Statistical Analysis of ARV Levels in Hair

Types of analyses done

Issues encountered and how handled

(Mainly general statistical issues)

Possible refinements

Hair level predicting/explaining viral outcomes

How to model hair level effects?

Categorize: tertiles, quartiles, quintiles

- How to pick?

Continuous: effect per 2-fold increase

- Check linearity – OK after log transformation

How to choose?

- Best fit to data.
- Intuitive and understandable.
- Impressive.

Best fit to data risks overfitting

Model fits random variations rather than underlying, generalizable pattern

Mitigate by limiting number of choices

Mitigate by also considering plausibility (e.g., see-sawing)

Example:

1. OR for virologic success 1.6 per 2-fold increase in hair level
2. OR 7.7 for highest tertile vs lowest

Better fit: 1. Simpler, more impressive: 2

Undetectable hair levels

No problem if categorized: put in lowest category

If continuous: single imputation of detection limit

Detection limits are reasonably low

log transformation can give a lot of importance to differences between low levels

E.g., 0.05 vs 0.15 is as large as 0.5 vs 1.5 after taking logs

Mitigate using log(detection limit + hair level) instead of log (hair level)

E.g., 0.05 vs 0.15 only 2/3 as large as 0.5 vs 1.5

Interpretation as “per 2-fold increase” still approximately right

Some more discussion at www.CTSpedia.org/LogTransformation

Prediction

Hair level as a predictor of liver toxicity

Possible feedback loop

Higher drug exposure (reflected by hair level) → harm to liver → worse liver function → lower clearance → higher drug exposure

Put effect after cause: Model liver function at *next* visit in terms of

current hair level

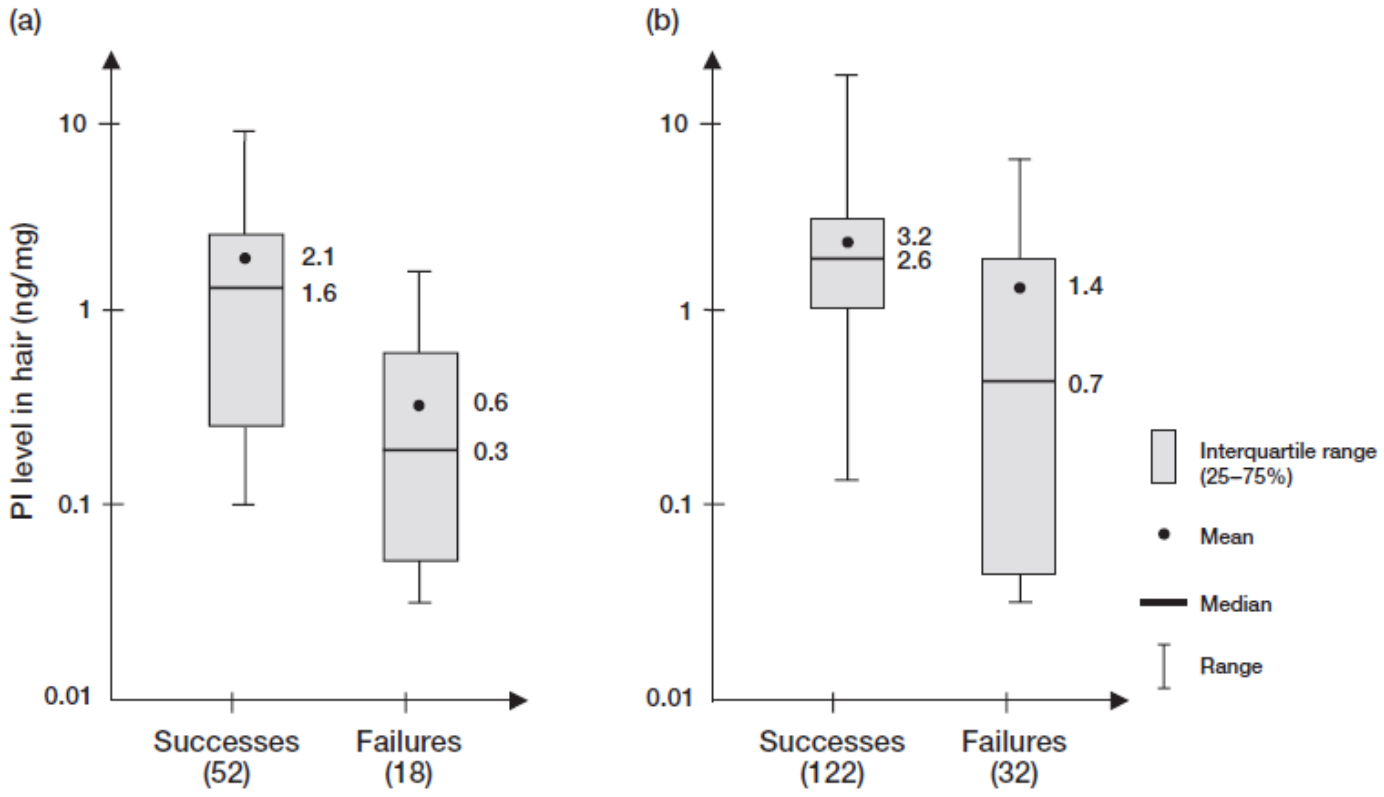
current liver function

NVP Quartile 4 vs 1, effect on next ALT: 2% (-8% to +12%) p=0.76

Hair level as outcome (pharmacogenomics)

Model as continuous outcome, after log transformation

- Matches importance better than raw values (predictive of VL, e.g.)
- Better statistical properties



LPV ATV

Can handle undetectable levels as left-censored

- Just know that the level was < limit
- Use that information only in the modeling

Single imputation of detection limit is probably also OK

- At vs below limit may not be an important distinction
- (but could still convey information about biological effects)

Influences on hair levels

- Adherence
- Pharmacokinetics
- Hair factors (color, treatment, growth rate, etc.) ?

A simple hypothesis:

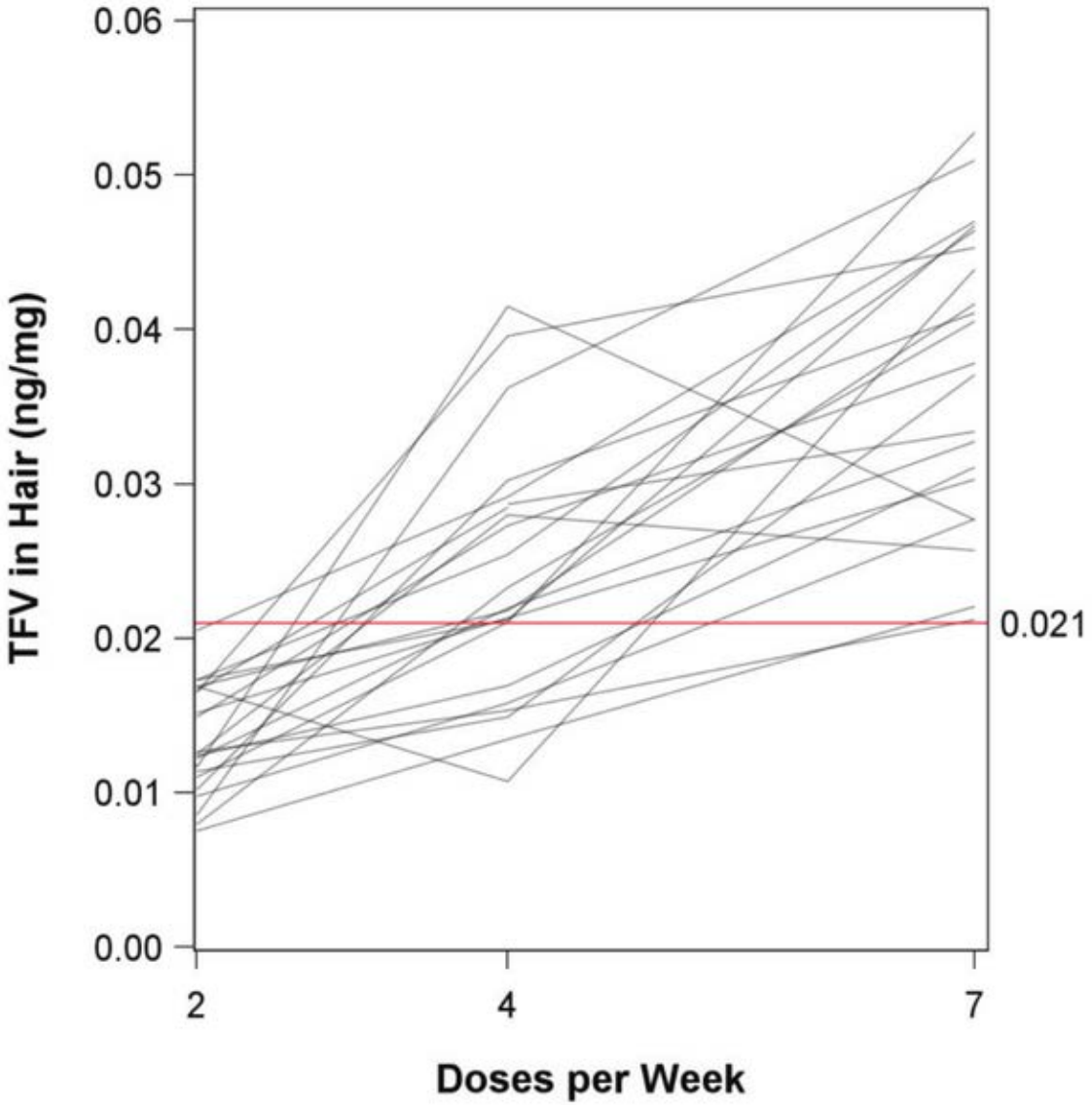
Hair level = (amount taken) × AUC

Log(hair level) = log(doses/week) + log(AUC)

STRAND study of TFV investigated this

- Varied doses per week in volunteers (2, 4, or 7)
- Did an iPK study during the 7 per week condition

STRAND hair data



STRAND estimated effects on hair levels of TFV

Per 2-fold increase in doses/week: 1.77-fold (1.62-1.94)

Per 2-fold increase in AUC: 1.15-fold (0.98-1.36)

78% of within-person variance explained by dose

10% of between-person variance explained by AUC

Hair color did not have much association in STRAND or other studies

Other investigations -- eliminate person-to-person variability

Sample “salt and pepper” hair
Sort strands by color
Assay separately and compare
White/gray averaged 10% to 40% lower, depending on drug

Split sample
Bleach half
Compare levels
Bleached averaged 5% to 25% lower
    Except emtricitrabine: 90% lower

Refinements?

Use external data (above) to adjust for hair color/treatments

Longitudinal studies associating change in adherence with change in hair levels, change in hair levels with viral outcomes

- Can mitigate person-to-person variability
- Decompose predictor into average level (fixed predictor)
  - and deviation from average (at each visit)