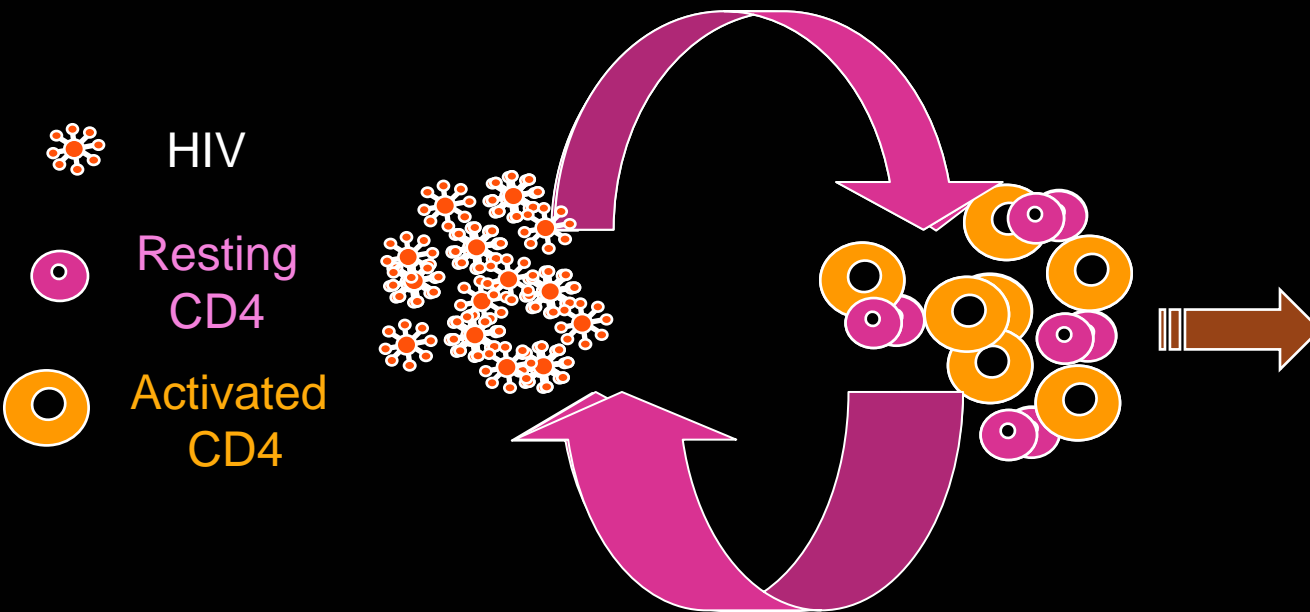


VS411: an immunomodulating drug combination to inhibit both HIV and immune activation

Franco Lori & Julianna Lisziewicz
RIGHT
Pavia, Italy
Bethesda, MD

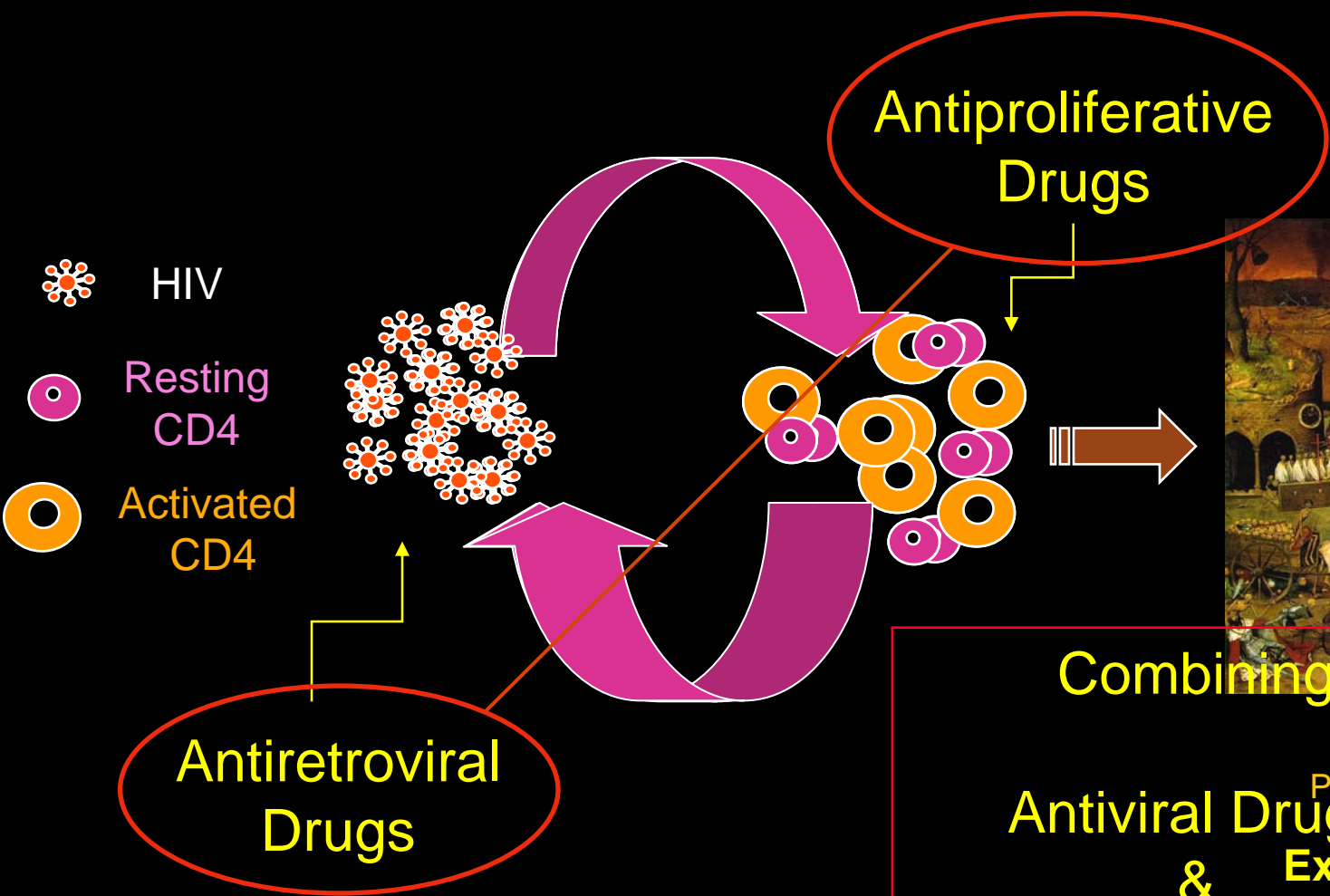
The self-renewing circular path of HIV/AIDS



The Triumph of Death
Pieter Brueghel the Elder ca. 1562

Excess of immune activation
leads to AIDS

Interrupting the self-renewing circular path of HIV/AIDS



Combining
Antiviral Drugs
& Excess of immune stimulation
Antiproliferative Drugs
leads to AIDS

The Triumph of Death
Pieter Bruegel the Elder ca. 1562

VS411 (HU+ddl) Development Criteria

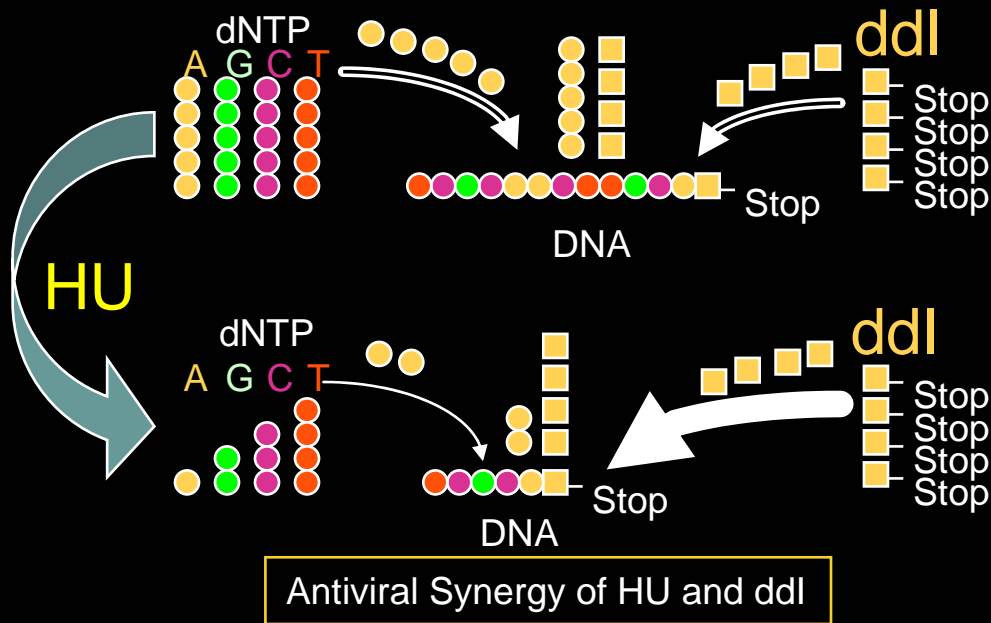
- ✓ Mechanism of action: dual
 - directly against the virus
 - indirectly against immune activation
- ✓ Resistance profile: unique
 - contained VL rebound in the absence of complete suppression
- ✓ Durability
- ✓ Administration: QD
- ✓ Cost: Dose/Manufacturing
- ✓ Toxicity: minimal
 - low dose HU
 - low dose ddl
 - low C_{max} ddl



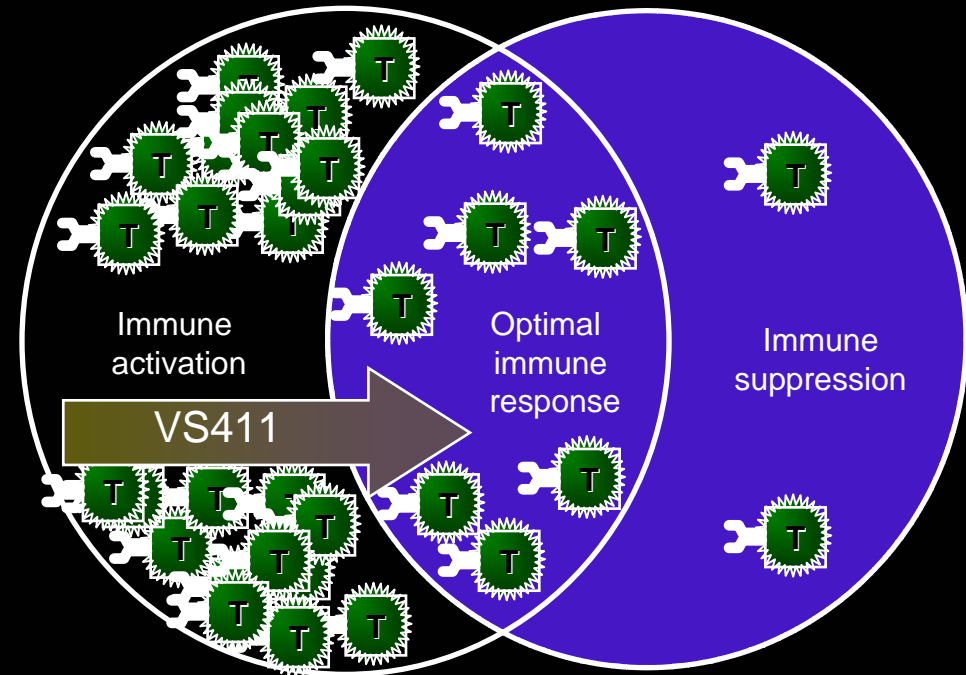
VS411: Attacking HIV from 2 fronts

Hydroxyurea (HU) & Didanosine (ddl)

Antiretroviral Effects



Antiproliferative Effects



- VS411 to inhibit HIV replication
 - ddl is incorporated in the DNA and blocks of reverse transcription
 - HU favors ddl incorporation

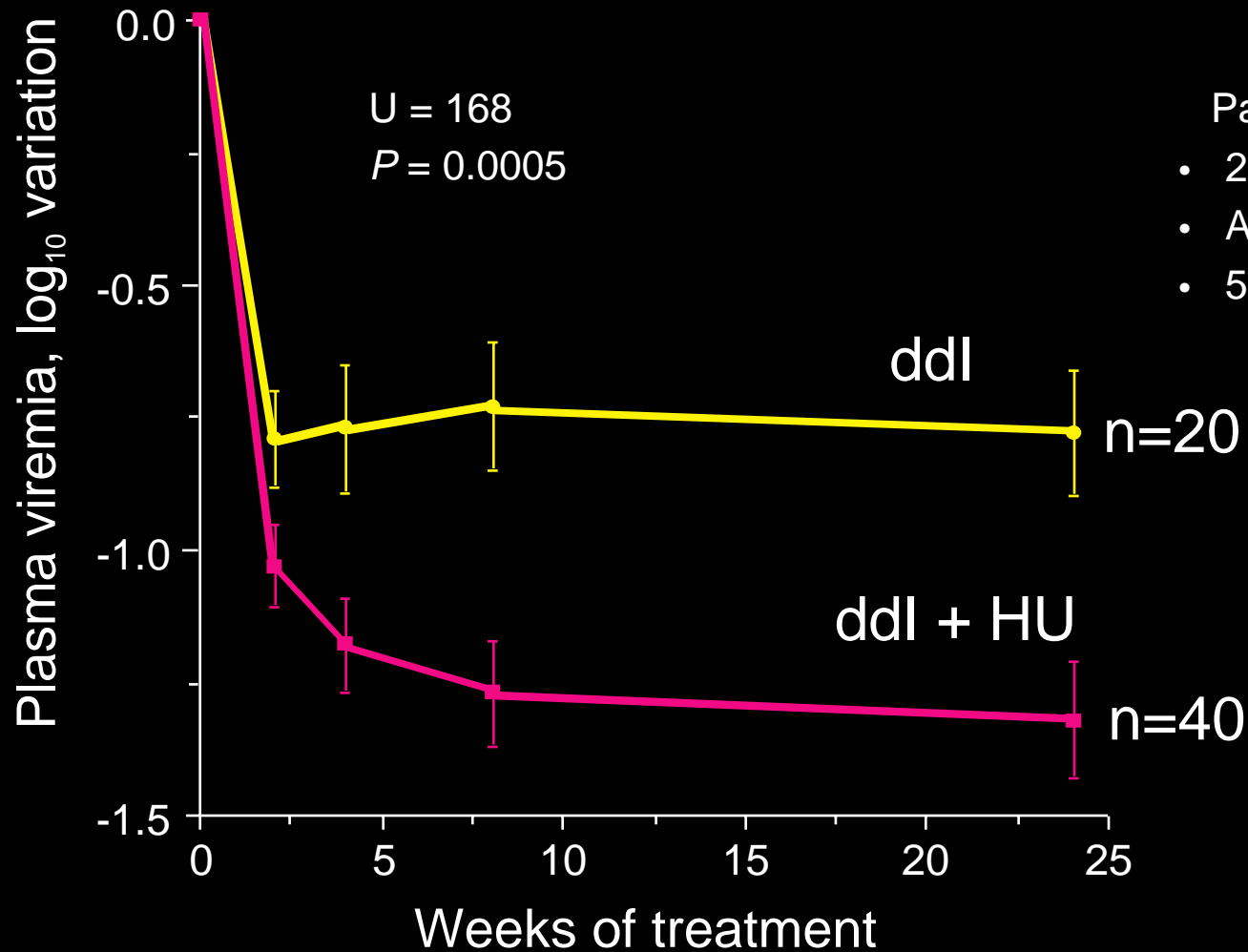
HU compensates for ddl resistance

- VS411 to decrease immune activation
 - ddl inhibits HIV (cause of activation)
 - HU limits cell proliferation (consequence of activation)

VS411 is not immune suppressive

VS411: Attacking HIV from 2 fronts

Antiviral Synergy of HU and ddl



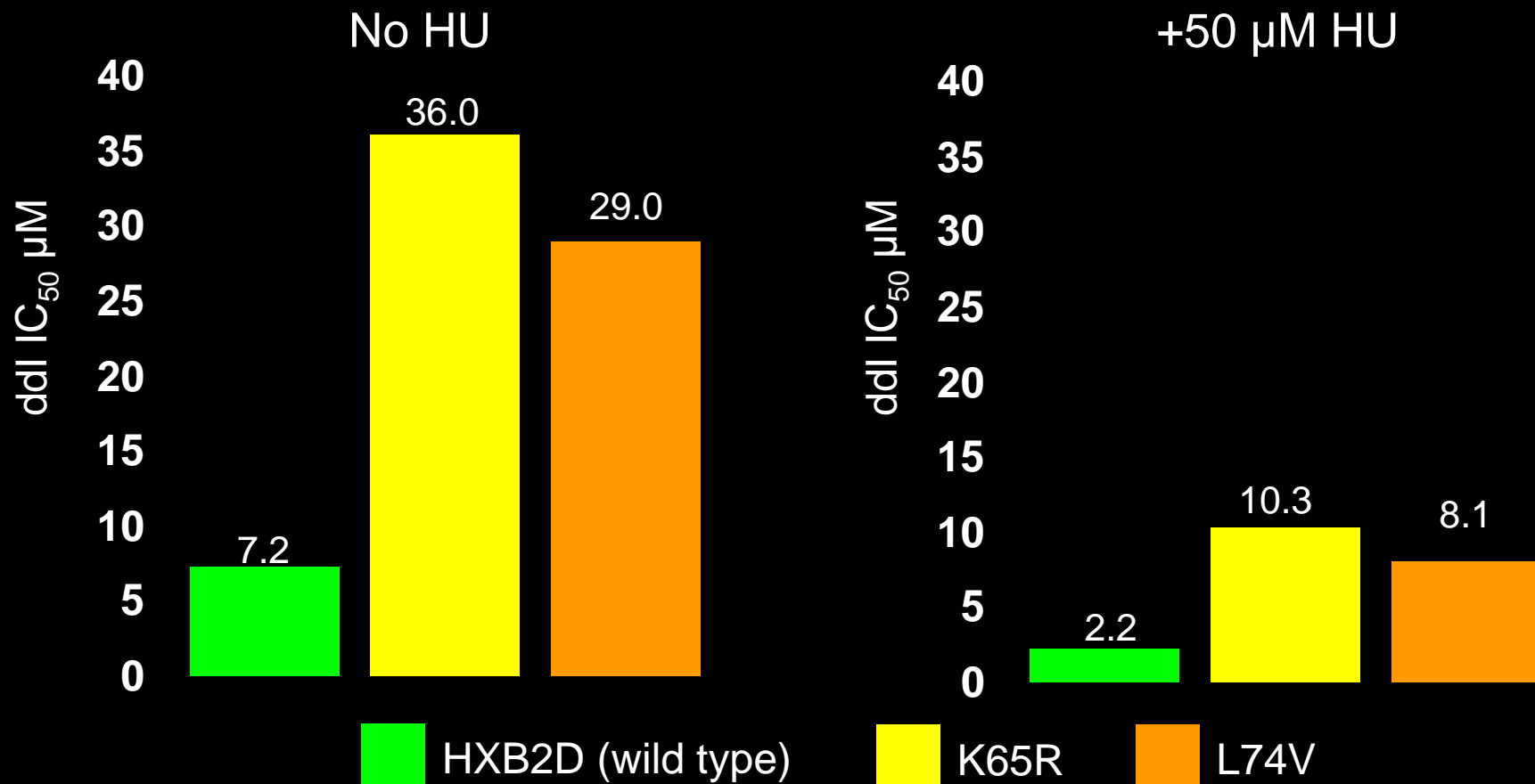
Patients characteristics

- 250-500 CD4/mm³
- Asymptomatic
- 50% therapy naive

VS411: Attacking HIV from 2 fronts

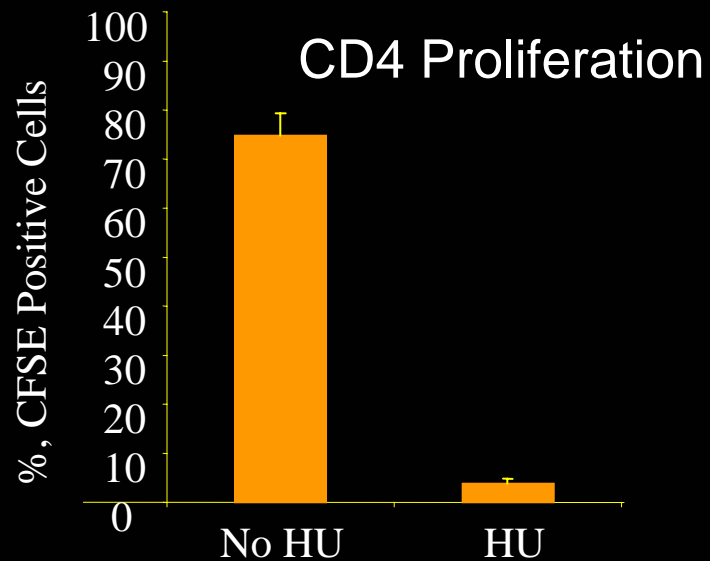
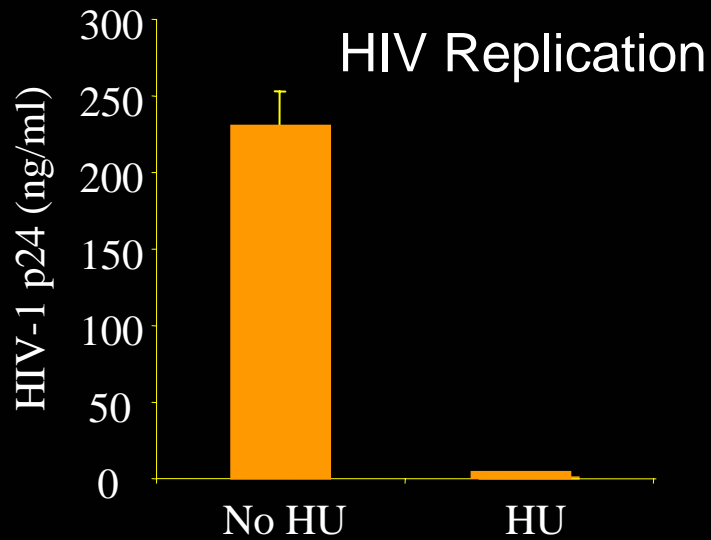
Unique resistance profile

HU Renders ddl-resistant Mutants Sensitive to ddl

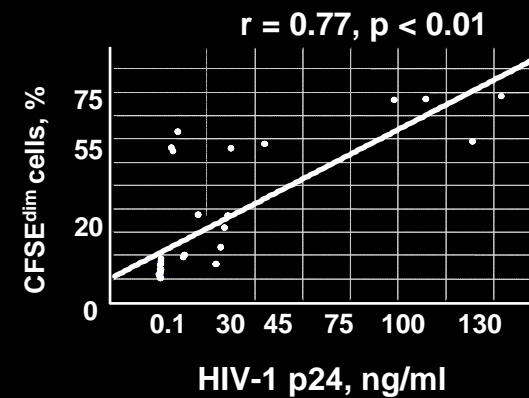
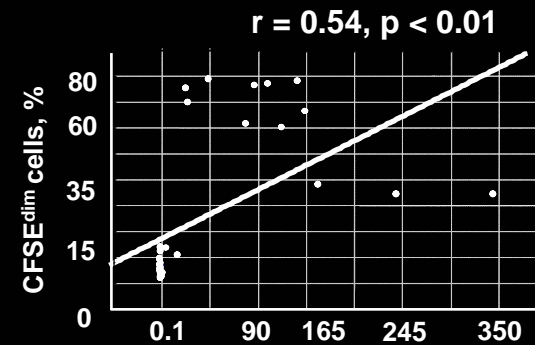


VS411: Attacking HIV from 2 fronts

HU Decreases Immune Activation



CD4 Proliferation

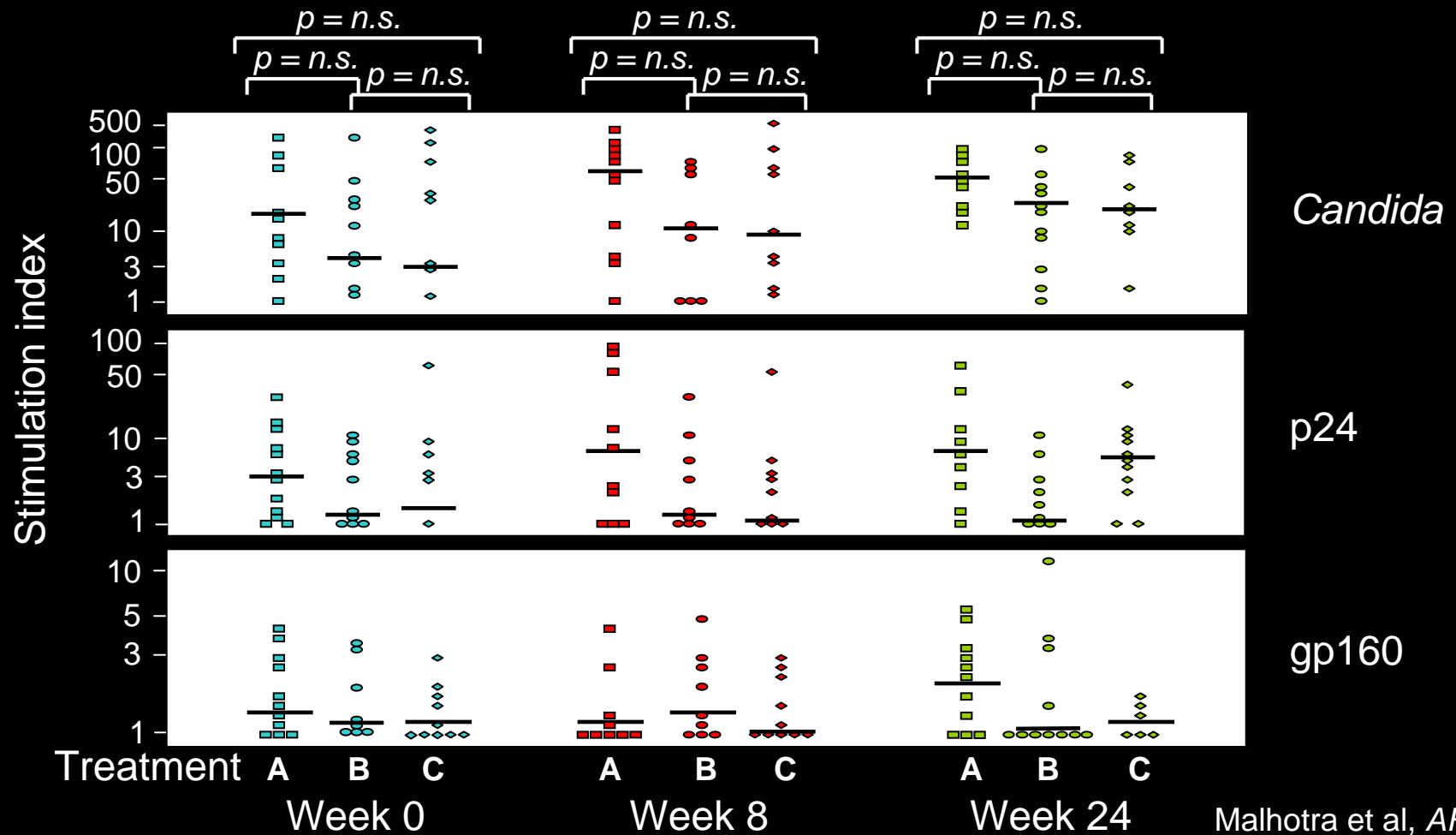


HIV Replication

ACTG 5025

HU is not Immune Suppressive

39 patients on HAART were randomized to switch to (A) IDV-ddI-d4T-HU placebo, (B) IDV-ddI-d4T-HU, or (C) continue with IDV-3TC-ZDV



VS411 Toxicity Profile

No Association between HU and Pancreatitis
ACTG Meta-Analysis > 8,000 subjects

- Rates of pancreatitis in ddl cohorts were dose-dependent
- Toxicity of ddl + HU not significantly different from ddl monotherapy
- No significant differences between HU and non-HU containing arms
- Other factors (co-morbidities and other known risk factor, such as lifestyle) might have contributed to the outcome of the ACTG 5025 study

VS411 Toxicity Profile

Lessons Learned

1st Phase

Initial trials* (>500 pts)

- (ddl with-w/o d4T) ± HU
- Single/double NRTI pretreated or naïve
- Baseline VL (mean): 4.5 log
- HU: 1000 mg
- ddl: 200 mg BID
- HU Antiviral activity: yes
- No pancreatitis

*RIGHT 411, ACTG 309,
Swiss Cohort, BMS 055

2nd Phase

ACTG 5025 (>200 pts)

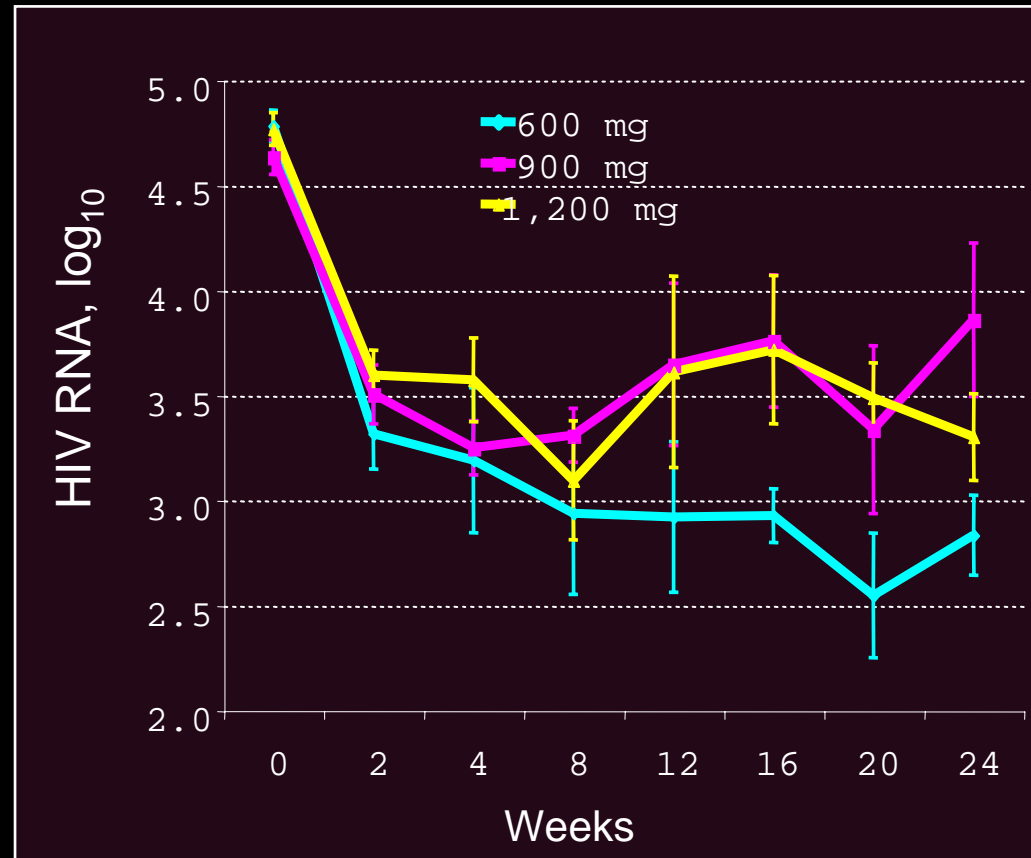
- (ddl + d4T + IDV) ± HU
- Pretreated (IDV+ZDV+3TC)
- Baseline VL < 200
- HU: 1200 mg
- ddl: 400 mg QD
- HU Antiviral activity: no
- Pancreatitis

ACTG 5025

VS411 Toxicity Profile

Lowering HU Dose Decreases Toxicity but not Efficacy

AEs	HU 600 mg n (%)	HU 8-900 mg n (%)	HU 1,200 mg n (%)
Nausea	6 (15)	8 (21)	10 (26)
Peripheral neuropathy	7 (18)	7 (18)	8 (21)
Diarrhea	7 (18)	8 (21)	5 (13)
Localized numbness	3 (8)	4 (11)	5 (13)
SGOT increased	2 (5)	4 (11)	6 (16)
Fatigue	2 (5)	2 (5)	6 (16)
Lipase increased	4 (10)	3 (8)	3 (8)
Neuropathy	3 (8)	5 (13)	1 (3)
Neutropenia	0 (0)	2 (5)	7 (18)
Headache	4 (10)	2 (5)	2 (5)
SGPT increased	1 (3)	2 (5)	5 (13)
Hyperglycemia	1 (3)	0 (0)	4 (11)
Total AEs	39	47	62



400 mg ddl (EC) and 40 mg d4T backbone

VS411 Development

Lowering the Dose of HU and EC ddl_{VS411}



	HU 600 mg 24 Patients	HU 300 mg 24 Patients
ddl 400 mg 24 Patients	HU 600 mg ddl 400 mg QD	HU 300 mg ddl 400 mg QD
ddl 200 mg 24 Patients	HU 600 mg ddl 200 mg QD	HU 300 mg ddl 200 mg QD
Controls	HU 600 mg QD 12 Patients	ddl 400 mg QD 12 Patients

POP multicenter, 4 weeks study in 72 ARV-naïve subjects

VS411 Development

QD administration

One QD Capsule containing both HU and ddl_{VS411}



Durability of HU+ddl

Observational Long-Term Study

The Johannesburg Cohort (160 subjects)

Median age (yrs): 34 (19 – 58)

Gender: male 72 (45%), female 88 (55%)

Ethnicity: African 114 (71%), Caucasian 41 (26%)

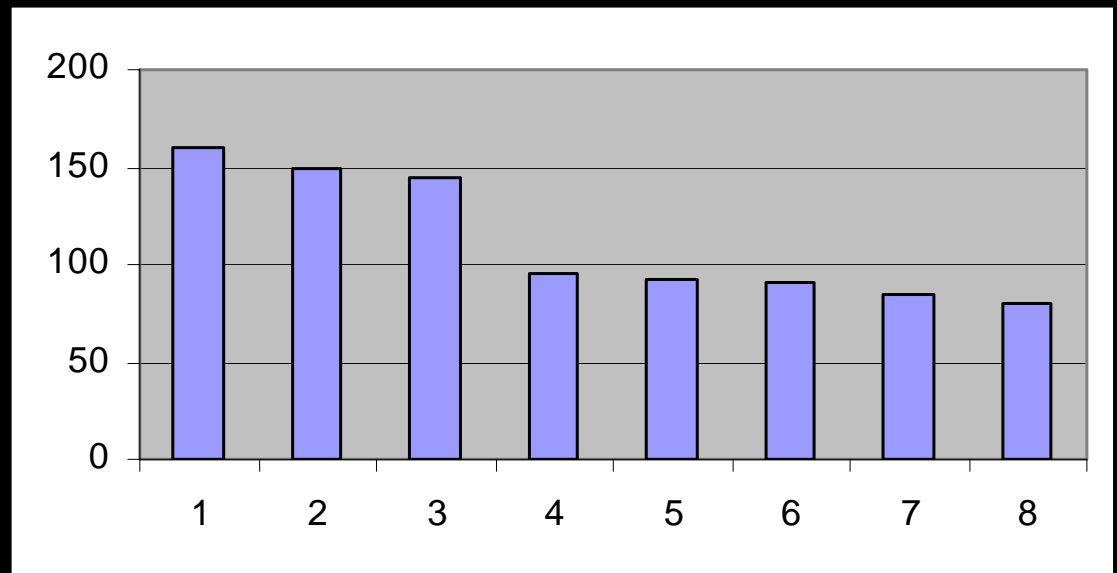
Risk behaviour: Heterosexual 128 (80%), MSM 30 (19%)

Patients on study

ddl 300mg QD + HU 500mg BID

No ddl dose adjustment

Treatment switched for grade III/IV toxicities and failure to reduce viral load to < 5 000 cp/mL



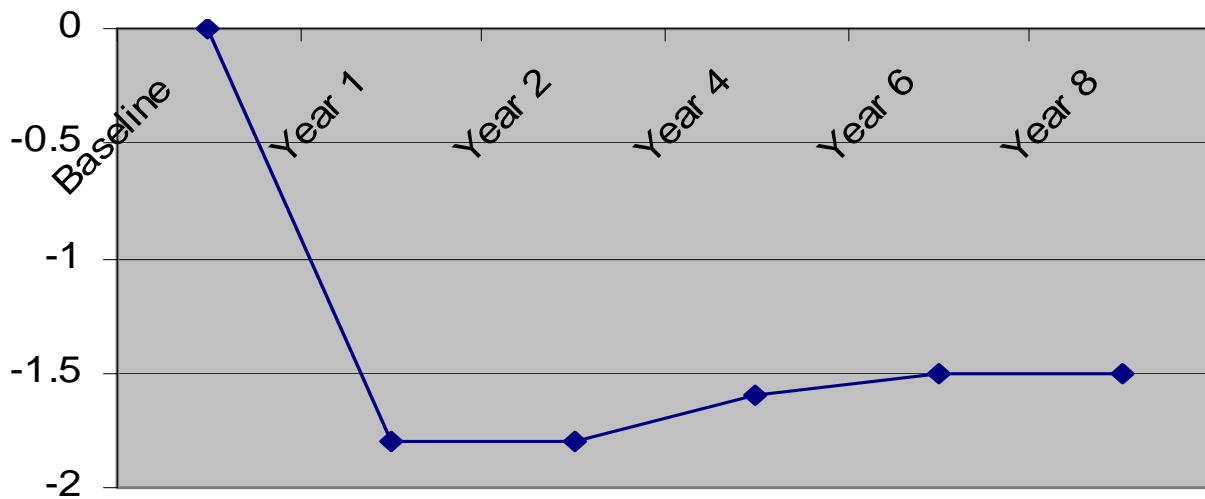
Durability of HU+ddl

Observational Long-Term Study

The Johannesburg Cohort (160 subjects)

Viral Load Change

Baseline (log 10): 4,2 (3,9 – 5,1)



	cp/mL
Baseline	22 000
Year 1	3 600
Year 2	3 900
Year 4	4 600
Year 8	4 500

Viral load <400 in 32%

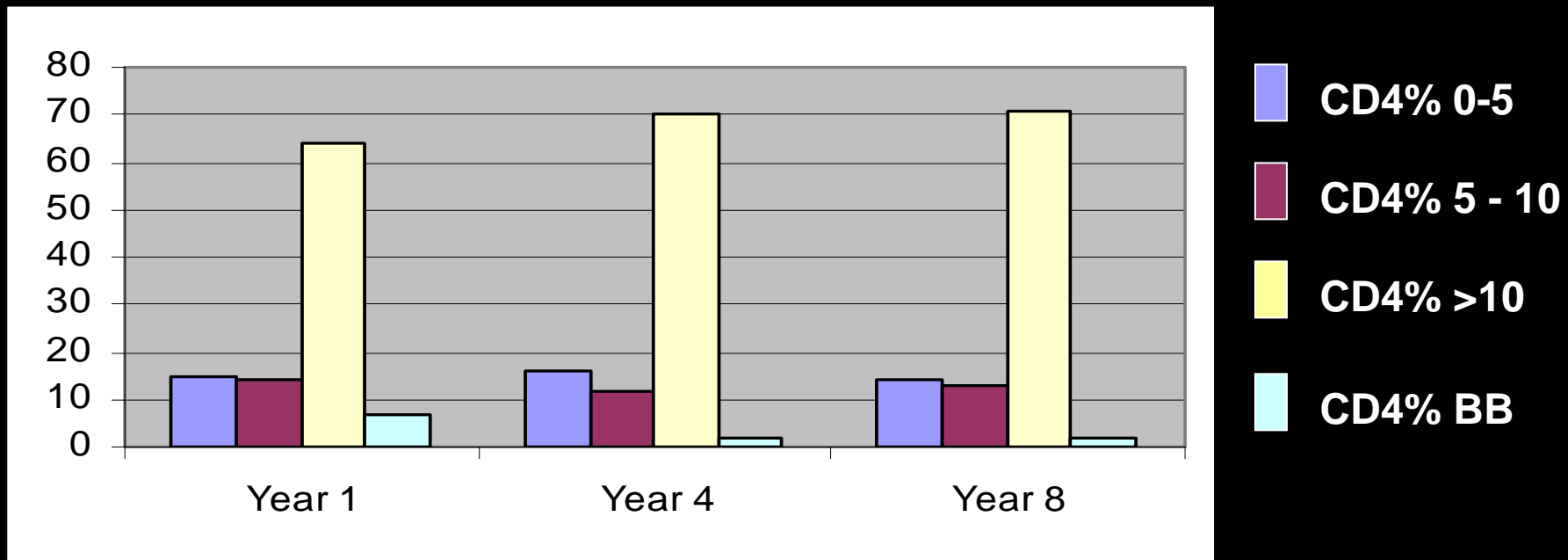
Durability of HU+ddl

Observational Long-Term Study

The Johannesburg Cohort (160 subjects)

CD4 Change

Baseline: 380 (90 – 499)



Durability of HU+ddl

Observational Long-Term Study

The Johannesburg Cohort (160 subjects)

Adverse events

Description	%	Treatment-limiting
Hyperpigmentation	65	0
GI upset	9	4 patients (2,5%)
Grade I/II PN	8	0
Recurrent genital HSV	4	0
Grade III/IV PN	3	5 patients (3%)
Grade III/IV thrombocytopenia	3	5 patients (3%)
Alopecia	3	3 patients (1,8%)
Grade III/IV neutropenia	2	3 patients (2%)
Lipoatrophy	1,25	2 patients (1,25%)
Progressive CNS disease	1,25	2 patients (1,25%)
Malignancy	<1%	1 patient
Lactic acidosis	0	0

VS411 = low dose HU + slow-release EC ddl_{VS411}

- ✓ Mechanism of action: dual
 - directly against the virus
 - indirectly against immune activation
- ✓ Resistance profile: unique
 - contained VL rebound in the absence of complete suppression
- ✓ Durability (up to 8 years)
- ✓ Administration: QD
- ✓ Low cost Dose/Manufacturing
- ✓ Toxicity: improved
 - low dose HU
 - low dose ddl
 - low C_{max} EC ddl_{VS411}





RIGHT Team

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Kinesis

Pharmaresa



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