The Use of Virtual Inhibitory Quotient in Antiretroviral Experienced Patients Taking Amprenavir/Lopinavir Combinations

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Therapeutic Drug Monitoring & Virtual Inhibitory Quotient

- Potential association between drugs levels **(C_{min})** and virologic outcome
  - Largest randomized trial to-date in naïve patients
- Target C_{min} levels higher for protease inhibitor experienced patients with multiple mutations
- VIQ (C_{min}/Virtual phenotype x PA IC_{50})
  - Controversial as to how to calculate and interpret
  - Accumulating data (lopinavir; indinavir)
- Specific importance for amprenavir/lopinavir
  - Negative PK interactions?

Objective

- To look at potential relationships between VIQ and virologic outcome in a group of PI experienced patients who had started combinations of lopinavir/r and amprenavir

Methods

- Patients were identified who had been on amprenavir/lopinavir combinations for at least 3 months
- C_{min} and C_{max} (4 hour) levels measured in 24 retrospectively identified PI-experienced patients (HPLC-UV)
- Virtual IQ calculated:
  - C_{min}/protein adjusted IC_{50}* x VP^{+}
- Differences between median C_{min} and VIQ for amprenavir and lopinavir were calculated per viral load response, NNRTI status)#

+from genotype report prior to start of current regimen

*Molla et al. Virology 1998; lop 0.059 µg/ml; amp 0 .22 µg/ml

#Continuous(Mann Whitney-U), categorical (Chi-square, Fischer exact)

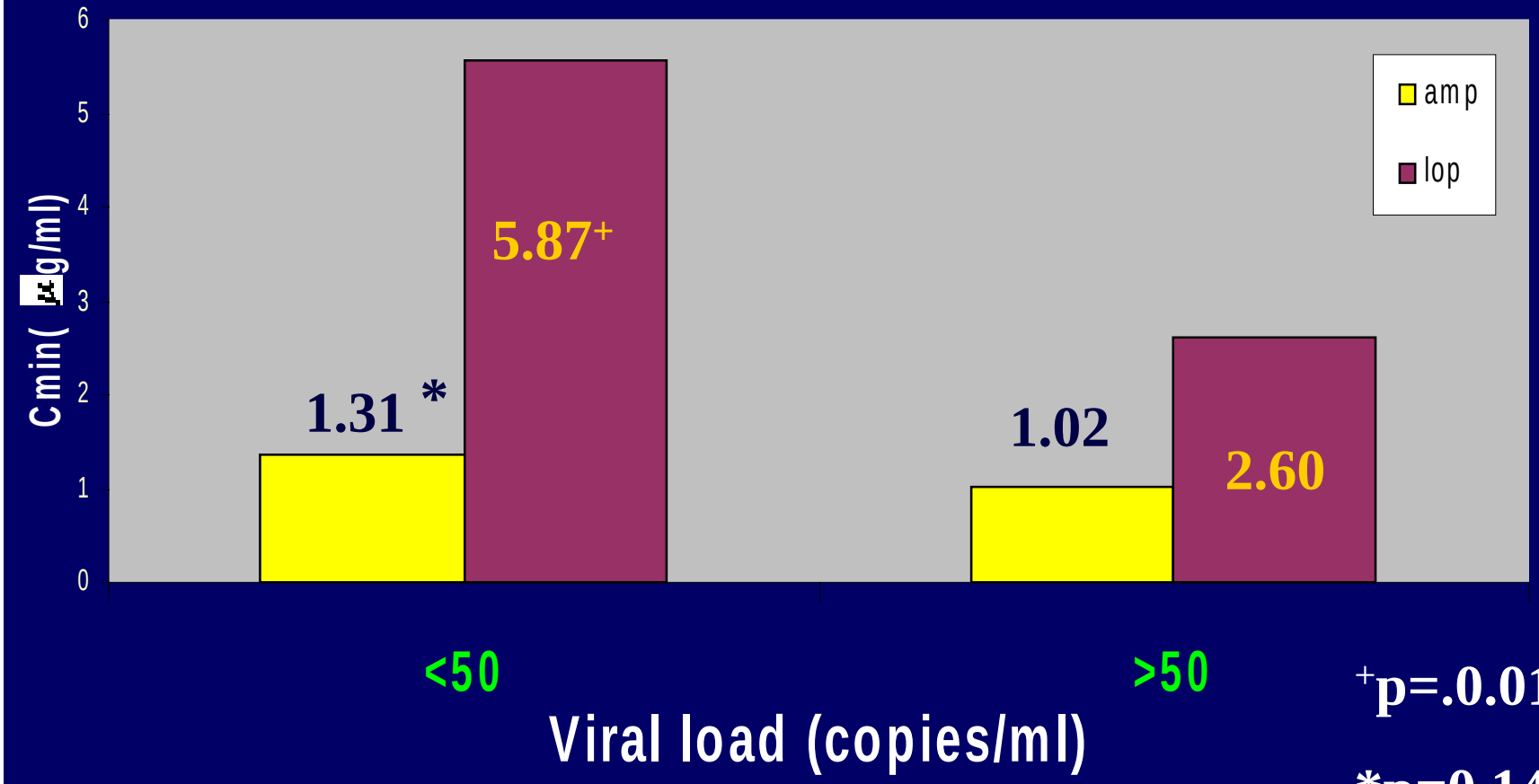
Results (1)

Variable	Result (n=24)
Median Age (SD)	44 (5.8)
Gender (M/F)	24/0
Mean baseline VL (SE) (copies/ml)	123739 *(33,833)*
Median time on treatment (range) (SD)	5 (3-20) *(4.8)*months
On NNRTI	13 (54%)
Median # PI mutations (SD)	5 *(3)*

Results(2)

Variable	Result (n=24)
Median $\log_{10}$ Δ viral load(SD)	1.05*(1.83)*
Viral load < 50 (%) (copies/ml)	7 (29%)
Median amprenavir C_{min} (range)*(SD)*	**1.027**(0.220-2.10)*(0.55)****μg/ml**
Median lopinavir C_{min} (range)*(SD)*	**2.776** (1.210-7.220)(*1.79*) **μg/ml**

Median Amprenavir/Lopinavir C_{min} According to Viral Load



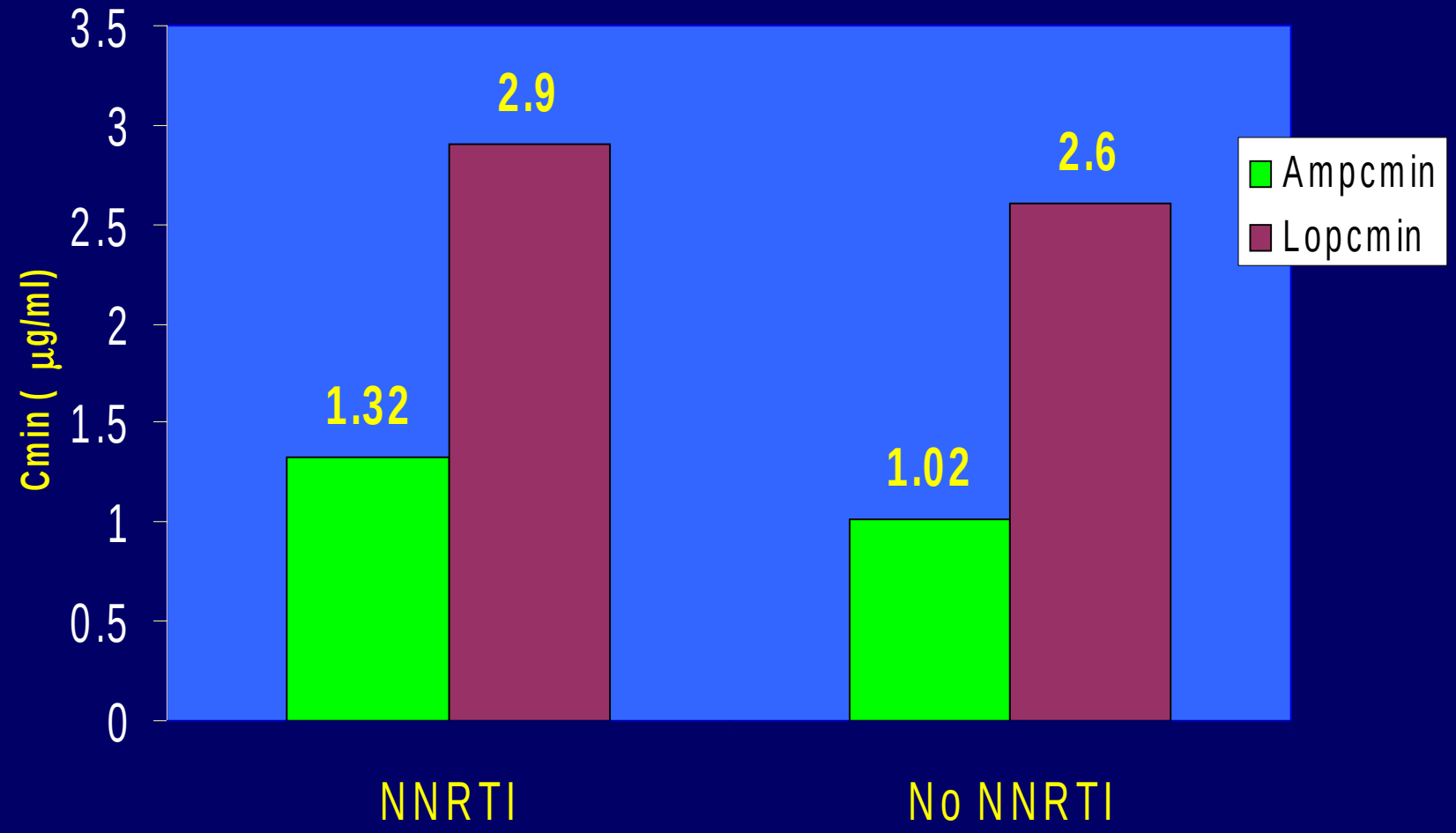
+p=.0.01

*p=0.14

Results

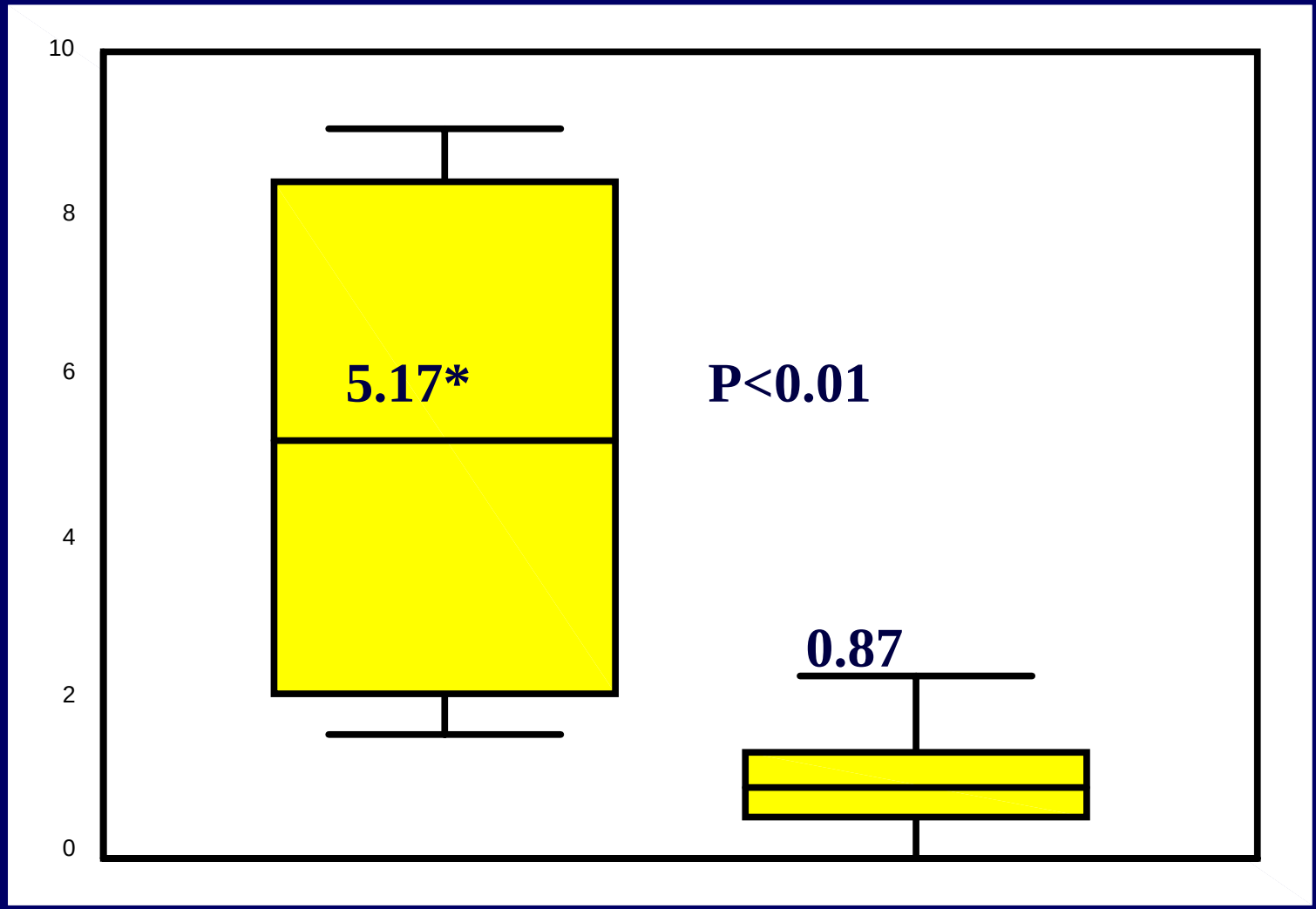
- Trend towards more patients in undetectable group on NNRTIs
  - 6/7 (86%) of patients in < 50 group were on NNRTIs versus 40% (7/17) of those detectable
  - Not reflect a difference in the dose of lopinavir/ritonavir

C_{min} versus NNRTI Status*

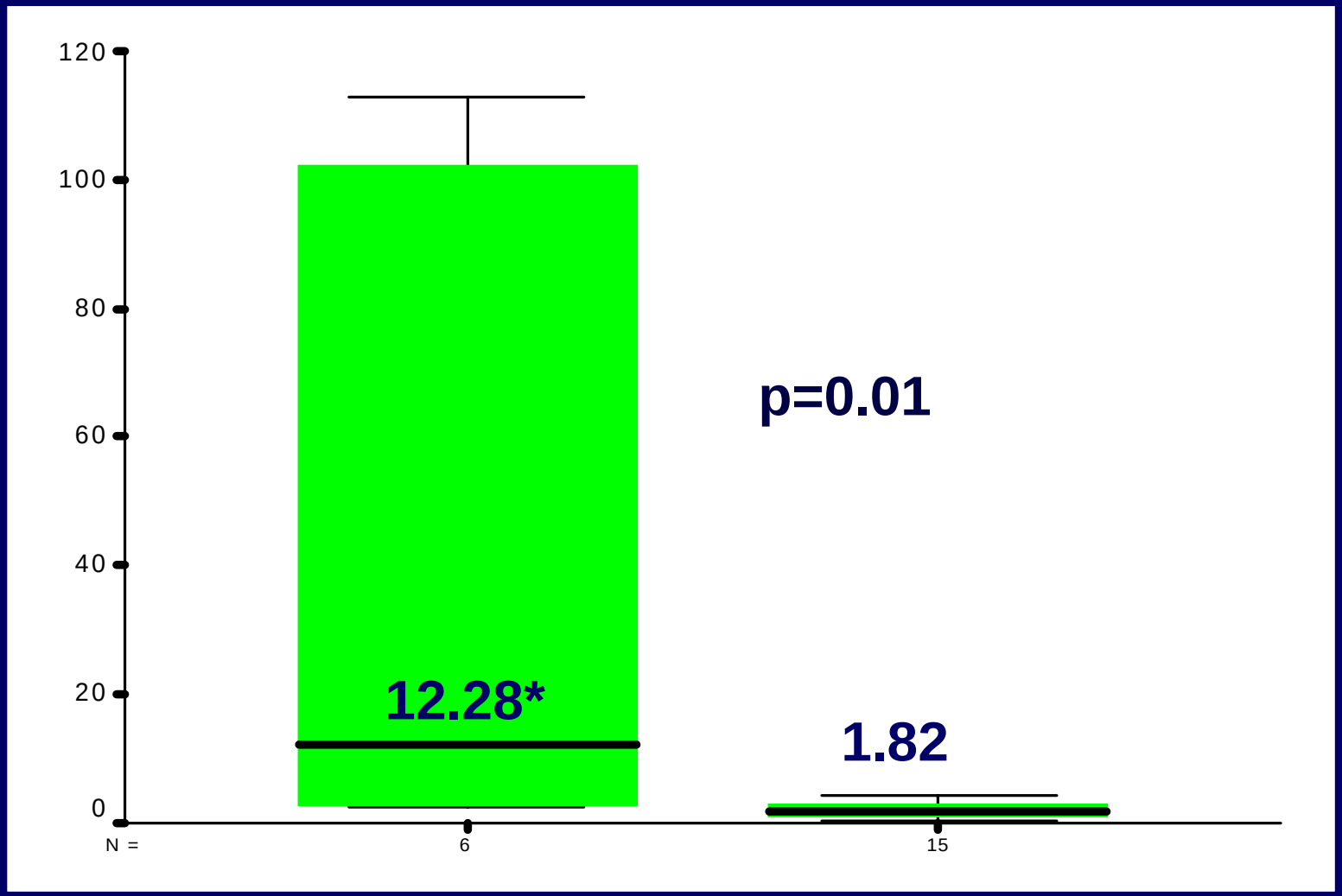


*p=0.3;p=0.45

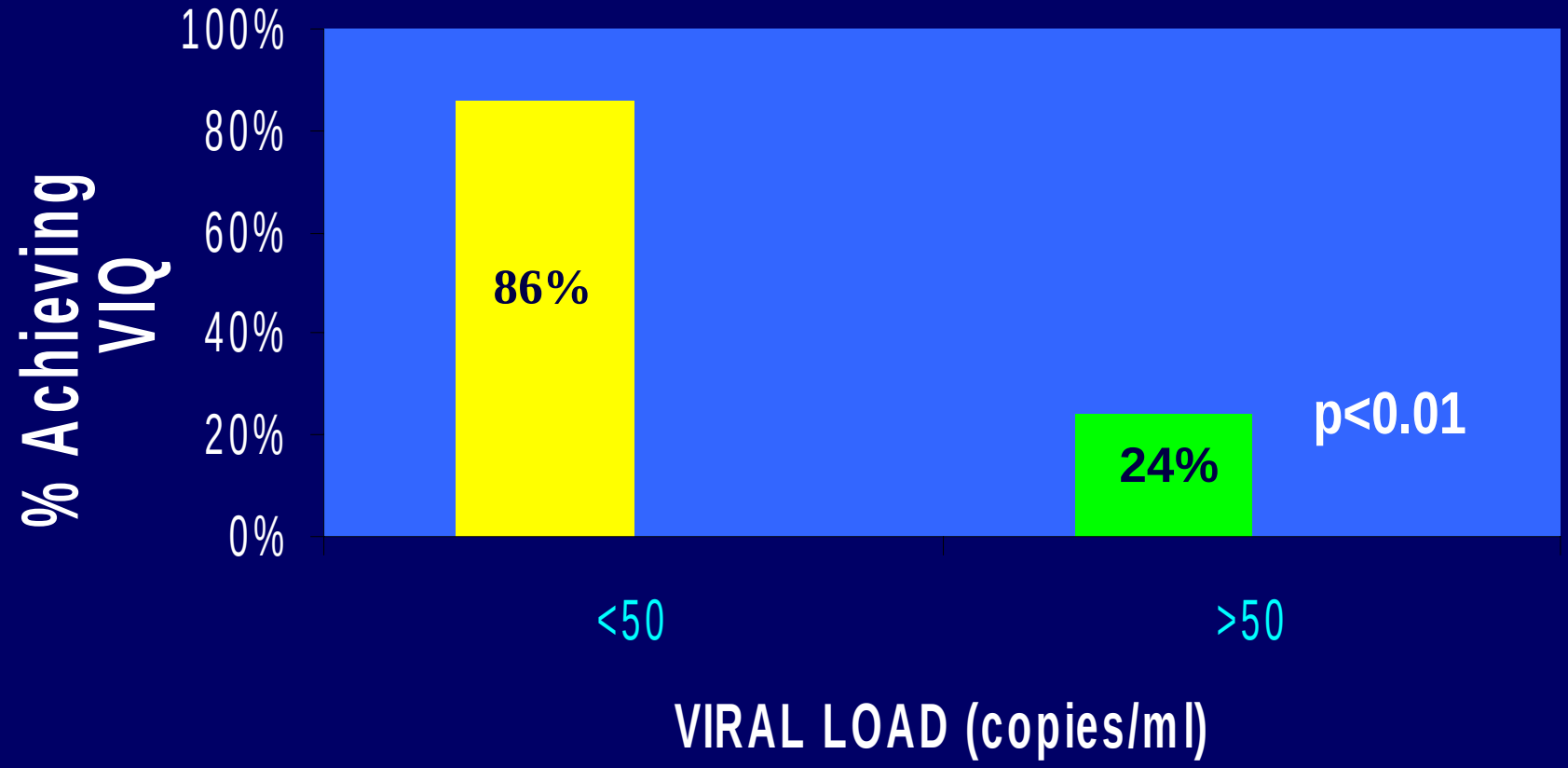
AMPRENAVIR VIQ



LOPINAVIR VIQ



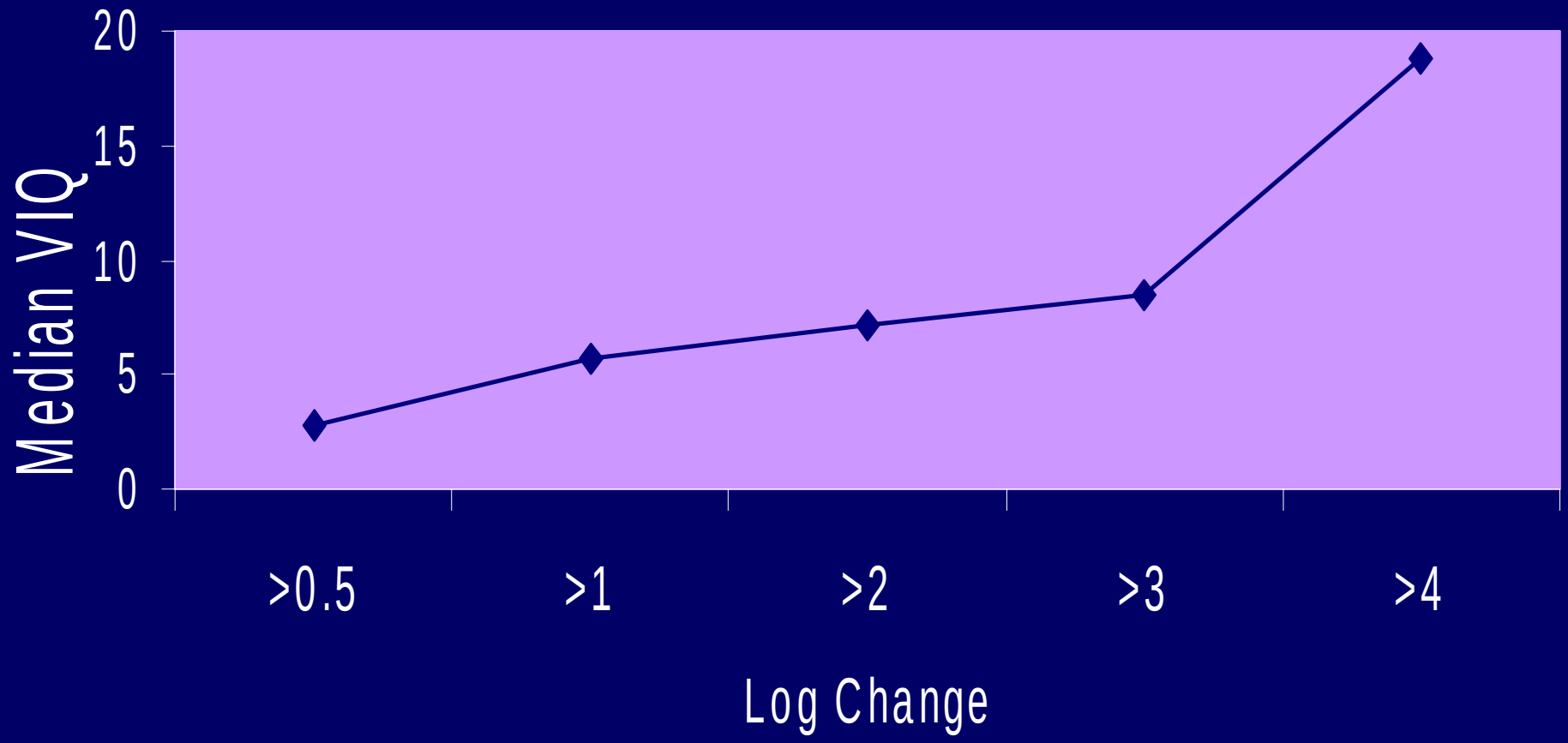
Lopinavir VIQ> 15
Amprenavir VIQ > 1.3



Results

- 100% of the 12/24 > 1 $\log_{10}$ decrease in viral load had lopinavir VIQ > 5

VIQ Lopinavir versus Log Change in Viral Load



Limitations

- Retrospective
- Uncontrolled
- Single sampling
- Sample size

Conclusions(1)

- Association between significantly higher VIQs and virologic suppression in this experienced population:
  - C_{min} amprenavir and lopinavir achieved well above that for wild-type virus (VIQ amprenavir > 1; lopinavir >20)
  - Degree of viral resistance and need to achieve higher C_{min} rather than differences in C_{min} per se may be driving this

Conclusions(2)

- Cumulative population data and controlled studies will be necessary to define:
  - relationships between VIQ and outcome
  - realistic VIQ targets for PI experienced patients
  - the utility of VIQ in the management of these patients