Are we overdosing Antivirals? YES-Standpoint

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Working Backwards to The Root of Dose Selection – Why Anti-infectives are Different

Goal: Ph3 Success

Ph3 Trials

Ph1/2 Trials

Drugs for Chronic Conditions
Tolerability just as important as efficacy

Studies may be designed/powered to demonstrate tolerability advantages or at least non-inferiority

Strong incentive to select dose based on TI, as marketing based on tolerability advantage adds value

Anti-infectives
Efficacy (and no resistance) trumps tolerability

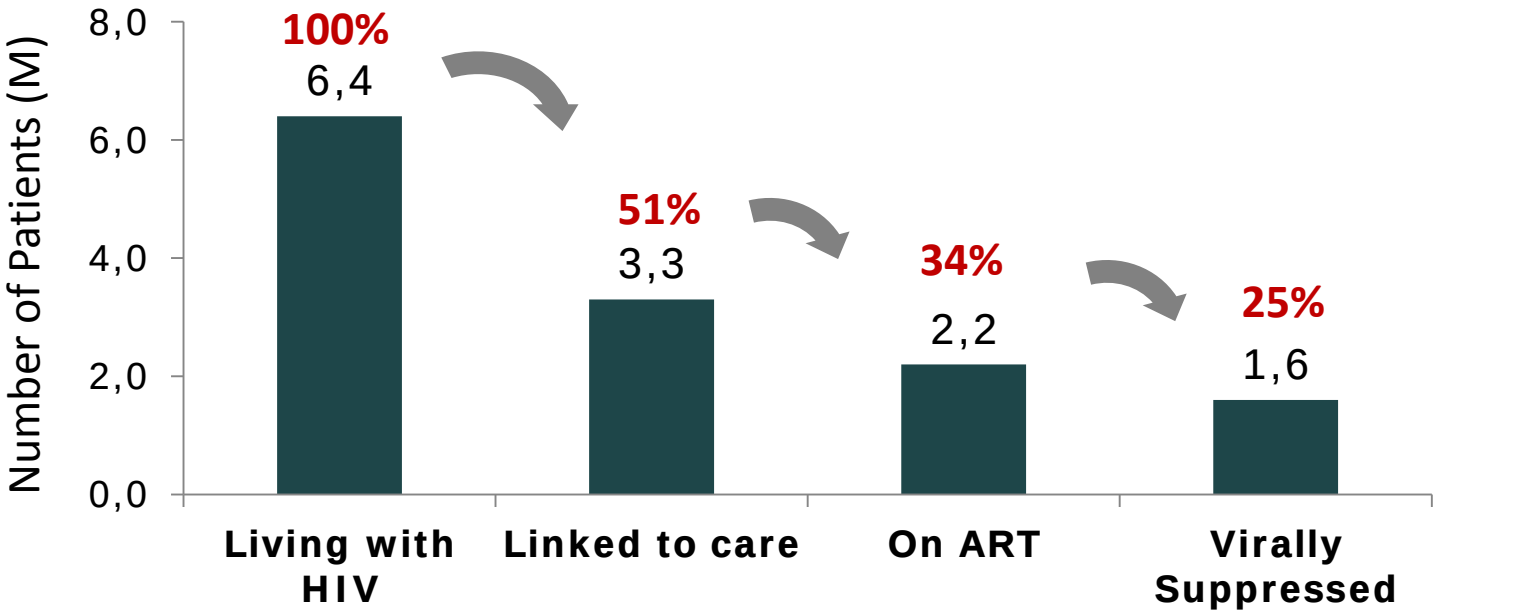
Studies not designed/powered to examine potential tolerability advantages, though is built into snapshot analysis

Commercial value maximized by time on market as tolerability advantage is not a significant marketing advantage

Dose				
Efficacy	+	+ +	+ +	+ +
Safety	+ +	+ +	+	-

Already many patients are lost along the treatment cascade; tolerability issues of ARVs exacerbate the issue

Treatment cascade, South Africa, 2012[1]

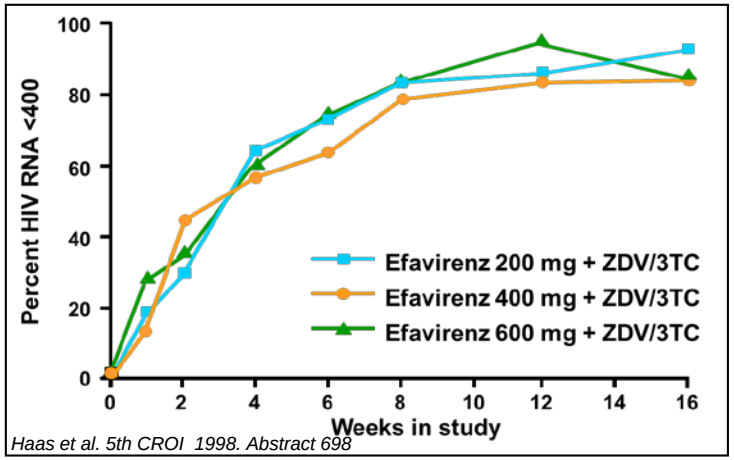


- Even in high-income countries, poor adherence can lead to poor viral suppression
  - Only 75% viral suppression amongst Ryan White HIV Program patients, dropping to 50% amongst those not retained in care[2]
- Adherence counselling, *especially where tolerability is not a concern*, can lead to re-suppression with the same regimen
  - A meta-analysis estimated 70% re-suppression rate amongst people who receive adherence support following a detectable viral load result[3]

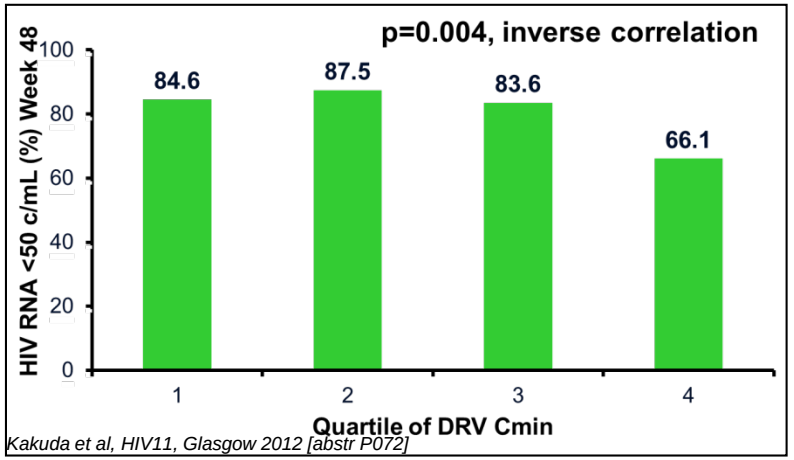
1) Takuva S et al. Disparities in engagement within HIV care in South Africa. CROI 2015, Seattle, abstract 154; 2) Continuum of HIV care among Ryan White HIV/AIDS Program clients, U.S., 2010 ; 2) Bonner K et al. (2013) J Acquir Immune Defic Syndr. 1;64(1)

HIV/AIDS drug development needs to change from an emergency response approach to a chronic treatment approach as HAART has extended life expectancy to that of healthy individuals

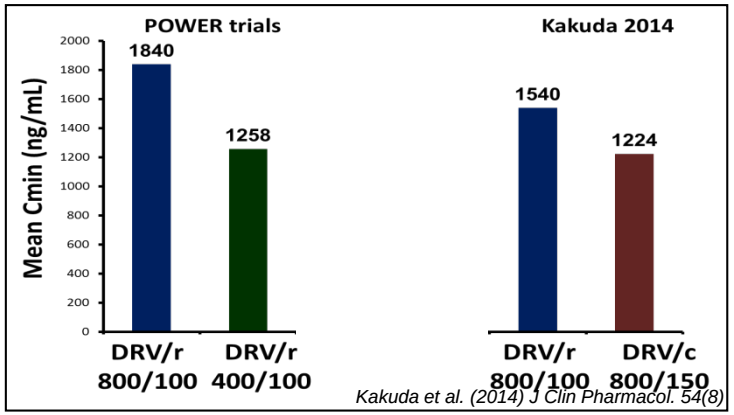
- Precedent for reducing drug doses in clinical practice due to long term tolerability issues, after trials showed no reduction in efficacy
  - Zidovudine (hematologic toxicity)
  - Didanosine (pancreatitis)
  - Stavudine (peripheral neuropathy)
- Data suggests dose reductions are warranted for today's and tomorrow's ARVs:



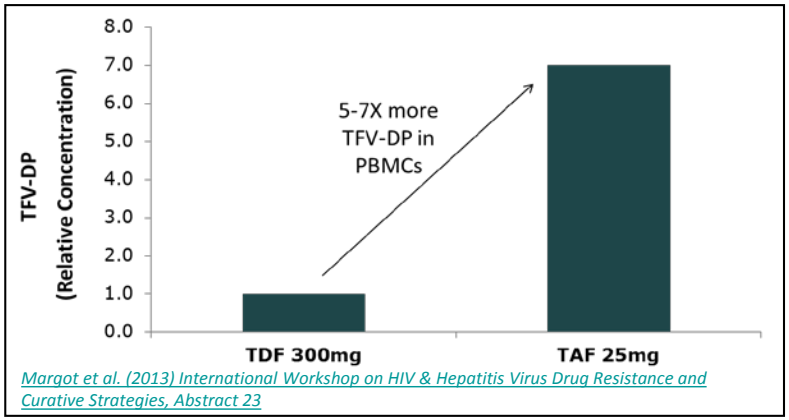
Haas et al. 5th CROI 1998. Abstract 698



Kakuda et al, HIV11, Glasgow 2012 [abstr P072]



Kakuda et al. (2014) J Clin Pharmacol. 54(8)



Margot et al. (2013) International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies, Abstract 23

Debunking the Resistance Argument

- No evidence to date that lower doses have lead to greater resistance, particularly in context of HAART
  - ENCORE-1 there was no evidence for an increased risk of resistance on 400mg, MEC of 1000ng/ml invalidated, but not enough failure to establish new MEC

- So long as virologic suppression remains the same, do not expect resistance to emerge in the absence of replication

- Likelihood of resistance may actually be higher for current doses if tolerability leads to poor adherence and therefore poor virologic suppression – this supports the use of the Snapshot methodology in studies

- Recent data from weekends off trial (BREATHER) suggests reexamining Cmin acceptability assumptions made for the relevant drugs