

Structured Treatment Interruption: New Findings – The End of an Era?

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Structured Treatment Interruption

- Three settings in which STI is under investigation:
 - Analytical treatment interruption
 - Therapeutic vaccines + HAART to boost immune responses
 - Chronic HIV infection in persons with multiple-drug resistant virus and treatment failure
 - Theory: Shift to wild-type (drug-sensitive) virus will improve virologic response to existing therapies
 - Chronic HIV infection in persons with undetectable viral load
 - Theory: “Autoimmunization” will improve virologic response
 - **Drug/cost conservation; to minimize side effects/toxicities**

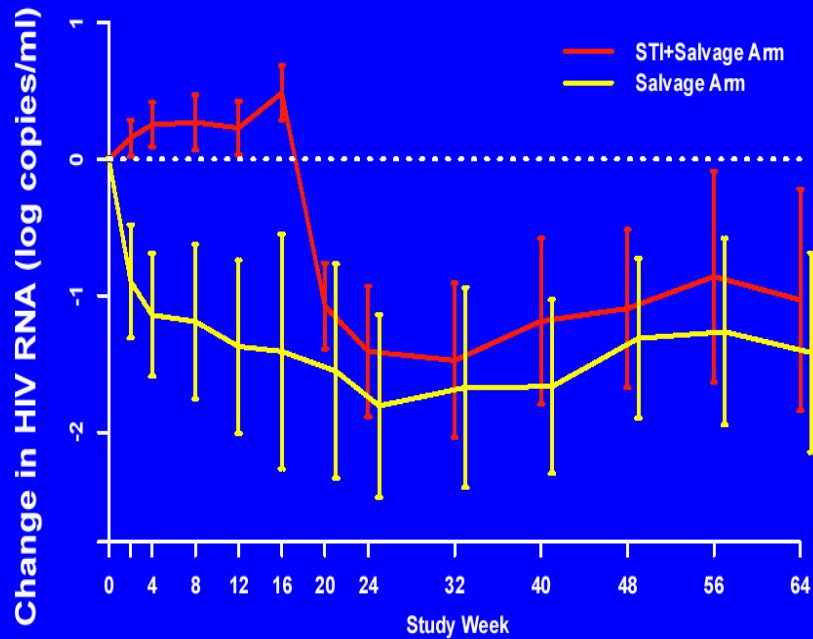
Example: STI in MDR HIV-1 Infection

	Lawrence	Ruiz	ANRS	ACTG 5086
Total N	270	46	68	41
Median BL CD4+	145	339	25	226
Median BL HIV RNA	5 log ₁₀	4.3 log ₁₀	5 log ₁₀	4.4 log ₁₀
Duration STI	16 wks	12 wks	8 wks	16 wks
Mean # drugs ART	3.6	5	7	4.3
% extensive shift	64%	35%	26%	28%
STI vs No STI				
GSS	0.8/0.9	----	----	1.6/1.1
PSS	1.5/1.8	----	----	2.6/1.8
% < 400 c/ml	19; 11	45; 46*	32; 12**	19; 33

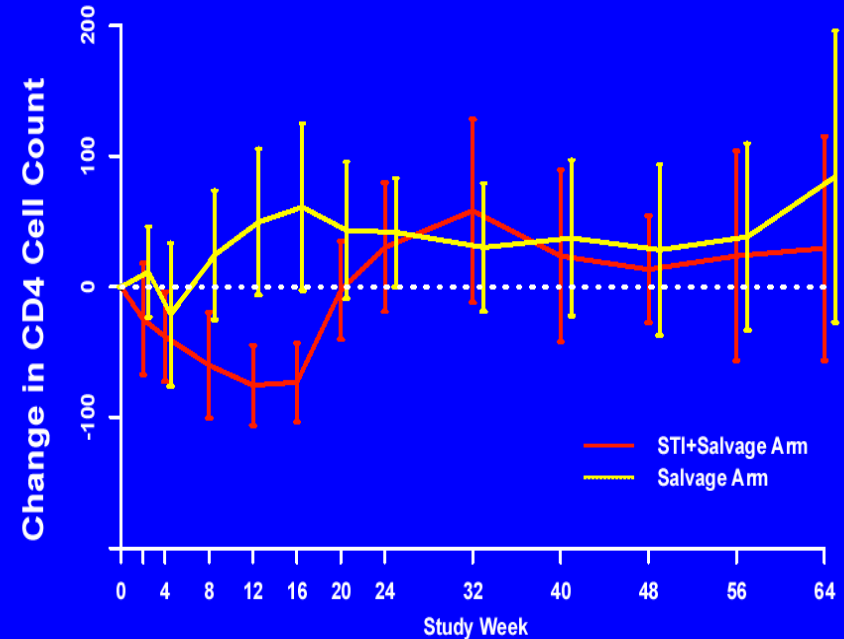
*< 50 c/ml; **Week 24 after randomization

Example: STI in MDR HIV-1

Mean Changes in HIV-1 RNA and CD4+ Cell Count Before and After STI



Rank test		p=0.005	p=0.31		p=0.57
STI+Salvage: n= 21	20	15	20	21	13
Salvage: n= 20	19	16	19	18	12



Rank test		p<0.001	p=0.65		p=0.48
STI+Salvage: n= 21	20	14	20	21	13
Salvage: n= 20	19	16	19	17	12

Example: STI as “Autoimmunization”

- The Swiss-Spanish Intermittent Therapy Trial
 - 133 patients on ART with BL VL < 50 copies/ml, and CD4+ > 300 cells/ μ L (median 740/ μ L)
 - Stopped ART for 2 weeks, treated for 8 weeks; repeat x 4 cycles then stop ART at week 40
- 17% had VL < 5,000 copies/ml off ART at 52 weeks; only 8% after 96 weeks
- 19% failed to control VL after restarting ART
 - One developed resistance and required alternative Rx
- Results do not support “autoimmunization” theory

**Can we use intermittent treatment
(STI) to reduce costs and/or
toxicities associated with HAART?**

STI: “Drug Conservation” Approaches vs Continuous HAART

TIME-BASED

Staccato

- One week on/one week off

Trivacan

- 4 months on/2 months off

Windows

- 8 weeks on/8 weeks off

ISS / PART

- 1, 2, 2, 3 months off

DART

- 12 weeks on/12 weeks off

CD4+ COUNT-GUIDED

Staccato

- 350 cells on/350 cells off

Trivacan

- 250 cells on/350 cells off

SMART

- 250 cells on/350 cells off

Staccato Trial

- Treatment-naïve; treated with HAART
 - HIV-1 RNA < 50 c/mL, CD4+ > 350 cells/ μ L for 6 mos
 - Median time on HAART 15 months
- Randomized to:
 - Continuous HAART (n=146) vs.
 - CD4+ guided STI: off ART after reaching > 350 cells/ μ L, on ART if < 350 cells/ μ L (N=284) vs.
 - Time-guided HAART one week on/one week off
 - Stopped early by DSMB for virologic failure
 - At 96 weeks (end of randomized Rx-EOR) all patients restarted continuous ART for 24 weeks (end of treatment-EOT)

Staccato Trial

- Rapid CD4+ decline first 8 wks then more gradual
- 6% with acute retroviral syndrome on STI arm
- More candidiasis and ↓ plt on STI; neuropathy and diarrhea on continuous ART; no differences in LDL-C or TG levels
- 5.6% RT and 2.4% PI mutations on STI
- 62% ART “savings”

	CD4-Guided	Cont'd ART	P-value
Time on ART	37.5%	99%	---
AIDS Events	0	0	NS
Deaths	1	1	NS
VL < 50 c/ml	90.3%	91.8%	NS
CD4+ > 350/μL	60.5%	96.2%	0.002
CD4+ > 350/μL	85.9%	96.9%	0.01

Trivacan Study

- Patients were HAART-naïve, CD4+ 150-350 cells/ μ L; VL < 300 c/ml on HAART for at least 6 months CD4+ > 350 cells/ μ L randomized to:
 - Continuous therapy (N=110)
 - CD4+ guided therapy (on ART at 250 cells/ μ L, off at 350 cells/ μ L) (N=216)
 - 4 months on therapy/2 months off (N=325)
 - CD4+ guided arm stopped; time-based arm is ongoing

Trivacan Study

- 2.5 x higher serious event rate in the CD4+ guided arm (logrank P = 0.003)
- More days in hospital, ↑'d # of clinic visits in CD4+ guided arm (P < 0.001)
- Lower CD4+ rise and plateau in the CD4+ guided arm

Event Rate/100 pt-yrs	CD4+ guided	Continuous ART	Relative Risk
Serious Event Rate	15.2	6.7	0.44
Death	1.2	0.6	0.48
Invasive Bacterial Infections	6.7	0.6	0.08
TB	3.6	2.3	0.65
Resistance	11%	5%	---

SMART Study Design

Participants with CD4+ > 350 cells/mm³

n = 3000

Virologic Suppression (VS) Strategy

[Use of ART to maintain viral load as low as possible throughout follow-up]

n = 3000

Drug Conservation (DC) Strategy

[Stop or defer ART until CD4+ < 250; then *episodic* ART based on CD4+ cell count to increase counts to > 350]

Plan: 910 primary endpoints, 8 years average follow-up

Findings (Jan 06): 164 primary endpoints, 14 months average follow-up, 2% lost to follow-up

SMART Study Design

- Primary endpoint
 - HIV clinical disease progression or death
- Secondary endpoints
 - Death
 - Serious HIV progression events
 - Serious complications including cardiovascular, hepatic and renal

Baseline Characteristics – 2

	DC	VS	Total
Median CD4+ (IQR)	596	599	598 (466,792)
Median Nadir CD4+ (IQR)	250	252	251 (154,360)
HIV RNA \leq 400 c/mL (%)	71.0	70.8	70.9
Prior Clinical AIDS (%)	24.7	23.4	24.1
ART Naïve (%)	4.5	4.8	4.7
Years of prior ART (IQR)	6	6	6 (3,8)

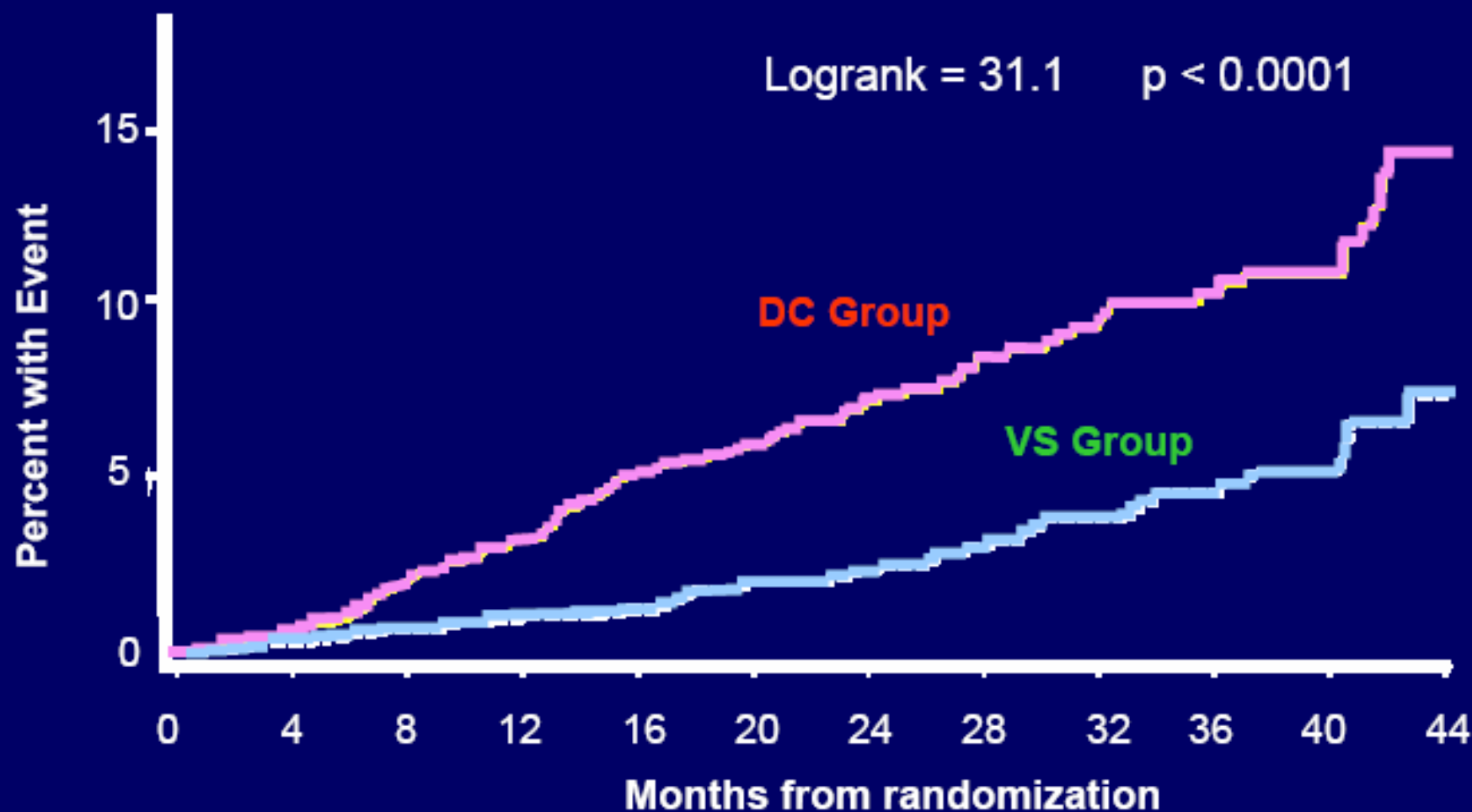
Primary Endpoint

Clinical Disease Progression or Death

DC Group		VS Group		RR (DC/VS)	
N	Rate*	N	Rate*	(95% CI)	P-value
117	3.7	47	1.5	2.5 (1.8, 3.6)	<0.0001

* Per 100 person-years

HIV Disease Progression or Death



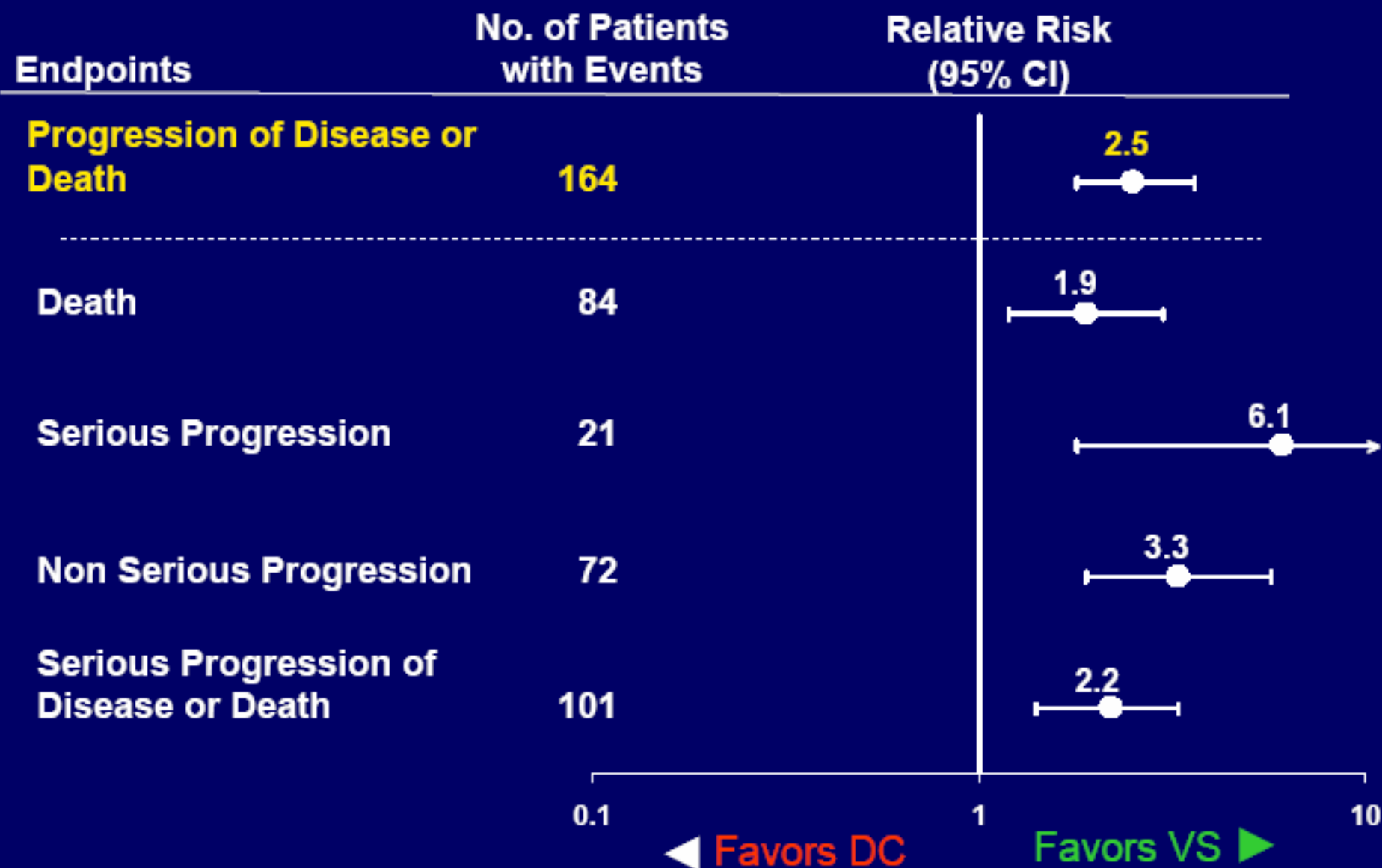
DC Group 2720
VS Group 2752

1170
1167

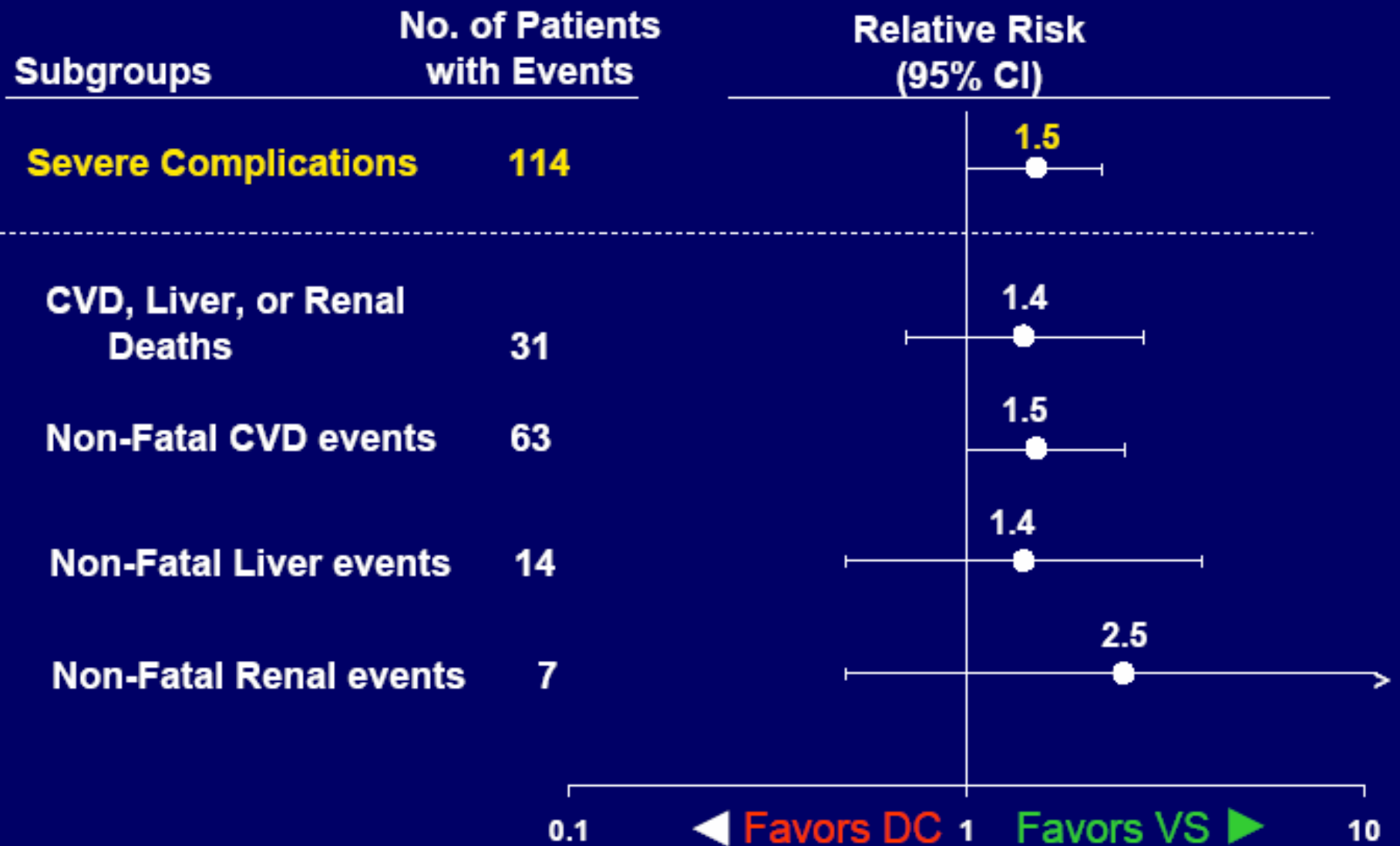
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625

322
334

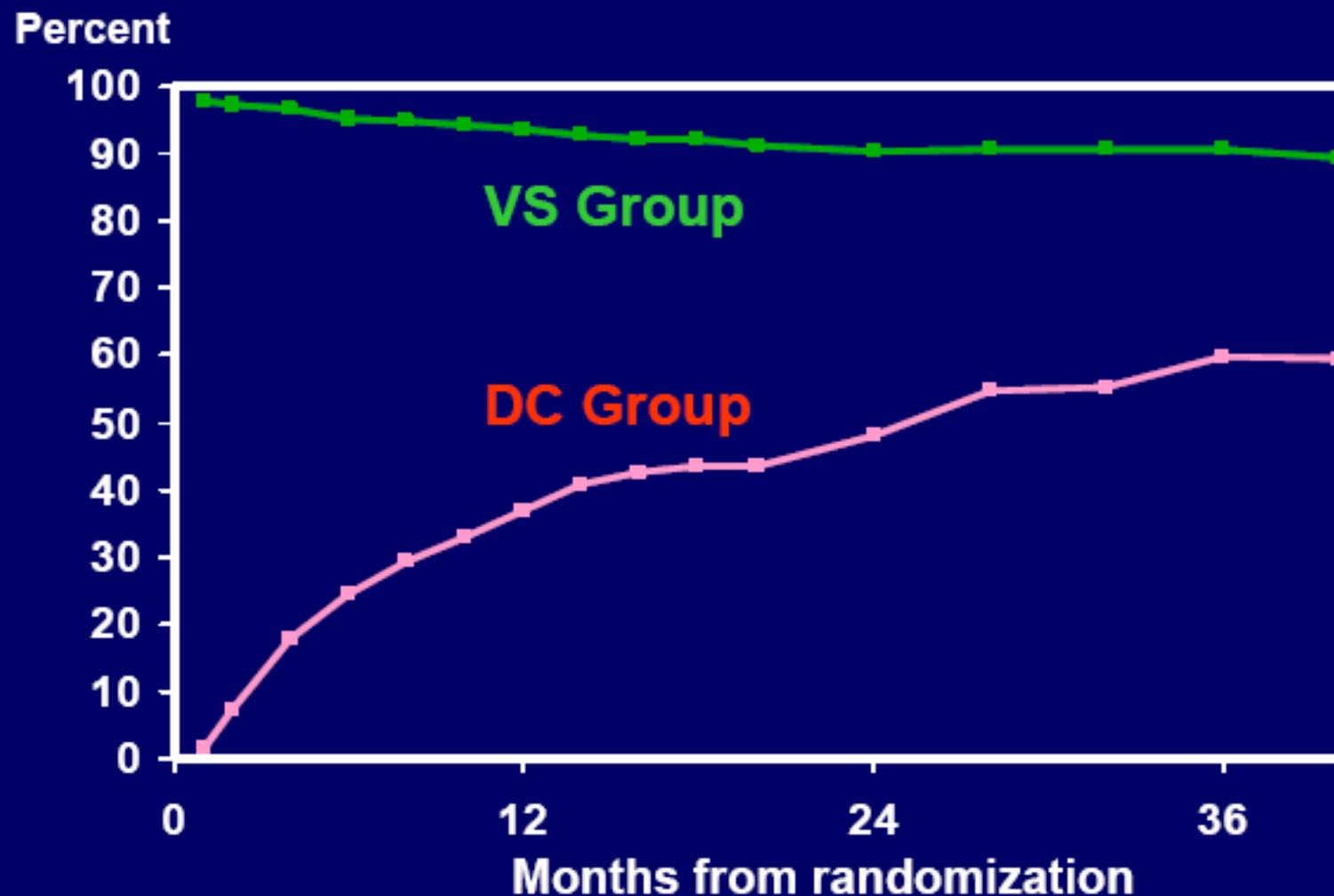
Primary Endpoint and Components



Severe Complications Endpoint and Components



Percent of Patients on ART at Each Month of Follow-up by Treatment Group



Number of patients

VS **2308**

DC **2328**

1167

1188

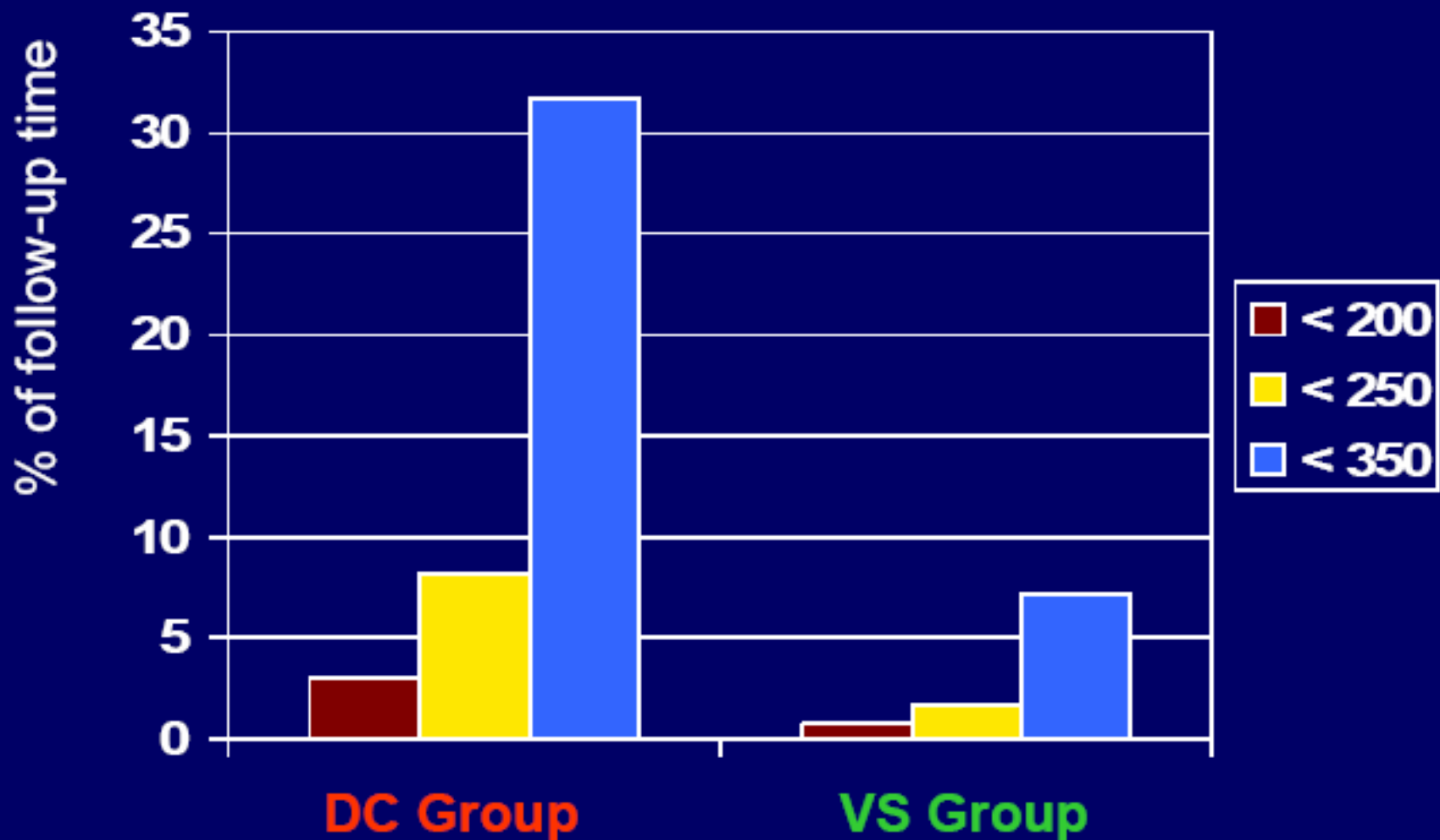
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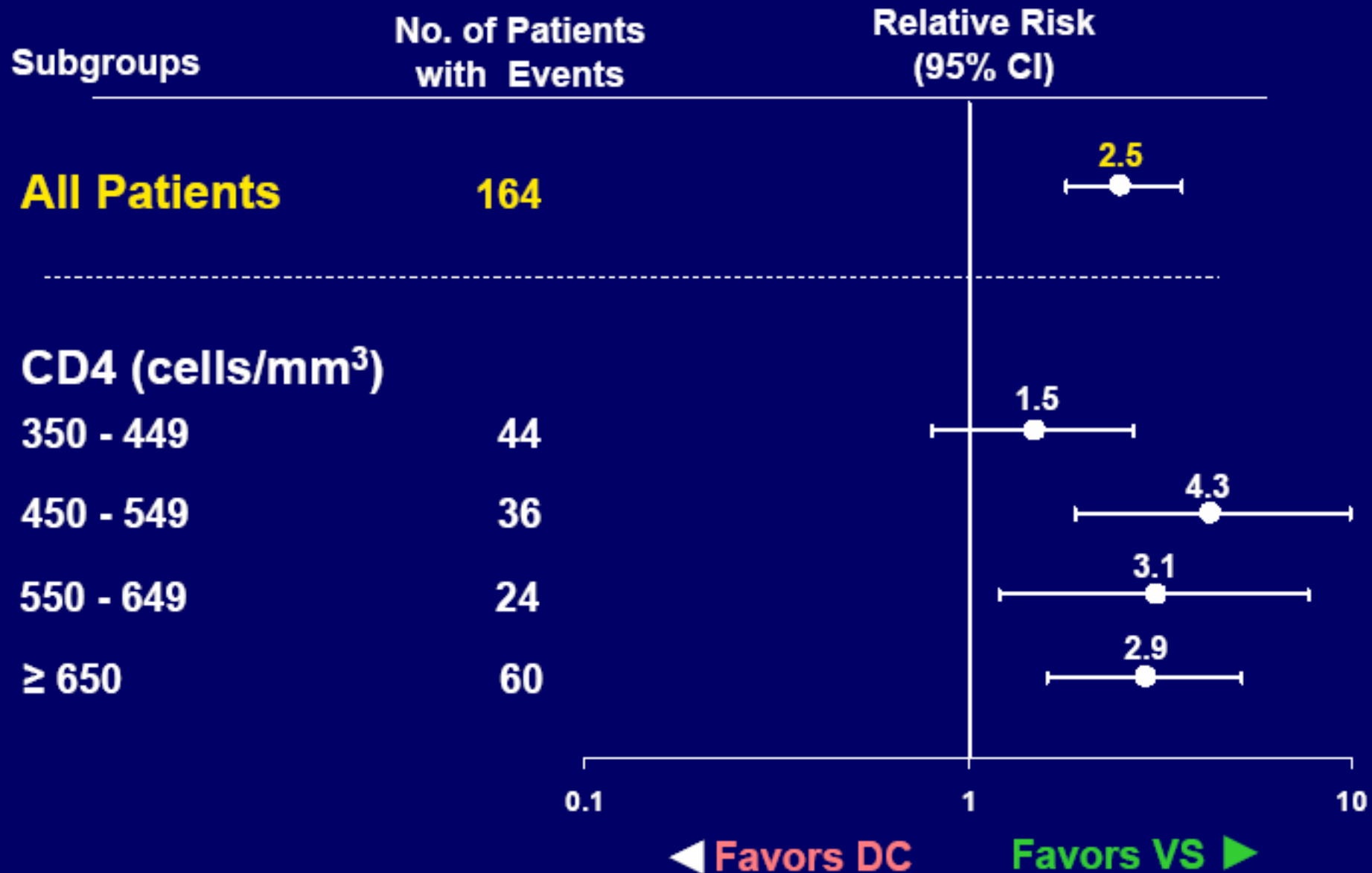
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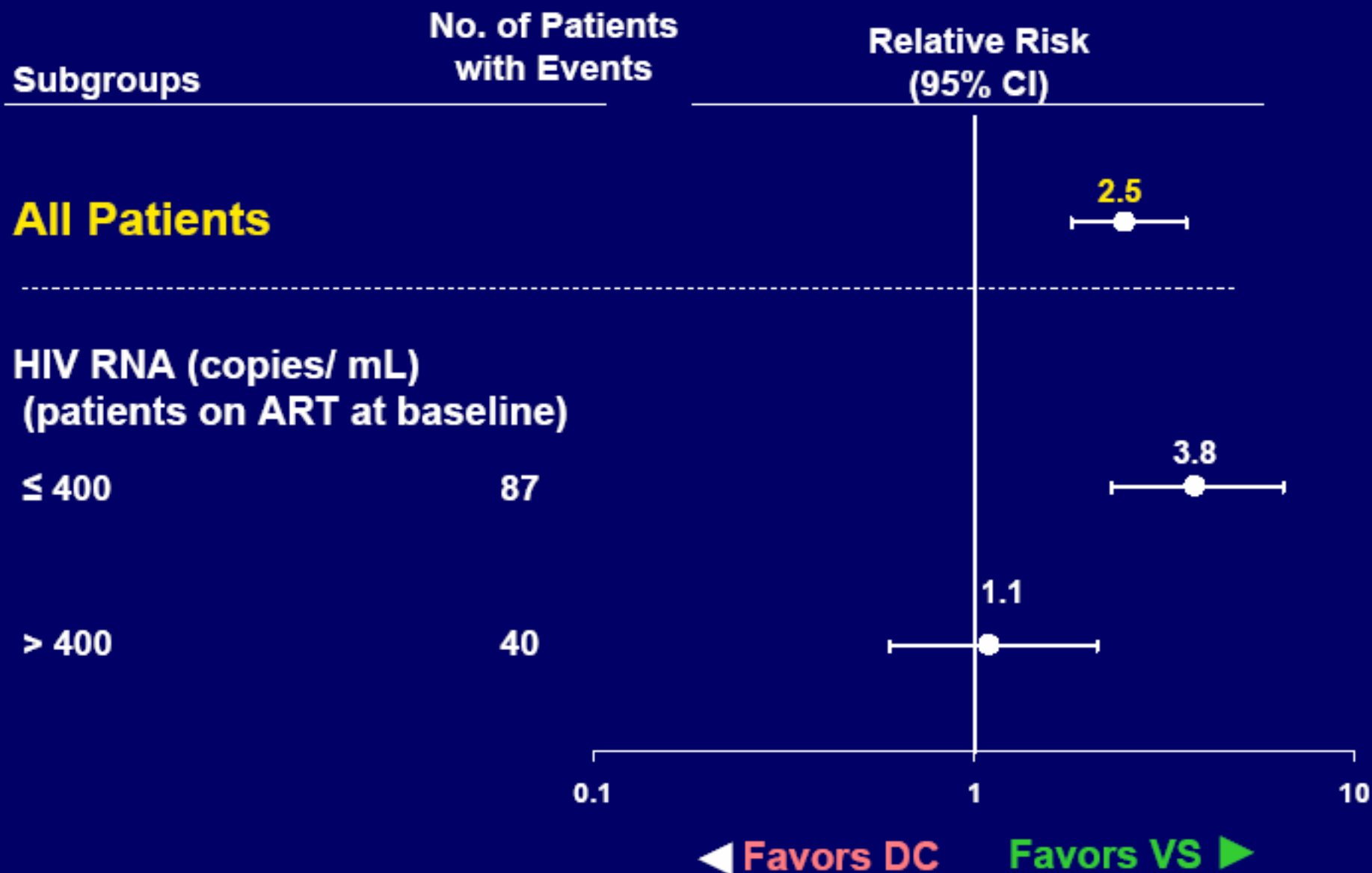
Percent of Follow-up Time Below CD4+ Cell Count Thresholds



Progression of Disease or Death By Baseline CD4+ Cell Count



Progression of Disease or Death By Baseline HIV RNA in Patients Taking ART



SMART Study: Summary

- The drug conservation strategy (compared to viral suppression) was associated with increased risk of:
 - HIV disease progression
 - Death
 - Serious complications
- The increased risk of HIV disease progression or death in the drug conservation arm:
 - Was not associated with nadir CD4+ count
 - Was 3-fold higher in those on ART with VL < 400 c/ml at baseline vs those with VL \geq 400 c/ml
- For other subgroups, risk was always increased in the drug conservation arm vs the viral suppression arm

The DART Trial

- 3314 treatment-naïve pts with CD4+ < 200 in Uganda and Zimbabwe
 - 813 pts with CD4 \geq 300 after 48 wks on HAART randomized to STI (12 weeks on/12 weeks off) vs continuous HAART

Outcome	STI	Continuous	P-value
New ADI or death*	8.3	3.2	0.003
Serious AEs*	5.9	7.3	0.46
Changes in ARVs* (for toxicity)	0.5	3.1	0.02

*Rates per 100 person-years of followup


STI Summary: Time-Based Strategies

Staccato	N = 44	1 wk on/1 wk off	STI higher rate of virologic failure & resistance
Window	N = 403	8 wks on/8 wks off	STI “not inferior” but lower CD4+ counts at end of study
Trivacan	N = 325	4 mos on/2 mos off	Continues
ISS/PART	N = 273	3 mos on/1,2,2,3 mos off	STI lower CD4+, lower % with VL < 50 after resuming ART
DART	N = 813	12 wks on/12 wks off	Study stopped for increased morbidity, mortality

STI Summary: CD4+ Driven Strategies

Staccato	N = 430	CD4 350 on/350 off	STI more HIV symptoms, less AEs, no VL difference
Trivacan	N = 326	CD4 250 on/350 off	Study stopped for increased morbidity, mortality
SMART	N = 5472	CD4 250 on/350 off	Study stopped for increased morbidity, mortality

STI: “Unintended Consequences”

- Negative impact on adherence
- “Covering the tail” of drug levels for ARVs with long plasma half-lives  drug resistance
- Costs of monitoring during treatment interruption
- Cost of treating minor and major HIV-related diagnoses

STI: Conclusions

- STI for therapeutic immunization
 - Analytical treatment interruption is necessary to observe immunological and virological responses to therapeutic vaccines
- STI in chronic MDR HIV-1
 - No clinical or virologic benefit; should not be done
- STI in chronic HIV-1 infection (“drug conservation strategy”)
 - Not appropriate for those who are otherwise candidates for ART
 - Safety of short-term interruption to treat toxicities needs to be established – how to define short-term?

The Dilemma of Clinical Endpoint Trials

- What we know from 25 years of HIV/AIDS research
 - Low CD4+ counts → increase risk of death
 - High VL → more rapid reduction in CD4+ count
 - ART → decreases VL; increases CD4+
 - ART → decreases mortality; prevents death from HIV/AIDS
- We do not want patients to die whether they are participating in clinical trials or not
 - Showing that treatments improve CD4+ counts and decrease VL should be sufficient - unless –
 - Treatments increase risk of death?

The Dilemma of Providing ART

- ART toxicities with existing drugs
 - Occur with all drugs
 - Can be recognized and diagnosed
 - Manageable and treatable
 - Patient and provider education
- Our challenge is to provide ART with fewer toxicities at lower cost and make them accessible, so that
- No patient should have to die

Thank You!

