An ideal trial for naives

Rob Camp (ACTG NCAB, ATAC DDC)
Simon Collins (HIV I-Base, EATG)

Why continue searching?

- “Next generation” compounds in known areas - RT, PI
  - Kinder, gentler versions*
- Newer targets - entry (fusion, co-receptors), integrase, maturation (Gag cascade), gut mucosa

- And for those for whom Atripla or other drugs are contraindicated (25-30%?)
  - Pregnant, the mentally ill, or history of or recreational hallucinogenic use, active TB..

- Tolerability linked with 40 yrs tx
- Improved PK
- Formulation & pill count
- Lipodystrophy (fat accumulation)

- Tomorrow, today’s tx will seem crude

Treatment is a lifelong event

Trials need to reflect that

- 24-week, 48- or even 96 wk trials are limited*

At failure / discontinuation, strategies need to be in place

Tx is for 40+ yrs, trials / cohorts need to mirror that, to help in making decisions…

Include community in design - it is a necessity that yields higher productivity and quality

Do

- Tolerability is still a real issue
  - Tx for life. How much toxicity is acceptable?
  - Cleaner nukes (after failure of TVD, go back to thymidine analogs?)
    - Are they needed at all?
  - Simplest, cleanest, organ-friendliest yet durable regimens
  - analysis of toxicity / tolerability as an endpoint
  - monitor all the underlying / possible toxicities that may “signal” something bigger later
  - Cleaner NNRTIs, also

Do

- Long trials that take close looks at impact on
  - bone density
  - fat metabolism
  - organ health, etc
  - This includes drug penetration to the brain and related cognitive issues.

Do

- Endpoints - loss due to tolerability
- Long-term follow up within “trial” - 20 years, where “steps” aren’t even necessarily defined yet
  - Like D:A:D
  - Contribute data to and mine databases (gov’t & institutional support for large-scale longitudinal cohorts)
    - Learn from the 20+ yrs of experience we have

Do

- Actively reflect populations affected
  - Women (hormonal agents, PK & dosing, safety / efficacy…), ped's, hepatic issues (co-infected people & tolerability, int'n data), racial/ethnic minorities (genetic variations) / poor, marginalised pop's (prisoners, homeless), younger pop's, older pop's, people on necessary and typical concomitant med's, people with comorbidities (TB, etc), transgendered, recovering addicts, other clades
  - Access to drug / tx "after" a trial

Do

- Understandable ICs
  - Some are up to 20 pages of mumbo-jumbo
  - Are they legal documents to protect the investigator or to help patient know their rights?
- Trials that reflect real life, with real life populations
  - Inclusion/exclusion criteria that allows quick enrollment, faster results
    - Only study pts who need tx
    - Not study exp tx in pts who need a proven tx
  - Enhance durability? Induction / maintenance*

Don’t

- Multiply toxicities *ad nauseum*
- Chronic obstructive pulmonary disease, diabetes, kidney failure, bleeding ulcers, depression, rectal cancer, osteoporosis, pneumonia(s), Parkinson’s, liver disease, the lipos
  - Overlapping toxicities of tx and ageing
  - Four nukes
    - Is 4 really better than three? Four NRTIs?
    - If we don’t do it here, is it ethical to do it there (notwithstanding TB interactions, refrigeration, etc)*

Don’t

- PI, especially with ritonavir
- /r alternative?
- Marketing driven studies that add no advantage to the current SOC

Other guiding principles

FDA must show and, if necessary, use teeth

- Sanctions, periodic public updates, Medwatch, clinician ed, strengthen safety and post-marketing systems
- More sites thru national IRB

backup

- NO functional monox
- Combine EAPs (coordinated by external agency?)
- Potential PK interactions need to be known
- ICC
  - , EAPs with maximum data collection and minimal paperwork …

So

- what do we start with
- what happens at failure
- why would a person stop who hasn't failed
- what to go to next (and what doors are closed because of what we started with)