebo	8200	7775	7643	7441	7325
Vaccine	8202	7797	7665	7471	7347

Cumulative No. of Infections

Placebo		32	52	67	76
Vaccine		17	37	50	56

B Per-Protocol Analysis



No. at Risk

Placebo	6366	6283	6220	6089	6002
Vaccine	6176	6140	6068	5958	5874

Cumulative No. of Infections

Placebo		16	31	44	50
Vaccine		5	22	32	36

All analysis showed decreased infections in the vaccinated group

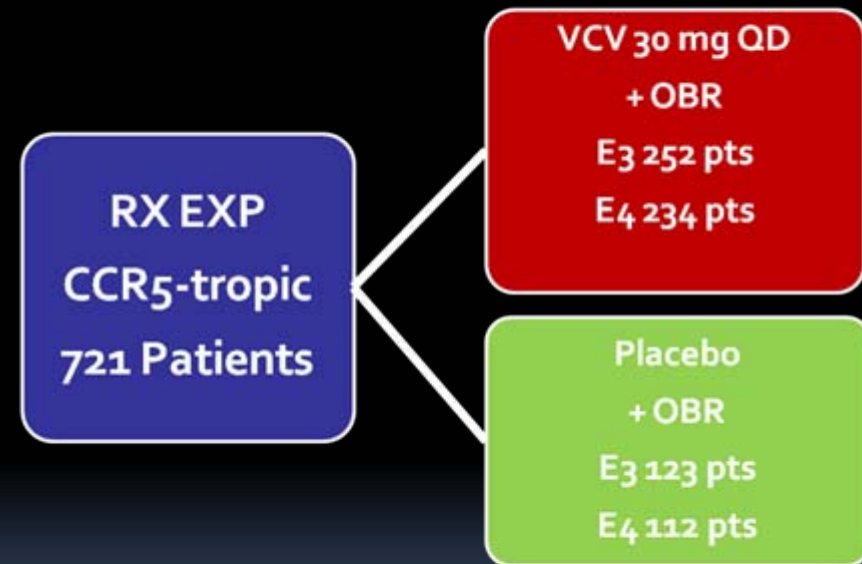


ANTIRETROVIRAL THERAPY

Phase 3 Trials of Vicriviroc (VCV) in Treatment-experienced Subjects

Pooled Analysis: VICTOR-E3 & VICTOR-E4

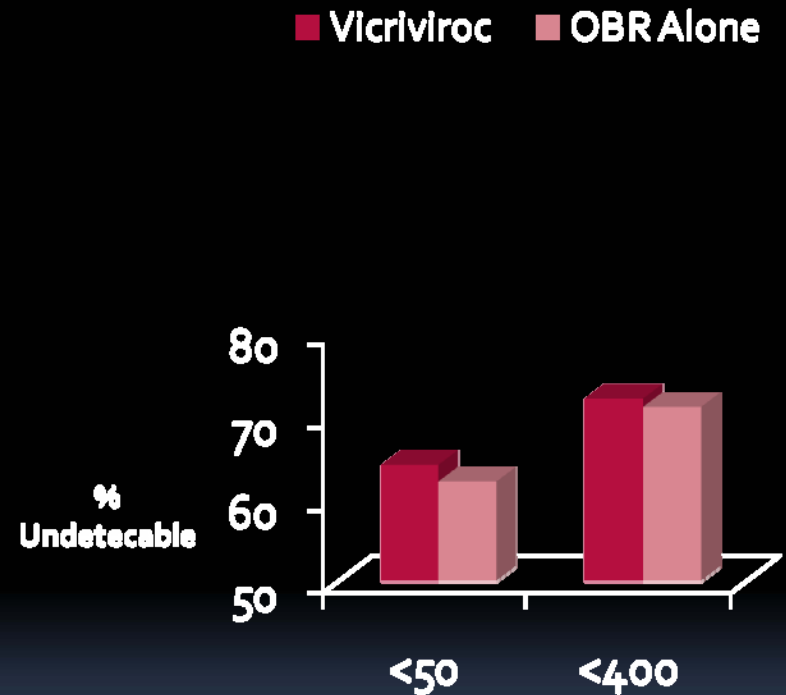
- Pooled analysis of phase III VICTOR-E₃ and VICTOR-E₄ trials evaluated safety and efficacy of VCV + OBR with PI/r_{tv} compared with OBR alone in treatment-experienced HIV-infected patients.
- Pooled mITT population 721 treated CCR5 HIV (by Trofile ES[®])
- Eligibility:
 - HIV-infected with CCR5-tropic HIV-1 only
 - HIV-1 RNA > 1000 copies/mL
 - Documented resistance to agents from ≥ 2 classes (NRTI, NNRTI, or PI)



Baseline characteristics:
Mean age 43, 29% females,
40% non-white,
Mean HIV RNA 4.6 log¹⁰ copies
Mean CD4 count 257 cells/ μ L

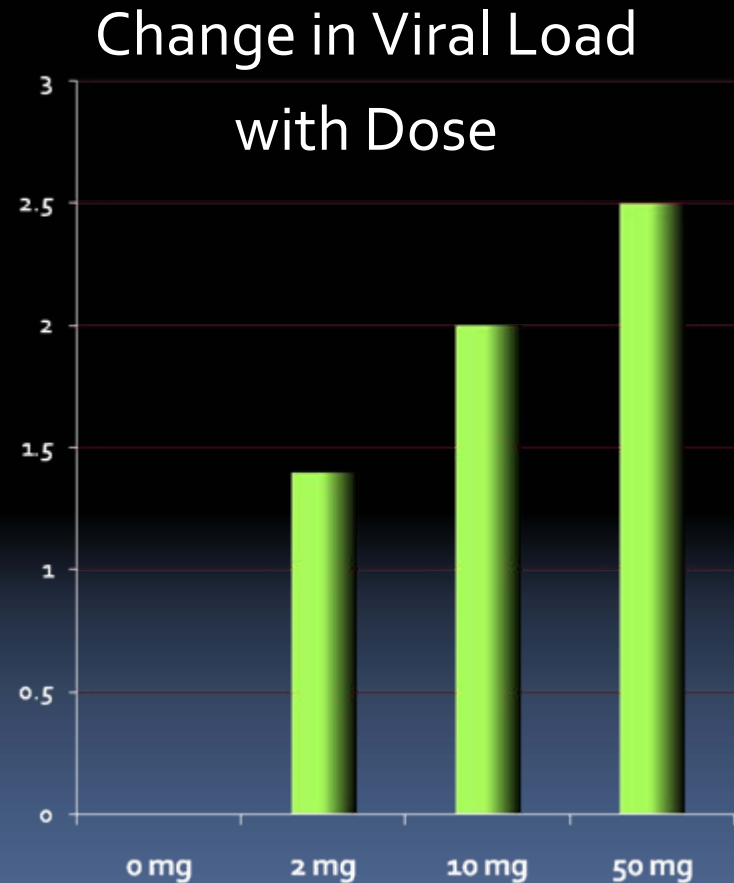
Pooled VICTOR-E3 and E4: Safe but Not Superior over Potent OBR Alone

- No significant differences between VCV and OBR ($p=0.6$)
- Subgroup analysis if ≤ 2 active drugs in OBT VCV efficacy ($p=0.02$)
- Post-hoc analysis showed that use of RAL and DRV in OBT strongly influenced outcome



Integrase Inh.(INI) S/GSK1349572⁵⁵

- One daily dosing,
- No cross resistance to other integrase inhibitors
- 2.5 log ↓ VL after 10 days of mono-therapy
- Two Phase IIB in progress in treatment naive and experienced

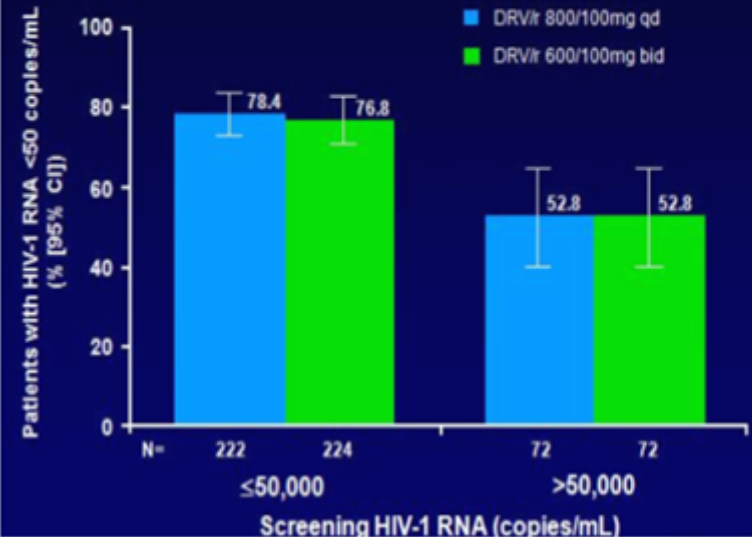


ODIN Trial: 48 Weeks Once vs. Twice Daily DRV/r in treatment-experienced with No DRV RAM

- Twice-daily DRV/RTV 600/100 mg approved for ARV experienced
- Once-daily DRV/RTV 800/100 mg approved for ARV naive
- Eligibility:
 - HIV-1 RNA > 1000 copies/mL
 - CD4 > 50 cell/mm³
 - No DRV RAMS: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V
 - No previous or current use of enfuvirtide, tipranavir, or darunavir
- Primary endpoints:
 - HIV-1 RNA < 50 copies/mL at Week 48

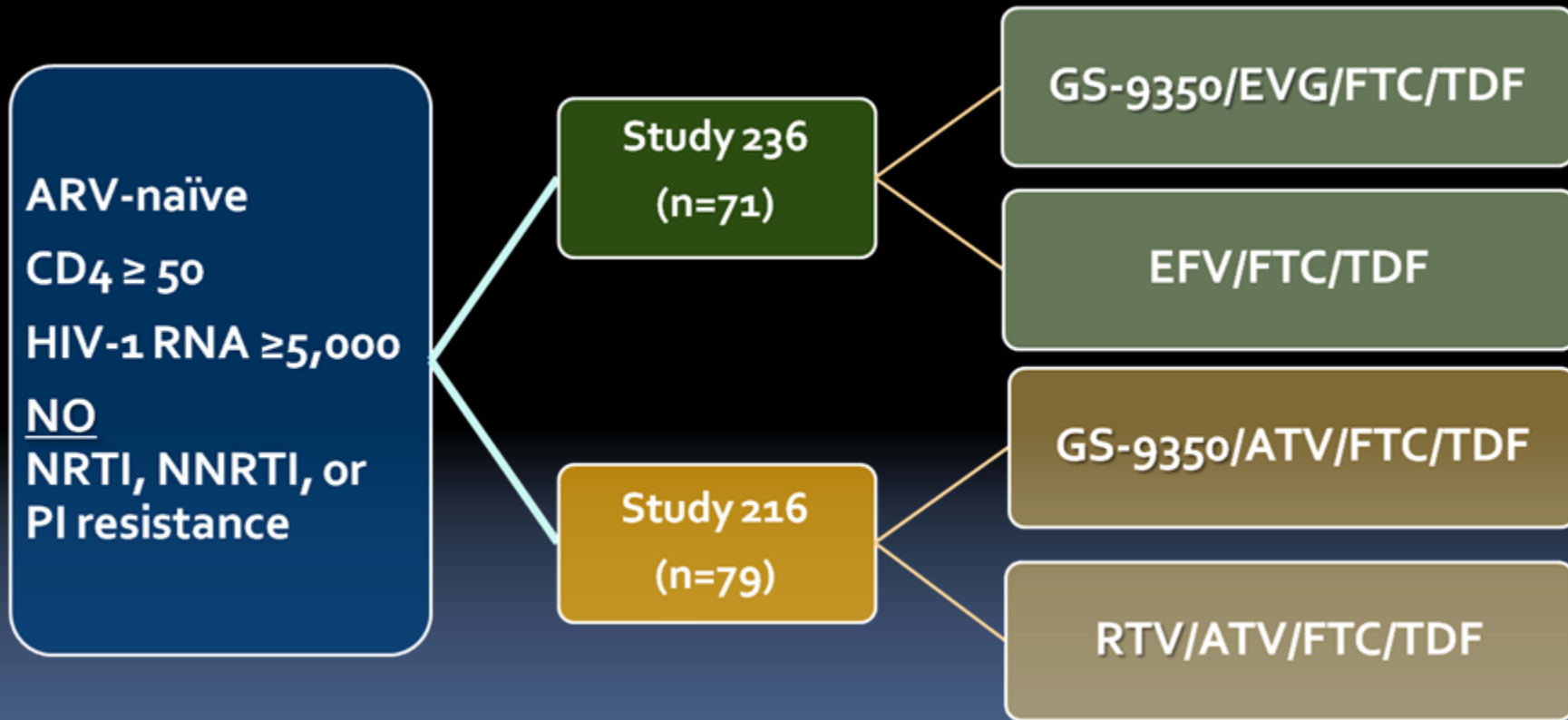
Baseline characteristics:
Mean age 40, 27% females, 65 % non-white
Mean HIV RNA 4.16 log¹⁰ copies
Mean CD4 count 228 cells/ μ L

ODIN: confirmed virologic response by screening HIV-1 RNA



Single-tablet, fixed dose Regimen (QUAD) 24 weeks results

QUAD (Cobicistat): Elvitegravir/Emtricitabine/Tenofovir/GS-9350



QUAD (Cobicistat)

Week 24 Outcome	QUAD (48 pts)	ATRIPLA (23 pts)	GS-9350/ATV + TRUVADA (50 pts)	RTV/ATV+ TRUVADA (29 pts)
ITT analysis HIV-1 RNA <50	90%	83%	84%	86%
Median CD4 Increase from BL	123	124	206	190
Treatment Related AE (any grade)	17 (35%)	13 (57%)	10 (20%)	7 (24%)
Study Discontinuations	6%	13%	8%	10%

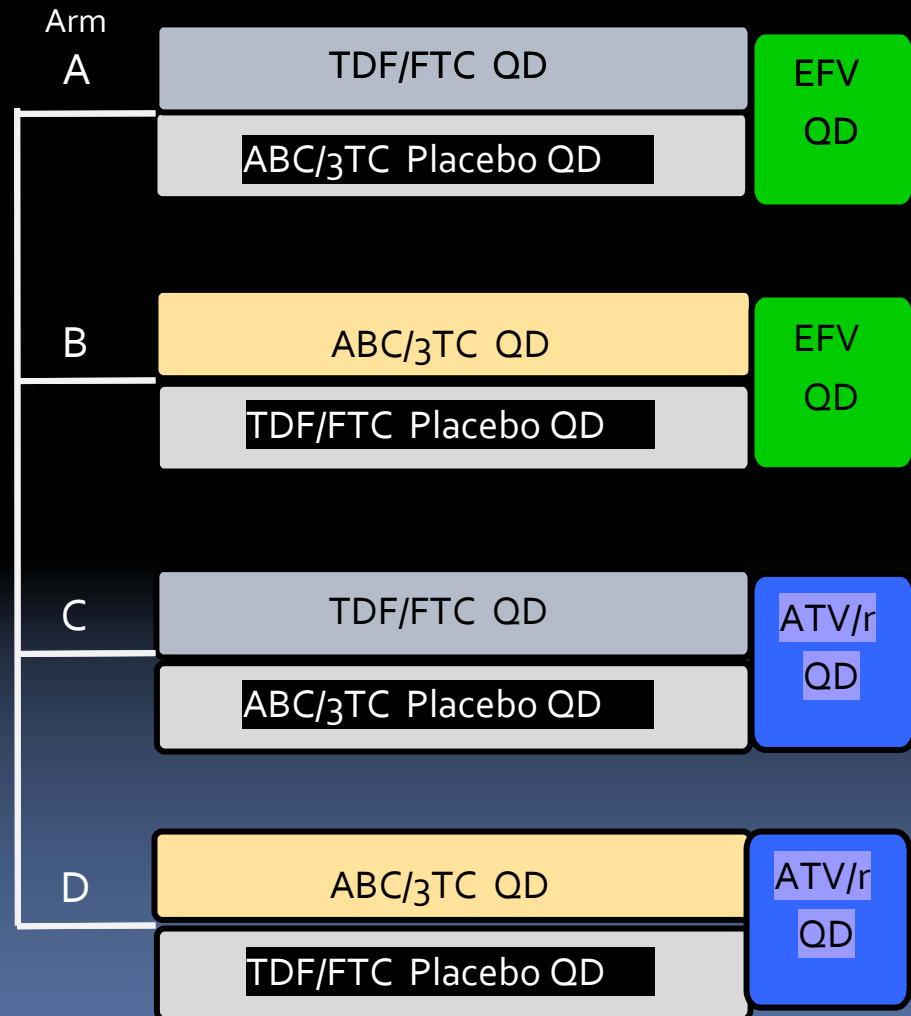
- Cobicistat-boosted non-inferior to Atripla (VL < 50 c/mL at Wk 24)
- Cobicistat-boosted ATV similar to rtv-boosted ATV (VL < 50 c/mL at Wk 24)
- Similar CD4+ cell count increases in both arms of each study

ACTG 5202: Study Design

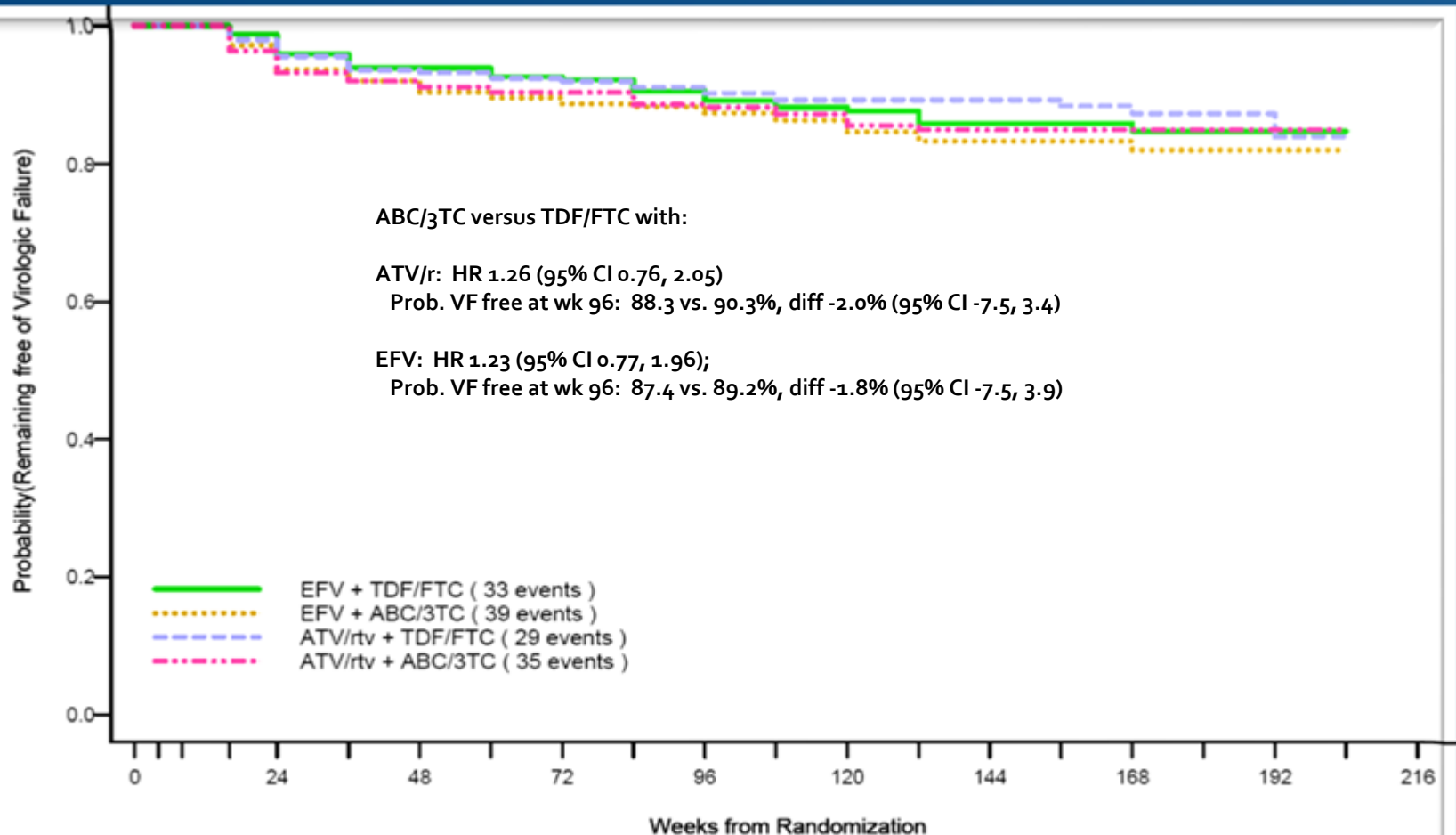
HIV-1 RNA ≥ 1000 c/mL
Any CD4+ count
 ≥ 16 years of age

ART naïve
1857 Enrolled
Randomized 1:1:1:1

- Stratified by screening HIV-1 RNA (< or $\geq 100,000$ c/mL)
- Enrolled 2005-2007
- Followed through Sept 2009, 96 wks after last pt enrolled



ACTG 5202 Time to Virologic Failure (End of Study: Low Viral Load Stratum)



	Number at risk:									
	0	24	48	72	96	120	144	168	192	216
EFV + TDF/FTC	265	246	229	220	205	163	120	78	26	
EFV + ABC/3TC	266	247	223	211	195	151	104	65	21	
ATV/r + TDF/FTC	265	245	233	220	212	164	123	80	26	
ATV/r + ABC/3TC	264	242	223	214	205	158	110	69	22	



HIV AND CO-INFECTIONS



Texas/Oklahoma
AIDS Education & Training Center

High Prevalence of Asymptomatic STI's in HIV-Positive MSM, Visiting HIV Outpatient Clinics

STD	LOCATION	TEST
<i>C. tracomatis</i>	Oral swabs, anal self swabs, urine	PCR
<i>N. gonorrhoea</i>	Oral swabs, anal self swabs, urine	PCR
<i>HBV</i>	serum	ABs
<i>HCV</i>	serum	ABs
<i>T. pallidum</i>	serum	RPR

- 659 MSM (median age 45.4)
 - HIV outpatient clinic of 2 academic hospitals
 - STI screening during a routine visit
- Patients spontaneously reporting STI symptoms were excluded
- MSM completed questionnaire about sexual behaviour previous 6 months.

High Prevalence of Asymptomatic Sexually Transmitted Infections in HIV-Positive MSM, Visiting HIV Outpatient Clinics in the Netherlands

Syphilis		# (%)
Known/treated syphilis		204/658 (31.0)
Newly detected early or late syphilis		33/658 (5.0)
Hepatitis B (HBV)		
Known (acute or chronic) HBV infection		39/650 (6.0)
Susceptible		91/650 (14.0)
Newly detected HBV infection		1/650 (0.5)
Hepatitis C (HCV)		
Known HCV Infection		27/649 (4.2)
Newly detected HCV infection		3/649 (0.5)
Chlamydia		
Anal		48/637 (7.5)
Urethral		9/626 (1.4)
Total		56/655 (8.6)
Gonorrhea		
Anal		20/637 (3.1)
Urethral		2/624 (0.3)
Total		22/655 (3.4)

More than 17% of HIV⁺ MSM attending HIV outpatient clinics in the Netherlands, had one or more asymptomatic STI, mostly CT and syphilis

Having had more than 2 steady or more than 2 casual partners, unsafe anal sex or other high-risk sexual techniques, and enema use were associated with the presence of asymptomatic STD.

Routine (bi-) annual screening for anal STI and syphilis, in HIV⁺ MSM reporting any of the factors associated with STI in this study, might be considered to prevent the further spread of STI.

HBV Vaccine

Functional Immunity: Predictive of Disease Progression

- Vaccine Non-Responders had Shorter Time to Development of Cancer⁷⁵⁹
 - Vaccine response rate in those with cancer vs cancer-free: 37% vs 60.7% ($p=0.015$)
- Vaccine Non-Responders had increased AIDS or Death⁶²⁵
 - 7-year incidence of AIDS or death: 25% vs 9% ($p<0.001$)
 - Adj.HR 0.56, 95% CI 0.33-0.96
- Vaccination Schedule
- Accelerated
 - Standard dose at T_{0,1} and 3 wks
 - Non-inferior efficacy only for those with CD₄ >500
- Alternate 4-part high dose
 - Double dose at T 0,4,8 & 24 wks
 - Better response than standard 3 dose series, especially:
 - Older age
 - VL >50
 - Males
 - CD₄ <350

Clinical Features of Subjects Infected with HIV and H1N1 Influenza Virus

- Time from onset to hospitalization inversely related to CD₄ counts and directly related to length of stay and death.
- Oseltamivir treatment was delayed in some patients with OI because the OI masked symptoms associated with H₁N₁ infection.
 - Higher death rates for those with OIs.
- During an outbreak "...AIDS patients with respiratory symptoms should all be screened for influenza or consideration should be given to empirically starting antiviral treatment if tests are not available or could be delayed."26

Poor Immunogenicity of the H1N1 2009 Vaccine in Well Controlled HIV-infected Individuals: Final Results of an Immunogenicity Trial

- 120 participants received a single dose of licensed, unadjuvanted H1N1 vaccine (Novartis, 2009).
- Seroconversion was defined as an anti-hemagglutinin Ab titer > 1:40 at 3 weeks.
- Overall 69 % had titers > 1:40 at 3 weeks, but 25 % of patients had baseline titers > 1:40.
- In the 89 patients with baseline titers < 1:40, 61 % had a response > 1:40 at 3 weeks.
- Conclusion: "... a modified vaccine schedule or adjuvanted vaccine should be considered for patients with immunosuppression due to HIV."



COMORBIDITIES

Risk Factors Associated with Renal Impairment: Cohort Analysis

Cohort	N	Increased Risk
Swiss HIV Cohort	2253	TDF Increasing Age Female Gender
French ANRS Aquitaine	2613	TDF Increasing Age Female Gender CE ₄ < 200
US ART Naive	4588	Prior CKD
D:A:D	30,000 pt/yrs	TDF

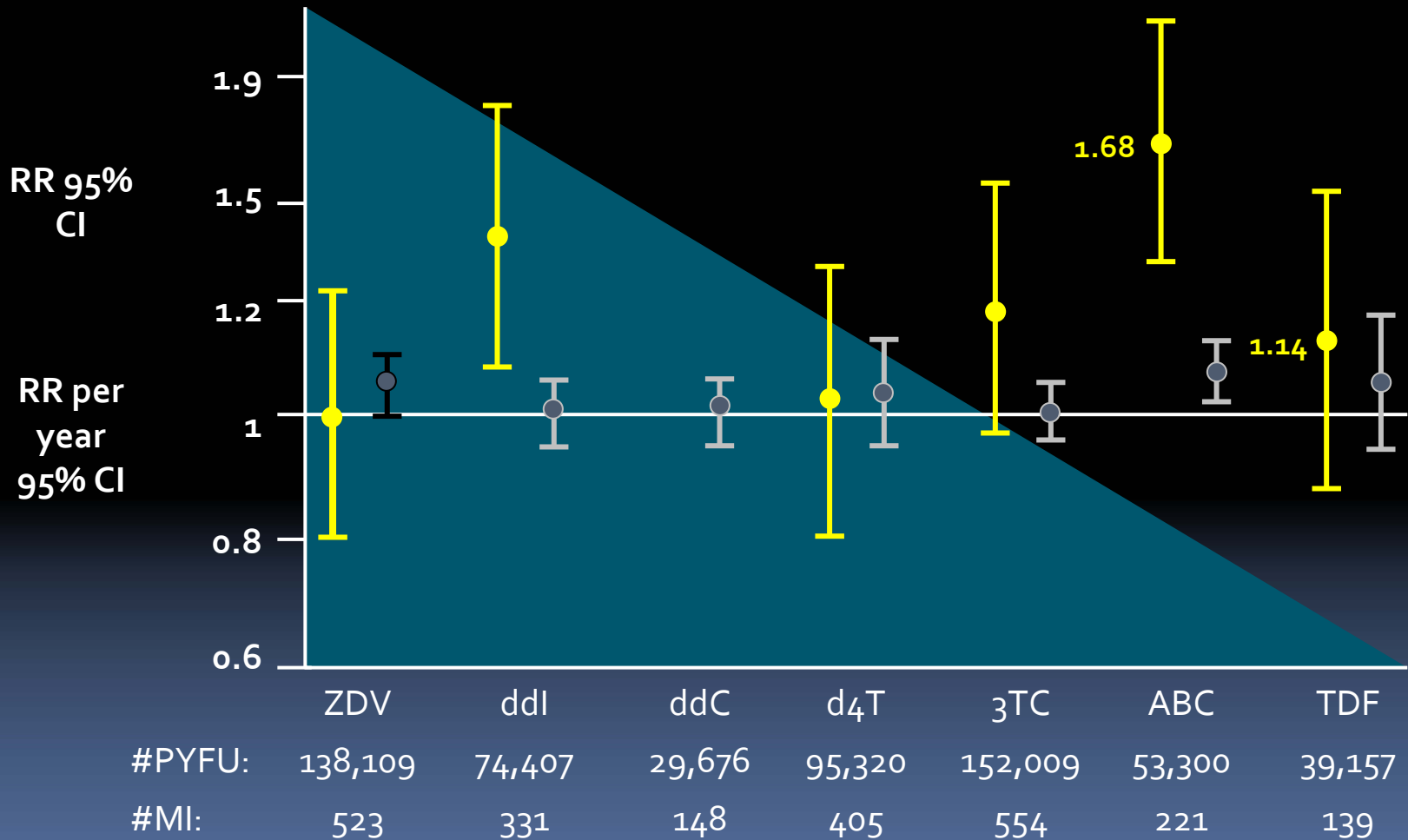
Risk Factors Associated with Renal Impairment: ACTG 5202 at 96 weeks



$P < 0.001$ for ATZ/r + TDF vs other regimens

NRTIs and Risk of MI:

Recent* and Cumulative Exposure



* Recent use defined as still using or stopped within last 6 months.

** Not shown (low number of patient currently on ddC)

Longitudinal Progression of Bone Mineral Density Loss

■ New York Cohort⁷⁴⁶:

Baseline DEXA

95 (42%) normal →
7.2 per 100 PY osteopenia incidence

DEXA After 2 Years

18 (19%) osteopenia

98 (43%) osteopenia →

29 (16%) osteoporosis

33 (15%) osteoporosis →

25 (76%) still osteoporosis

■ French Cohort⁷⁴⁷:

Baseline DEXA

72 (28%) normal →

DEXA After 2 Years

20 (28%) osteopenia

183 (72%) osteopenia →

29 (16%) osteoporosis

9.57 per 1000PY incidence osteoporosis

Vitamin D

- **Normal Functions⁷⁵³:**
 - Calcium homeostasis & bone metabolism
 - Antineoplastic & anti-inflammatory processes
 - Immunity – involved in:
 - Induction of antimicrobial peptide that kills MTB & others
 - Macrophage phagocytosis, monocyte H₂O₂ secretion, neutrophil motility

- **Possible Deficiency-Related Complications ^{751, 753}:**
 - Diabetes, CVD, renal disease
 - HIV-wasting, anemia, maternal disease progression

	Normal Metabolism	Altered Metabolism ⁷⁵⁰
Vit D	Produced in skin from sun exposure Absorbed from food consumed	- Sun block, melanin, cloudy weather - Insufficient intake
25 (OH)D	Hydroxylated in liver	- EFV induces P450 conversion to inactive calcitronic acid
1,25 (OH)D	α-Hydroxylated in kidneys	- RTV inhibition of α-OH - Renal insufficiency - EFV induces P450 conversion to inactive calcitronic acid

Vitamin D Deficiency in HIV

- Higher Rates During Cloudy Season
 - Switzerland: 42-52% vs 14-18%⁷⁵²
 - Italy: 43% vs 9%, adjOR 8.3 (p 0.0001)⁷⁵¹
- Other Factors Associated with Deficiency⁷⁵¹
 - Older age, non-caucasian race, lower BMI, lower CD4, prior exposure to NNRTI
- Not Associated with TDF-Related BMD Loss⁷⁴⁹
 - 25(OH)D deficiency not correlated with TDF use
 - Hyper-PTH correlated with GFR <60 and prior AIDS but not with TDF use

Pregnancy Outcomes with Non-AZT Containing regimens

- European cohort : 26 centers in 10 European countries.
- 7353 pregnancies on HAART between 2008-2009
 - 6374 on AZT-HAART
 - 1199 on non-AZT-HAART
- No difference in risk of:
 - Detectable VL at delivery.
 - Congenital abnormality.
 - MTCT.

CSF Viral Loads

- **Plasma viral load** → strongest correlate of CSF viral load → importance of systemic HIV suppression for control of HIV in the nervous system
- **Without ART**– higher CSF viral loads correlate with older age + more advanced current and past immune suppression
- **With ART**– detectable CSF viral loads associated with worse adherence & worse estimated antiretroviral penetration & non-white ethnicity
- Both correlated with longer duration of HIV + more advanced HIV disease
Non-white ethnicity also associated with HCV co-infection
- **Without ART**, the 13% that had CSF viral loads that were at least as high as plasma viral loads had worse global neurocognitive performance
- Explanation for why the relative rather than the absolute value of CSF viral loads was associated with outcome remains to be determined.

Correlates of CSF Viral Loads: The Charter Cohort 1221 volunteers

CNS Penetration-Effectiveness Ranks 2010

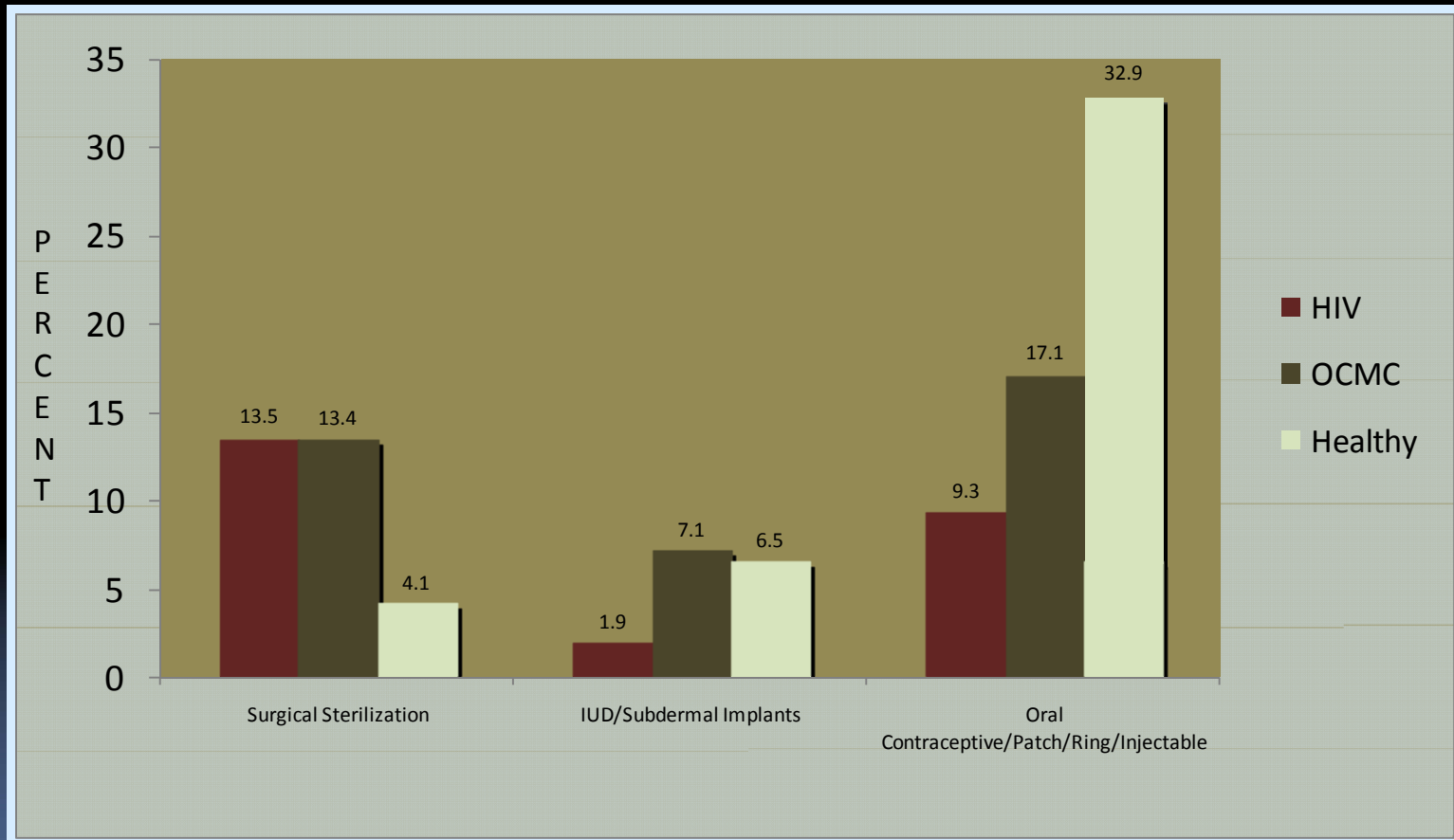
	4	3	2	1
NRTIs	Zidovudine	Abacavir <i>Emtricitabine</i>	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	<i>Nevirapine</i>	Delavirdine <i>Efavirenz</i>	<i>Etravirine</i>	
PIs	<i>Indinavir-r</i>	<i>Darunavir-r</i> <i>Fosamprenavir-r</i> Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		



WOMEN AND CHILDREN

Contraception in HIV

Effective Contraception Use Among Women



Contraception in HIV

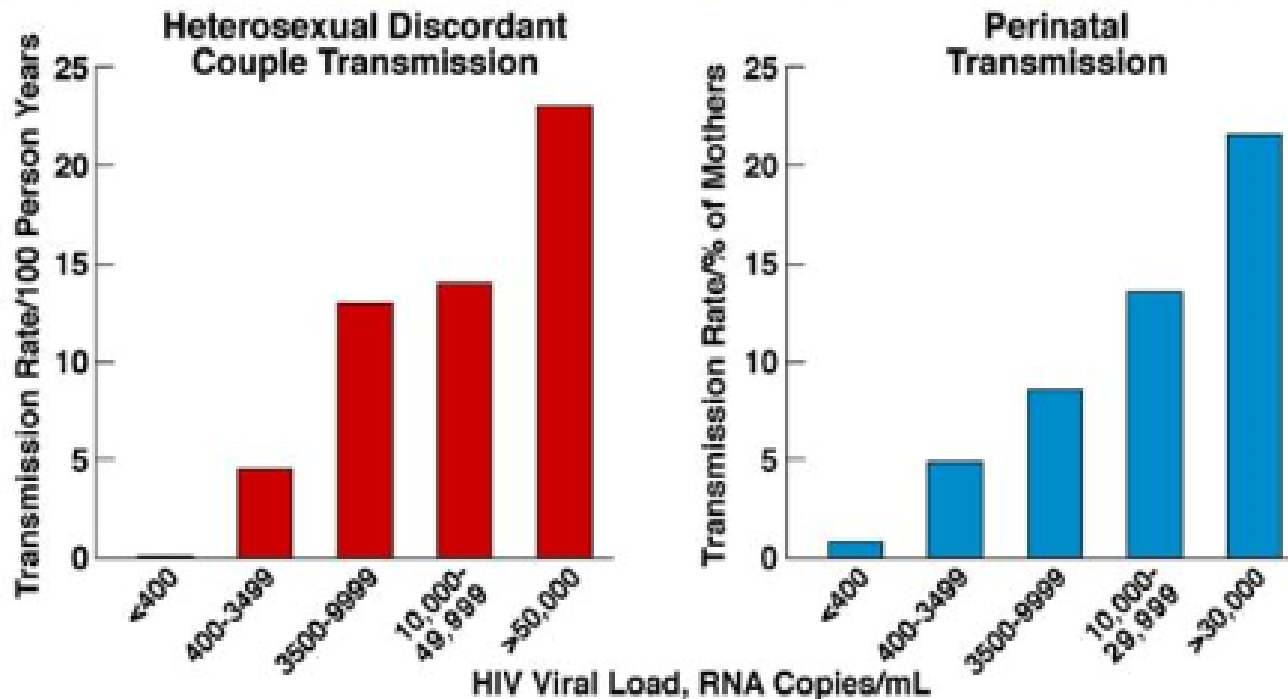
Effective Contraception Use Among Women

- HIV+ women contraception:
 - Effective reversible contraception less utilized (all forms) than healthy or women with other chronic medical conditions (OCMC)
 - Less effective methods more commonly utilized (condoms only or abstinence)
- Use of levonorgestrel IUD
 - No increase on viral shedding, inflammatory cytokines or STIs
 - Effective, acceptable, tolerable
- Emergency contraception with Levonorgestrel and EFV
 - Lower mean AUC,(58%), Cmax (45%) and Cmin (69%)

ARV in Children

- 3 Pediatric formulations of RAL
- Qday Elvitegravir + Pir safe and tolerated in adolescents
- Few DRV RAM noted in children
- >180 weeks sustained virologic response with FPV/r in naïve and experienced perinatally infected children
- RTV but not LPV had significant increase in Total Cholesterol
- DO NOT CRUSH LPV/r
 - Decrease by 40%

Rates of Sexual and Perinatal HIV Transmission According to Viral Load



Sources: Guinn et al., NEJM, 2000; Cooper et al., JAIDS, 2002

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Tariq S, et. al; Poster 895.

Patterns of non-ZDV HAART use

Figure 1. Use of non-ZDV HAART over time

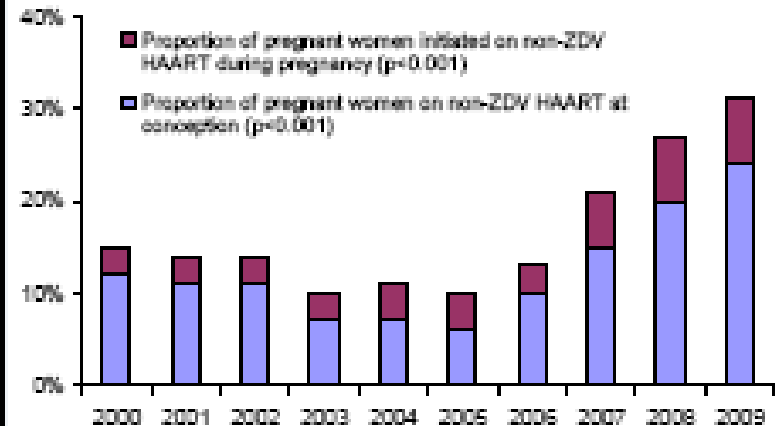
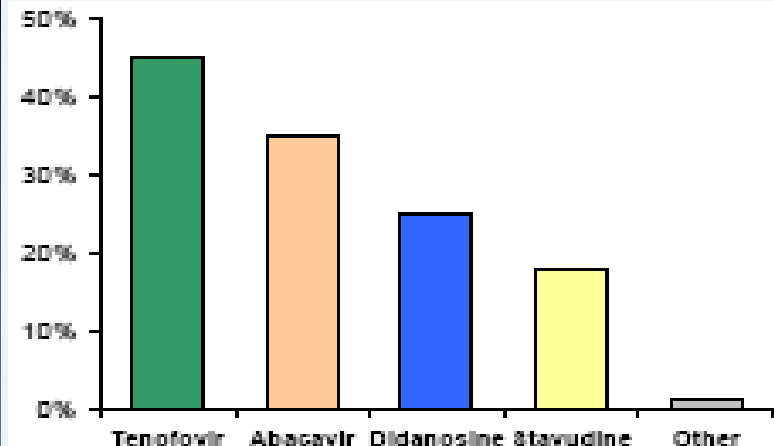


Figure 2. Non-ZDV drugs used in pregnancy





FUTURE DIRECTIONS

Our Common Goal:

“Controlling and Ultimately Ending the HIV/AIDS Pandemic”

“High Risk- High Impact Strategies”

Anthony Fauci

NIAID, NIH Director

Why and How?

- Aggressively “seek, test and treat”
 - Improved survival time from 26 weeks to 3-5 decades
 - Test and treat: Lowering Community VL
- Cure existing infections
 - Current treatment paradigm is not enough and not sustainable
 - Sterilizing vs. Functional
- Prevent new infections
 - Access to research proven modalities
 - Microbicides and PrEP
 - Vaccines

Understanding The Host

- Chronic immune activation can be attributed to microbial translocation
 - High Mobility Group Box Protein (HMGB₁)
 - Marker of tissue necrosis and immune activation
 - Lipopolysaccharid (LPS)
 - Marker of bacterial translocation
 - Both plasma leveles elevated before treatment
 - VL was 74% higher in those with elevated HMGB₁ and LPS above median
 - After 2 yearst of ART
 - LPS reduced to the same median as control
 - HMGB₁ reduced but not normalized

