

Vicriviroc: A Next-Generation CCR5 Antagonist for Treatment of HIV

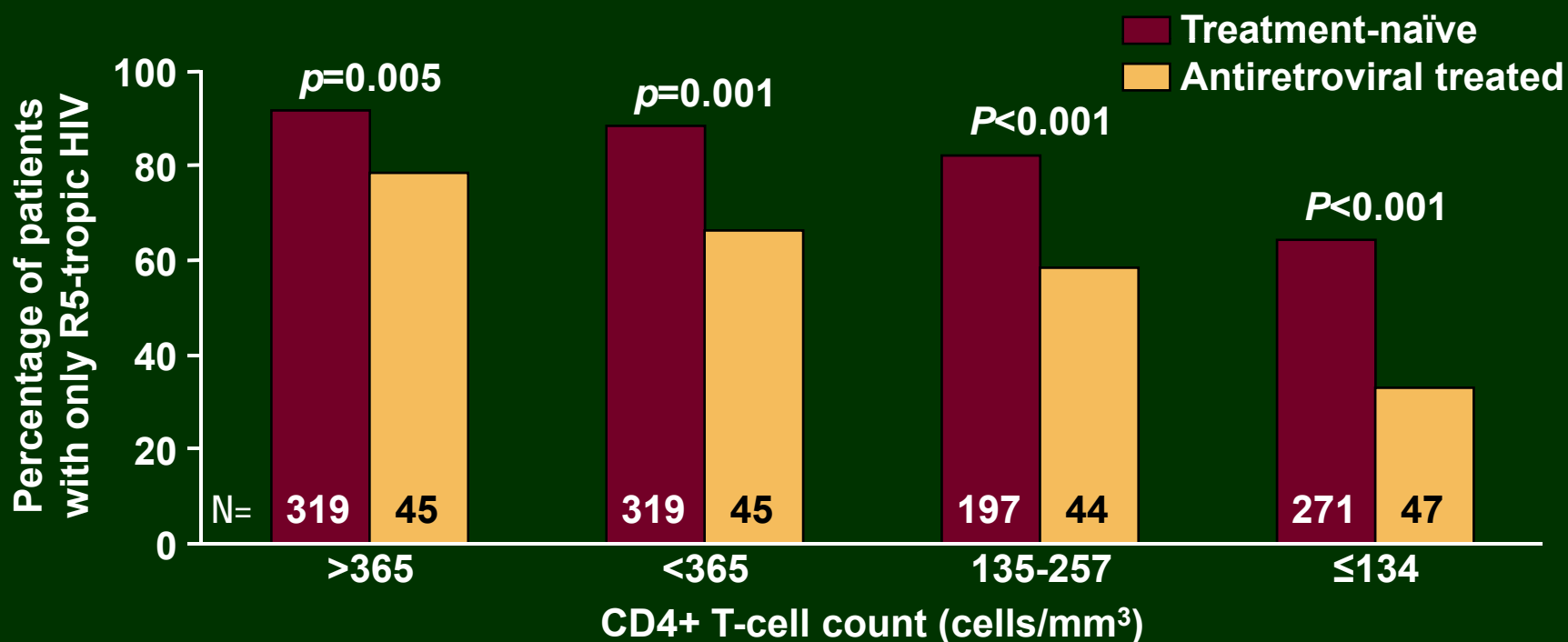
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HIV DART 2008*

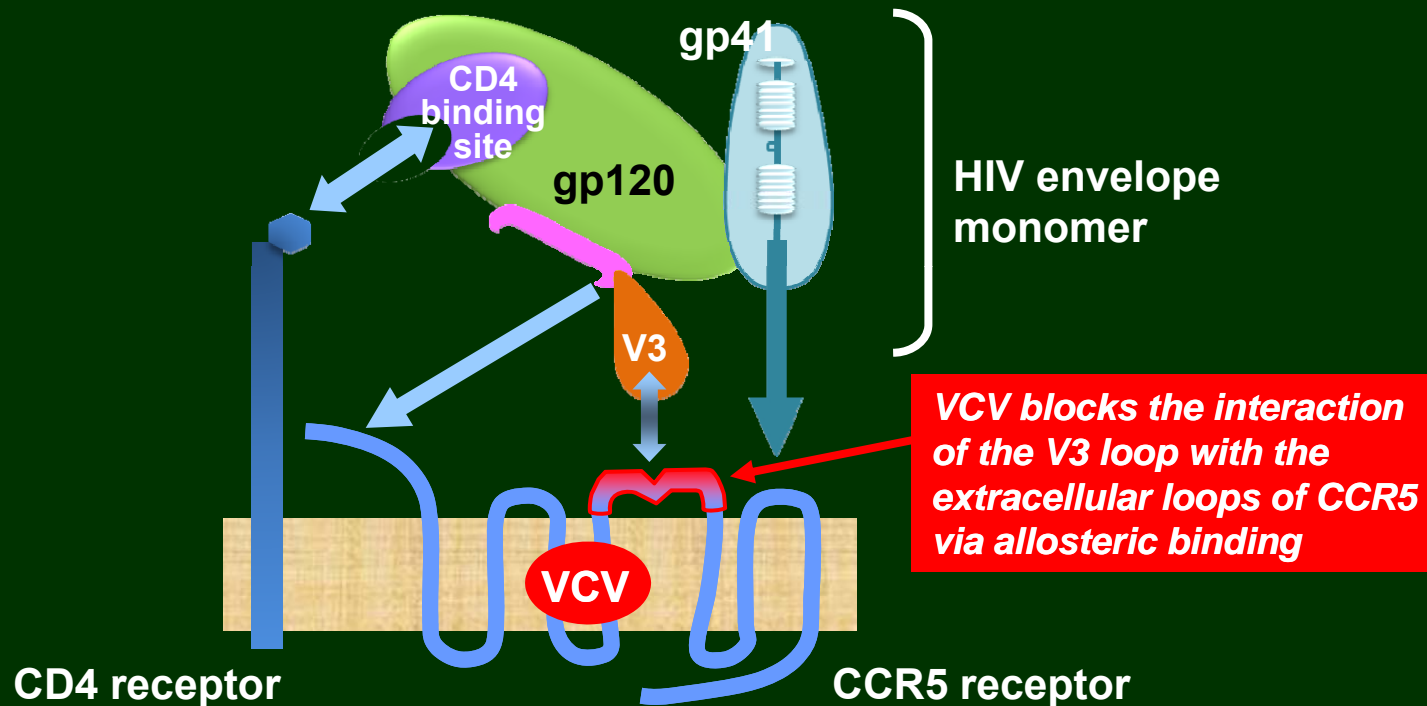
Stage of Disease and Prevalence of CCR5-Tropic HIV

- CCR5 is co-receptor for the majority of newly transmitted HIV, R5 tropism maintained throughout infection in many patients
- Clinical consequences of X4 emergence during treatment with a CCR5 antagonist appears to differ from those observed in the natural course of infection



Hunt PW, et al. *JID* 2006; Fätkenheuer G, et al. *NEJM* 2008; van der Ryst E and Westby M. ICAAC 2007.

Vicriviroc Mechanism of Action



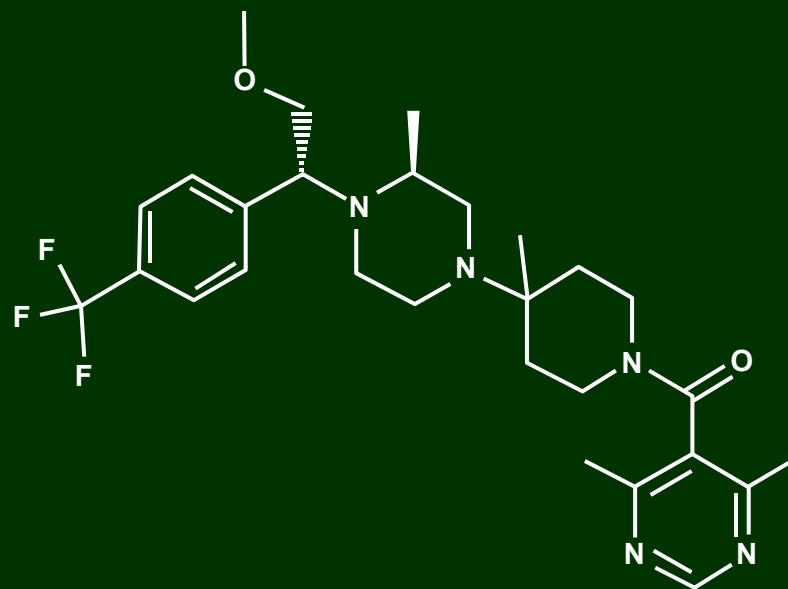
Adapted from Nolan KM, et al. *J Virol.* 2008.

- Congenital absence of CCR5 ($\Delta 32$ homozygous mutation) protects against HIV infection
 - Heterozygosity results in delayed HIV disease progression
- Recent bone-marrow transplant of CCR5(-) cells claimed to elicit a “functional cure” of HIV (Schoofs M. Wall Street Journal 7 Nov 2008)

Dean M, et al. *Science.* 1996; Smith MW, et al. *Science* 1997; Hütter G, et al. *CROI* 2008

Vicriviroc Preclinical Characteristics

- *In vitro* mean IC90 = 6 nM
- Plasma half-life >24 hours
- Additive to synergistic activity with other antiretrovirals
 - Lack of drug interactions:
Not a CYP3A inhibitor or inducer;
not a PGP substrate
- CYP3A4 inhibitor, e.g., ritonavir, increases AUC 5-6 times
- In the presence of CYP3A4 inhibition, no vicriviroc dose adjustment required by interactions with other antiretrovirals



Seiberling M, et al. IAS 2005; Sansone A, et al. ICAAC 2005; Strizki J, et al. Antimicrob Agents Chemother 2005; Li C, et al. Retrovirology 2005; Sansone A, et al. CROI 2006.

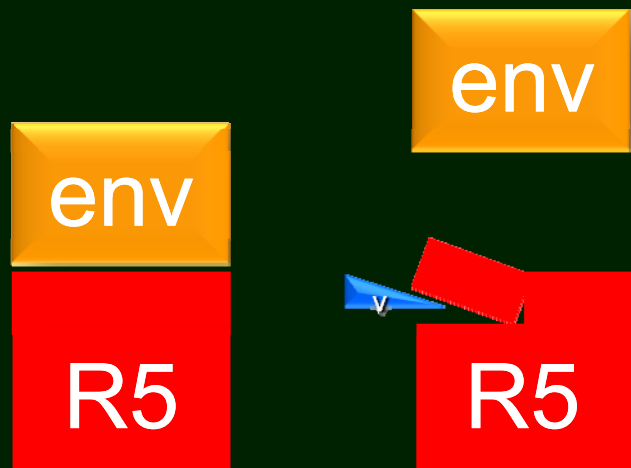
Viral Breakthrough

Two Distinct Mechanisms (1)

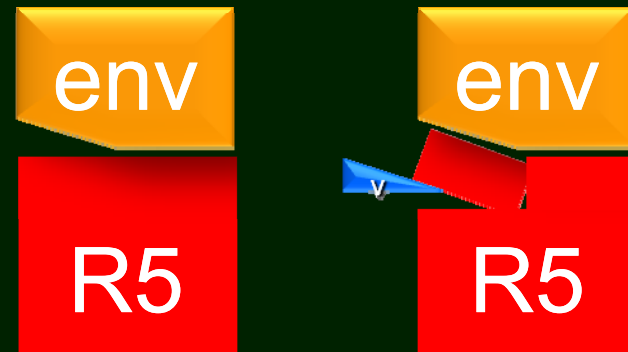
VCV Resistance Mutations


- Viral envelope mutates to bind to CCR5 receptor + VCV
- Slow to develop *in vitro* and *in vivo*
- No consistent envelope mutations identified to predict resistance

Sensitive Virus



Resistant Virus



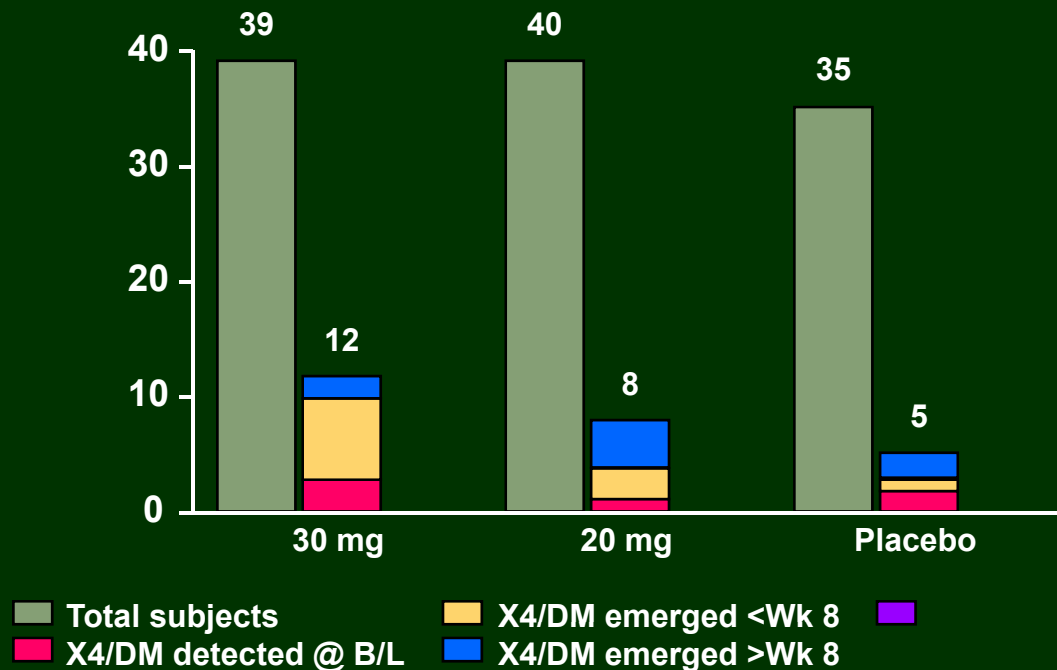
 = VCV

Viral Breakthrough

Two Distinct Mechanisms (2)

Capability of Using X4 Receptors

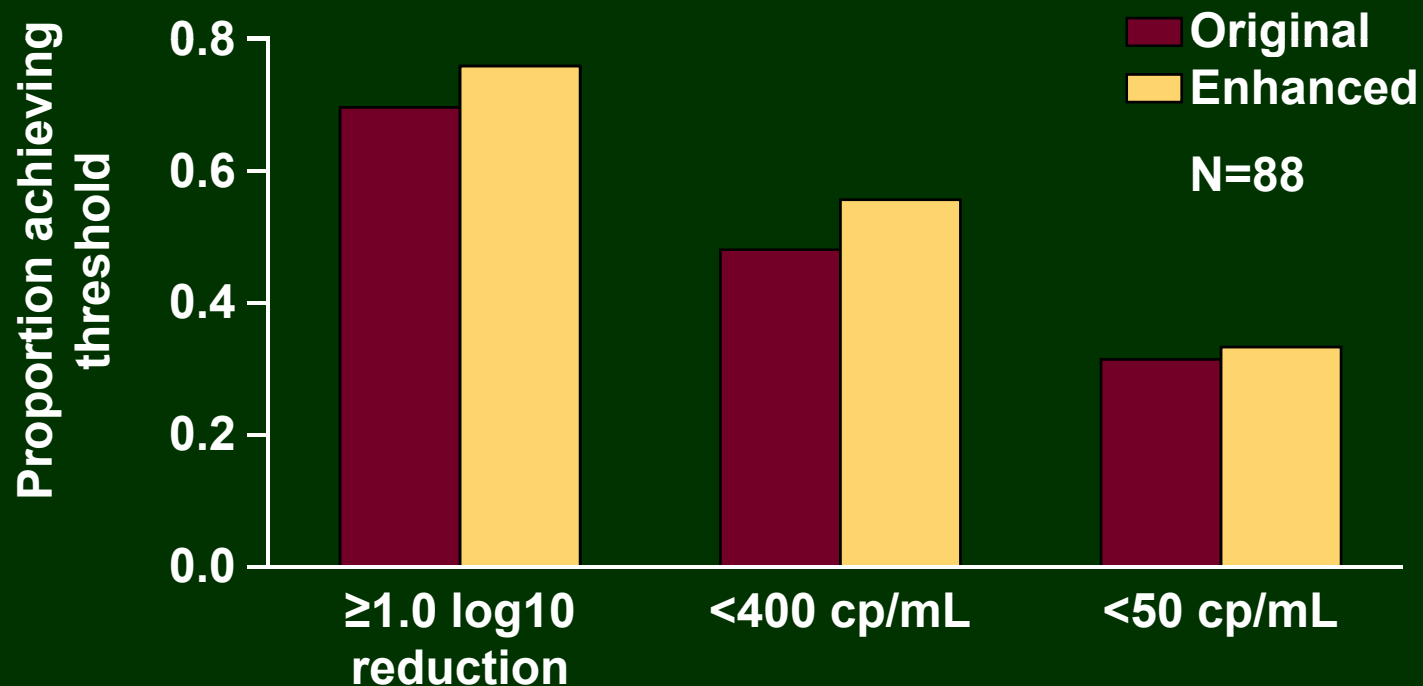
- Generally results from minor preexisting CXCR4-using viral populations detected during VCV therapy
- X4-using virus usually detected within the first weeks of treatment
- Pretreatment tropism distribution usually reappears after stopping VCV



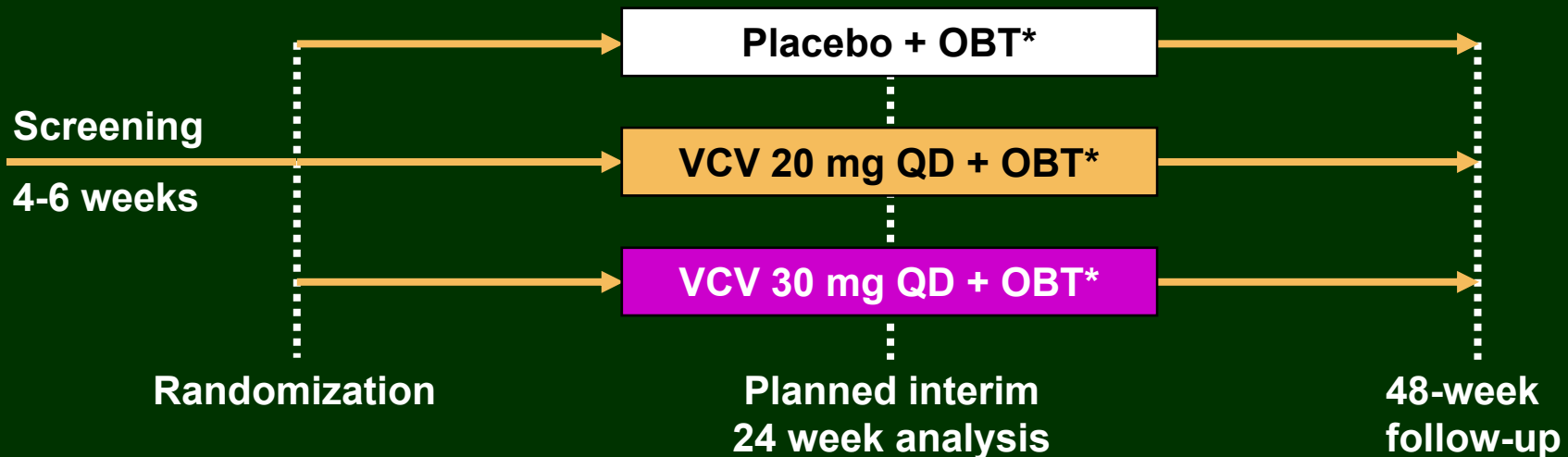
Zingman B, et al. CROI 2008; van der Ryst E and Westby M. ICAAC 2007.

Trofile ES[®] Assay ACTG 5211 Reanalysis

Detection of small pretreatment populations of X4-using HIV not predictive of full virologic suppression on VCV-containing regimen



Treatment-Experienced Phase 2 VICTOR-E1 Trial Design



Key Eligibility Criteria

- R5 tropic virus; HBV/HCV co-infection allowed
- Triple-class experienced: ≥ 1 RTI and ≥ 1 PI resistance mutation required
- HIV-RNA ≥ 1000 copies/mL
- Stable ARV ≥ 6 weeks prior to screening
- Acceptable laboratory parameters

Primary Efficacy Endpoint

- Mean change in \log_{10} HIV RNA at Wk 48

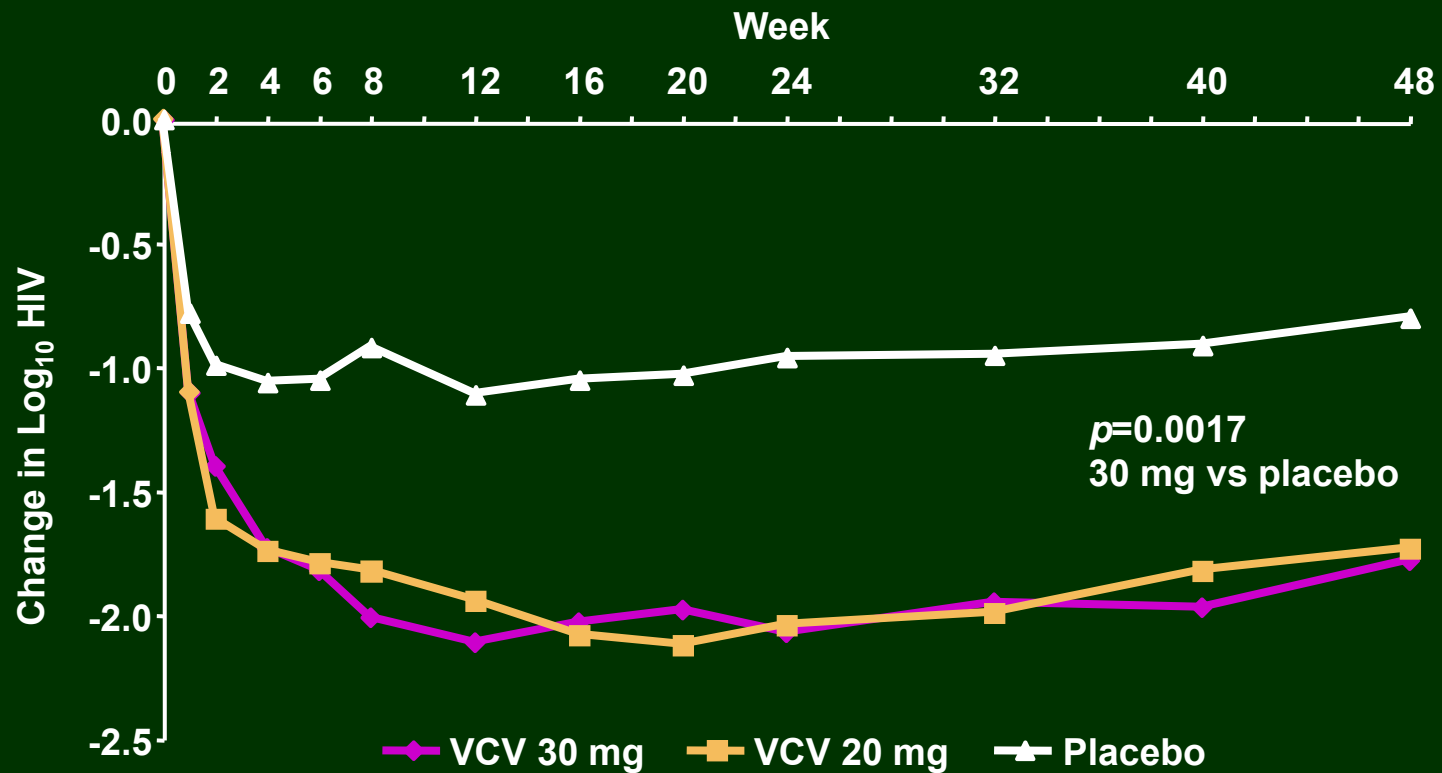
Secondary Efficacy Endpoints

- % subjects < 50 copies/mL
- % subjects < 400 copies/mL

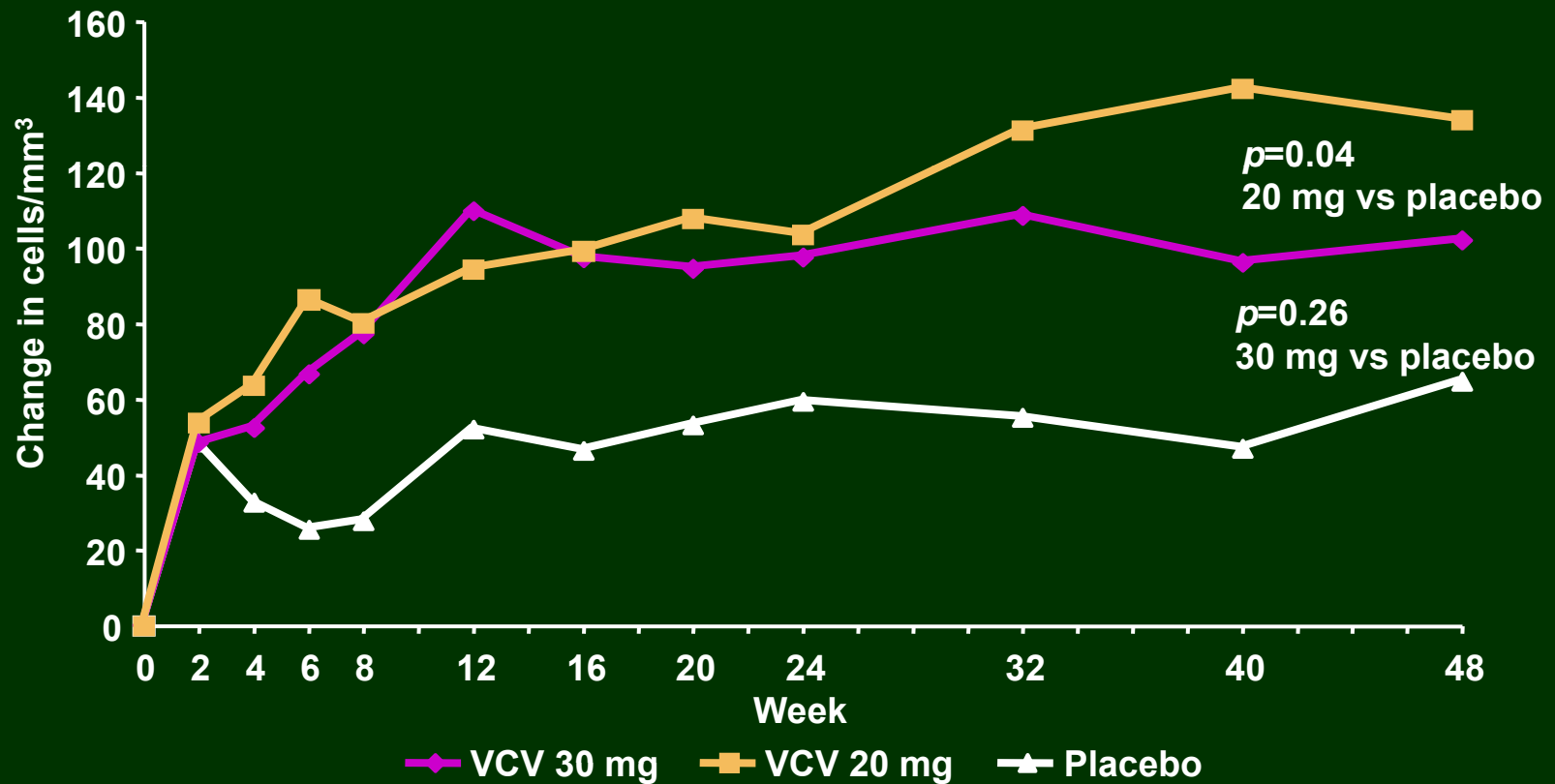
*Optimized background therapy; ≥ 3 drugs, including a PI with ≥ 100 mg RTV.

Zingman B, et al. CROI 2008.

VICTOR-E1: Mean Change in HIV-RNA



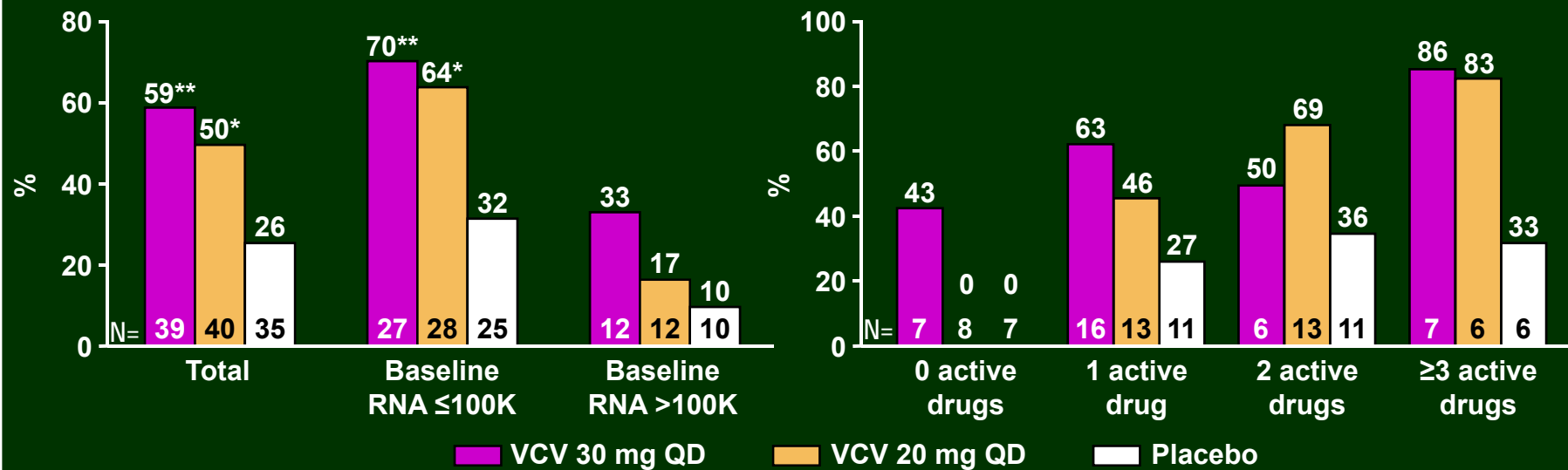
VICTOR-E1: Mean Change in CD4+ Cells



Zingman B, et al. CROI 2008.

VICTOR-E1: % <50 copies/mL at 48 weeks

- Overall, 59% of patients (VCV 30 mg) vs 25% (OBT) fully suppressed at 48 weeks
 - 43% (VCV 30 mg) when there were 0 active drugs in the OBT
 - 86% (VCV 30 mg) when there were >3 active drugs in the OBT
- The VCV 30 mg dose suggested superiority over VCV 20 mg in:
 - Subjects with HIV RNA >100,000 copies/mL
 - Subjects with <2 active drugs in OBT



VCV vs placebo: ** $p < 0.01$, * $p < 0.05$, using the Cochran-Mantel Haenszel Test adjusted for T-20 use in current OBT and for baseline HIV-1 RNA.

Schering-Plough Corp. Data on file.

VICTOR-E1 Safety Profile

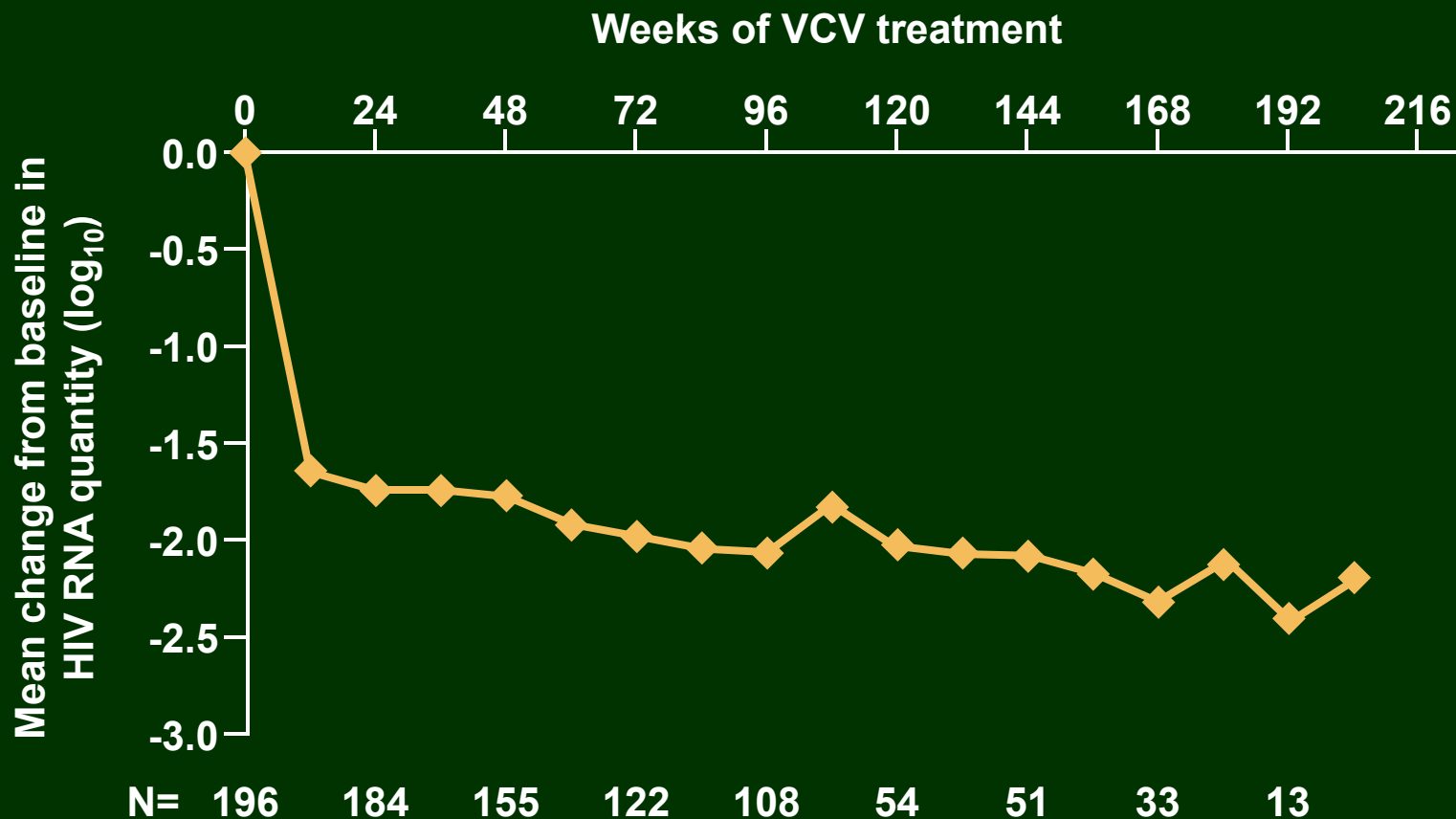
Overall incidence of adverse events similar in placebo and two vicriviroc groups

All causes and severities All patients receiving one dose	Placebo + OBT rate	VCV 20 mg + OBT rate	VCV 30 mg + OBT rate
Total exposure in person-yrs*	22.4	34.7	33.2
Diarrhea	40.2	31.7	45.2
Headache	31.3	8.7	15.1
Depression	26.8	11.5	9.0
Nausea	22.3	8.7	15.1
Pyrexia	17.9	11.5	15.1
Flatulence	17.9	5.8	3.0
Dizziness	17.9	2.9	15.1
Anorexia	13.4	0	0
Fatigue	13.4	14.4	6.0
Asthenia	13.4	5.8	6.0
Musculoskeletal pain	13.4	2.9	0
Lymphadenopathy	8.9	20.2	9.0
Cough	8.9	14.4	9.0
Tinea pedis	4.5	0	12.1
Upper abdominal pain	0	14.4	3.0

*Rate >10/100 person-years.

Schering-Plough Corp. Data on file.

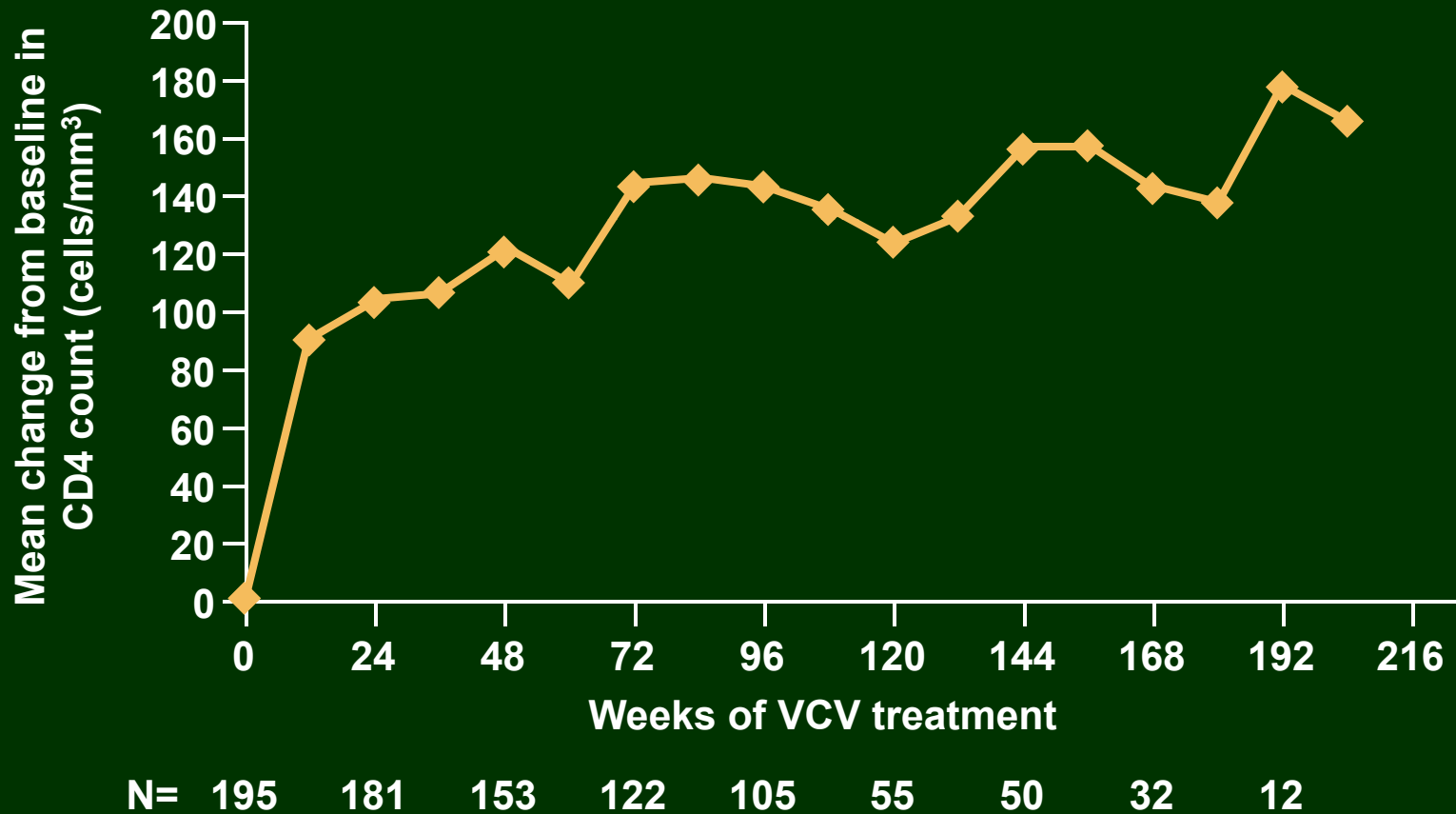
Long-term Virologic Results ACTG 5211 & VICTOR-E1 Extensions



Dunkle L, et al. ICAAC 2008.

Long-term Immunologic Results

ACTG 5211 & VICTOR-E1 Extensions



Dunkle L, et al. ICAAC 2008.

Long-term Safety Results

ACTG 5211 & VICTOR-E1 Extensions

- **AIDS-associated opportunistic infections observed infrequently**
- **Respiratory tract infections the only other common infections**
- **AST, ALT, bilirubin elevations common but considered unrelated to VCV**

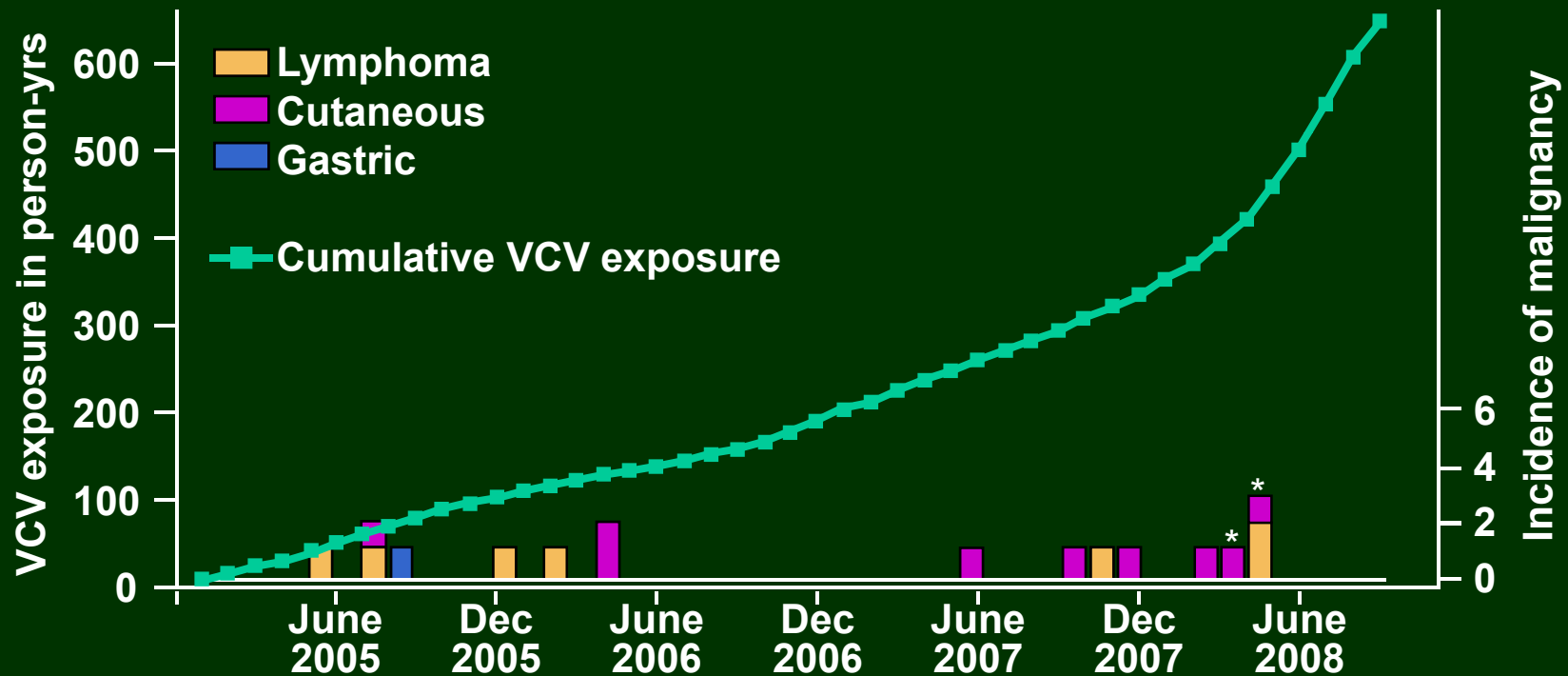
*Judged to be not related to VCV.

†All associated with atazanavir in OBT, and none associated with elevated AST or ALT

Treatment-emergent adverse event	No. of subjects
AIDS-associated Opportunistic Infections	
Cytomegalovirus disease	3
Cytomegalovirus retinitis	1
Candidiasis, esophageal	1
Coccidioidomycosis, disseminated	1
Tuberculosis	1
Pneumocystis pneumonia	1
Toxoplasmosis, central nervous system	1
Other AIDS-associated Conditions	
Wasting syndrome	2
Progressive multifocal leukoencephalopathy (PML)	1
Other Infections Occurring in ≥5% of Subjects	
Sinusitis	22
Bronchitis	19
Upper respiratory infection	18
Herpes simplex virus	12
Influenza	10
Pneumonia	10
Liver-related	
Hepatic cirrhosis	1
Hepatosplenomegaly	1
Elevated AST	17*
Elevated ALT	14*
Elevated LFT (unspecified)	4
Hyperbilirubinemia	25†

Dunkle L, et al. ICAAC 2008.

All Treatment-Experienced Trials: No Increase in Malignancies



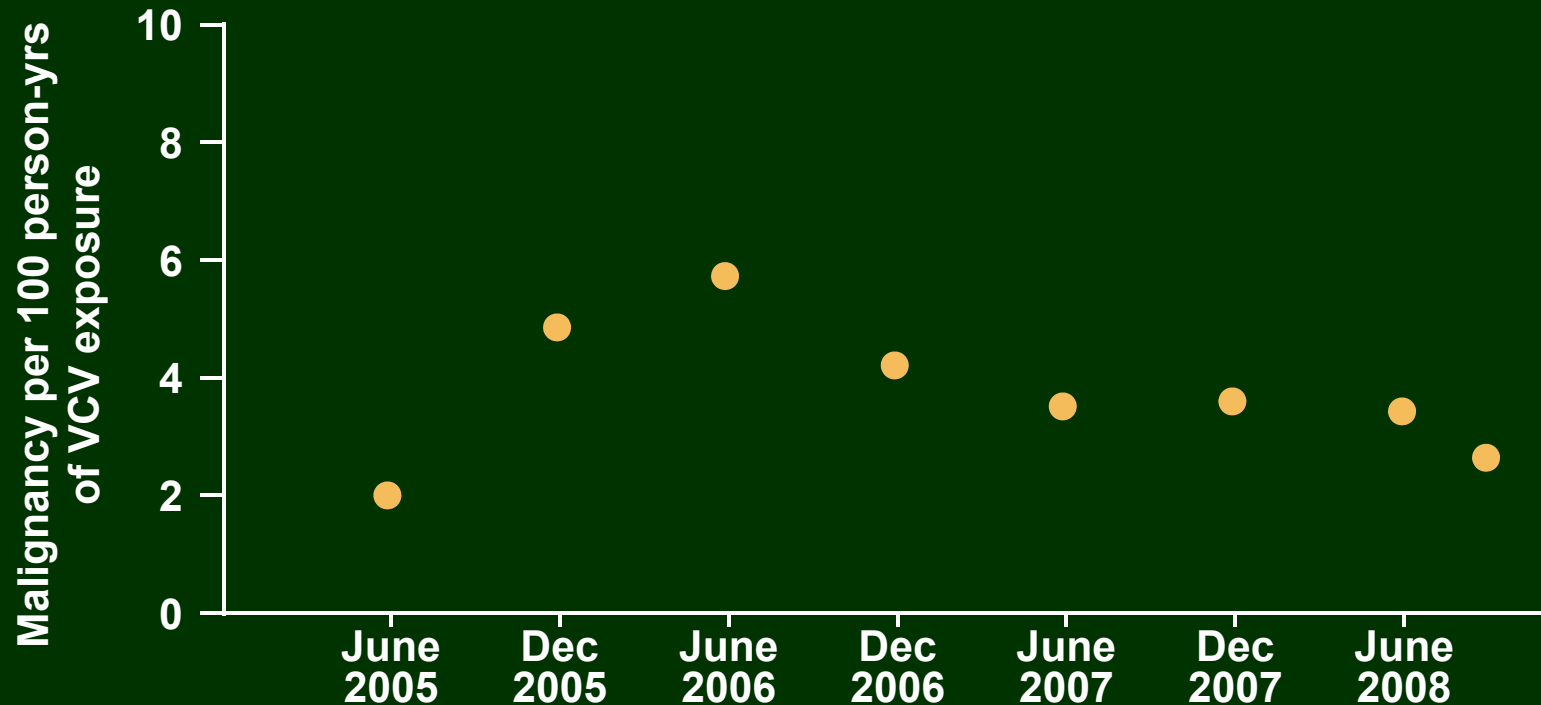
*2 cutaneous (Apr/May 08) and 1 lymphoma (May 08) not yet unblinded currently ascribed to VCV.

†Exposure: 1126 subjects from studies P03802, ACTG5211, P04100, P03672, P04405, P04889, P04875, P05057.

Dunkle L, et al. ICAAC 2008.

All Treatment-Experienced Trials: Rates of Malignancy Declined

Malignancy rates declined with longer follow-up of more patients

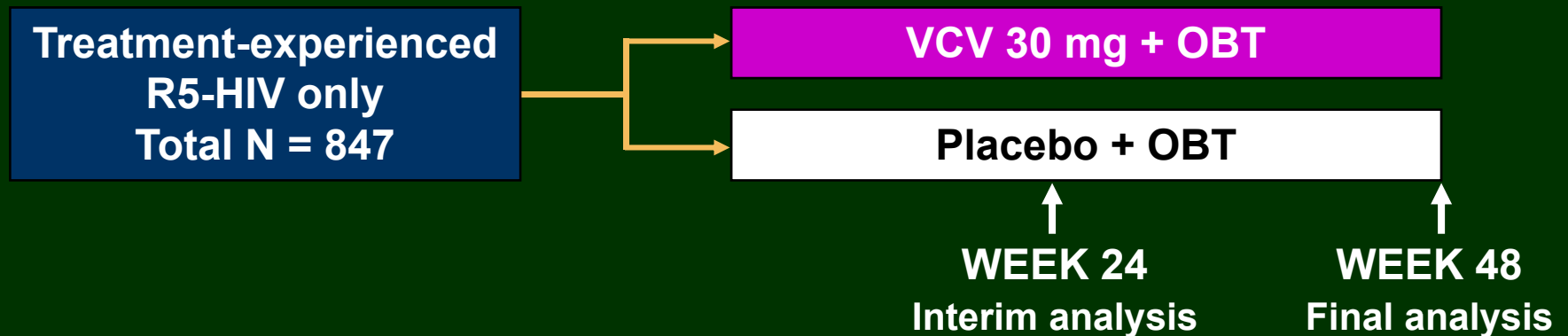


*2 cutaneous (Apr/May 08) and 1 lymphoma (May 08) not yet unblinded currently ascribed to VCV.

Dunkle L, et al. ICAAC 2008.

VICTOR-E3 and E4: Phase 3 Treatment-Experienced Trials

- CCR5-tropic HIV only
- 30 mg VCV plus OBT containing PI/r vs. OBT containing PI/r
 - At least 2 active drugs in OBT
- Documented resistance to at least 2 of the following drug classes: NRTI, NNRTI, PI
 - OR: ART experience for at least 6 months with at least 2 of the following:
1 NRTI, 1 NNRTI, 2 PIs (excluding low-dose ritonavir)
- HCV and HBV coinfection allowed
- Phase 3 trials fully accrued in mid-2008

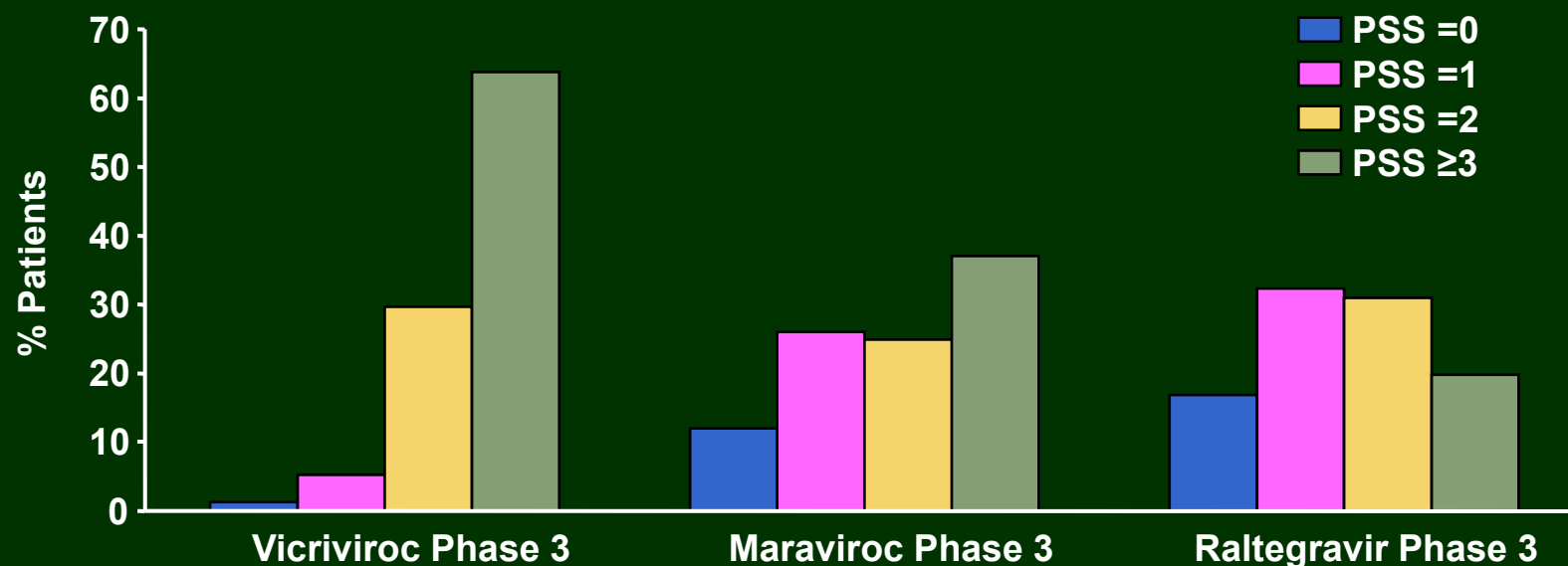


OBT = optimized background therapy (contains protease inhibitor plus ritonavir).

Schering-Plough Corp. Data on file.

Background Therapy in Recent Treatment-Experienced Trials: Vicriviroc, Maraviroc, Raltegravir

- PSS indicates total number of fully active drugs in background regimen
- Most vicriviroc trial participants have fully active background regimens
 - More than 90% have >2 active drugs in OBT
 - 163 (19%) receiving darunavir *and* raltegravir, 140 (17%) darunavir, 86 (10%) raltegravir in OBT



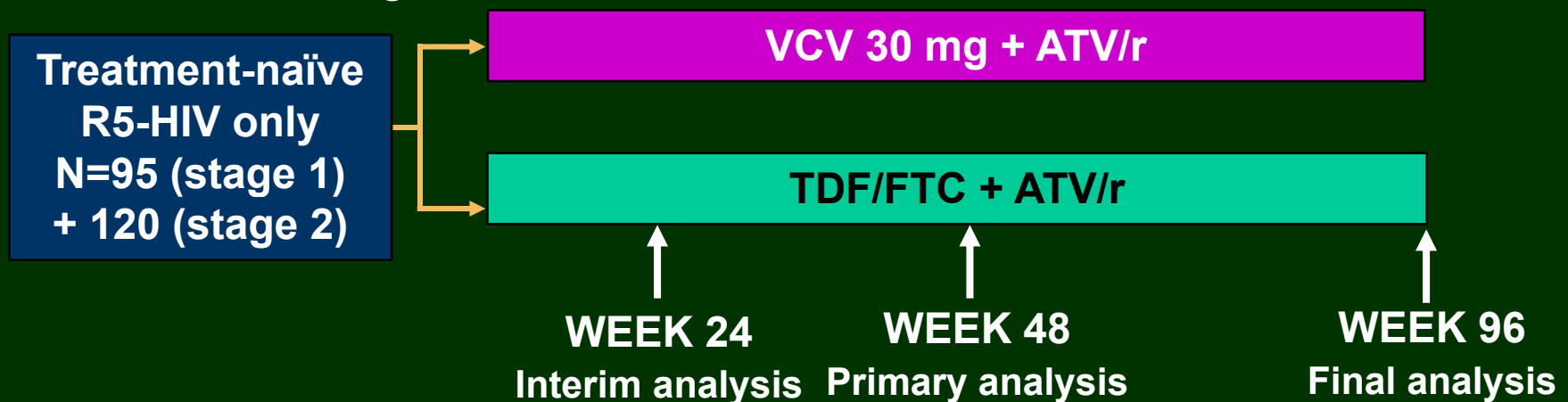
Schering-Plough Corp. Data on file; Fätkenheuer G, et al. NEJM. 2008; Steigbigel RT, et al. NEJM, 2008.

VCV Phase 3 Treatment-Experienced Program Summary

- **Phase 3 trials differ substantially from recently reported trials**
- **Baseline demographics indicate a study population in early stage of treatment-experience**
 - **Introduces VCV into patient population with higher prevalence of R5-tropic HIV**
- **Majority of patients receiving fully active regimens**
 - **Newer agents part of OBT-- darunavir, raltegravir; etravirine being introduced into long-term extensions**
- **May best reflect desired future of later stages of therapy**

First-Line Treatment: A New Paradigm

- Preserves NRTIs with long term toxicity for later stages of treatment
 - Preserves NNRTIs with low barrier to resistance for later use
 - ATV/r lacks cross-resistance with other PIs, preserving most of PI class for later use
 - Early use of CCR5 inhibitor may preserve memory T-cells
 - Convenient QD dosing
- First patient initiated 1/08; stage 1 (n=95) fully enrolled 8/08
 - No virologic failures to date



Schering-Plough Corp. Data on file.

Conclusions

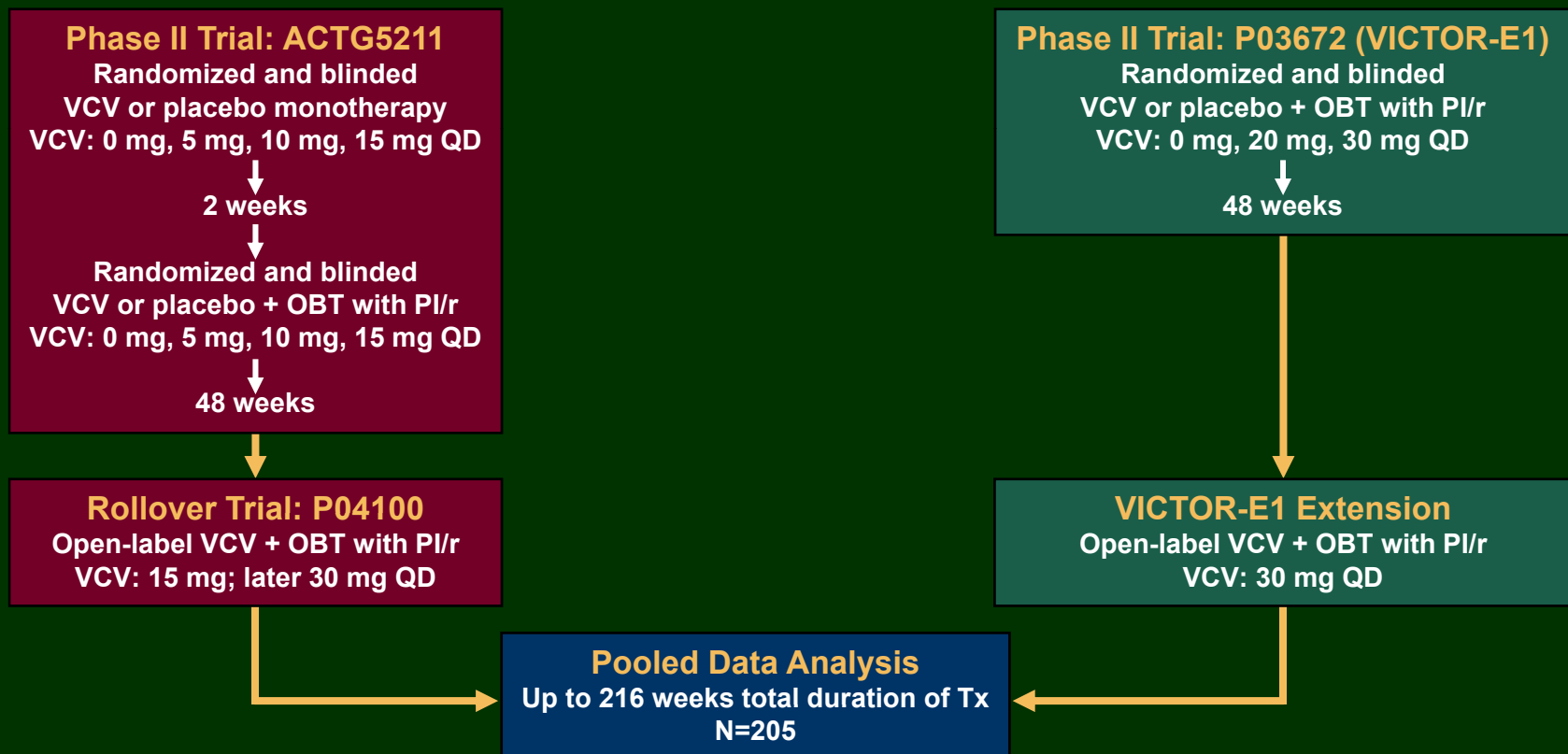
- **VCV has antiviral potency similar to other new agents**
- **More potent effect on CD4s warrants further study**
- **Resistance appears infrequently and slowly**
- **Long-term safety profile promising**
 - **Detectable on-treatment tropism changes primarily assay-related**
 - **Malignancy rates declined with longer follow-up of larger population**
 - **No apparent signature toxicity**

Acknowledgements

- **VICTOR-E1, E3, E4, and ACTG 5211 study investigators**
- **Global VCV network of study personnel**
- **Patients participating in all VCV clinical trials**
- **Carmen Mak and Junwu Shen (SPRI statisticians for the Vicriviroc Clinical Development Program)**

ACTG 5211 and VICTOR-E1: Combined Long-Term Efficacy and Safety Study Design

All patients received VCV 30 mg QD after Week 48



Advantages of Investigational Paradigm

- **Spares multiple classes for later lines of therapy**
 - **Delays exposure to classes with long-term multisystem toxicity**
- **Provides convenient QD dosing**
- **Introduces VCV into population with highest incidence of R5-tropic HIV**
- **May preserve the CCR5+ memory T-cells**