Comparison of central and local HIV-1 RNA quantification from two international clinical trials.

Name: Janaki Amin, Matthew Law, Anthony Keller, Rebekah Puls, David A Cooper, Sean Emery
Affiliation: The Kirby Institute, University of New South Wales Australia

Introduction

Commonly in HIV treatment clinical trials plasma viral load (pVL) is tested at a central laboratory on the assumption that this will result in less variability than would arise from testing at local laboratories. However, additional processing is required for central testing resulting in additional potential sources of error. Further, central testing incurs substantial cost and predominantly cannot beused for clinical management.

Aim:
The aim of this paper is to determine whether **local** pVL test results give clinically consistent indications to **centrally** tested pVL.

Methods

Data sources
ENCORE: randomised trial, week 48, ART naïve
SECONDLINE: randomised trial,week 48, failed first line ART

pVL assesment
pVL measured as HIV RNA copies/mL

Local
Quantified at acredited local laboratories with lower limits of detection less than 50 copies<mL.

Central
Quantified at St Vincent's Centre for Applied Research, Sydney, Australia. Central Abbott m2000 Real Team HIV-1 Test™ (Abbott Molecular Inc, Des Plaines, IL, USA) with a lower limit of detection of 40 copies/mL.

Trial outcome
Between arm difference and 95% CI in viral suppression (<200 copies HIV RNA/mL).

Agreement between measures
Bland and Altman plots of agreement between local and central determinations of $\log_{10}$ pVL were drawn for study weeks 0 and 48. Only time points where both local and central measures were available were analysed. The 95% limits of agreement were estimated as the mean difference between measures ± 1.96 times the standard deviation (SD) of the differences.

Results

Table Comparison of trial primary endpoints as determined by central versus local pVL.

Trial		pVL <200copies/mL		
		Experimental arm	Control arm	Difference (95%CI)
		n/N (%)	n/N (%)	
ENCORE	Central	302/321 (94%)	285/309 (92%)	1.8 (-2.1, 5.8)
	Local	301/321 (94%)	282/309 (91%)	2.5 (-1.6, 6.6)
SECOND-LINE	Central	223/270 (83%)	219/271 (81%)	1.8 (-4.7, 8.3)
	Local	218/270 (81%)	218/271 (80%)	0.3 (-6.4, 7.0)

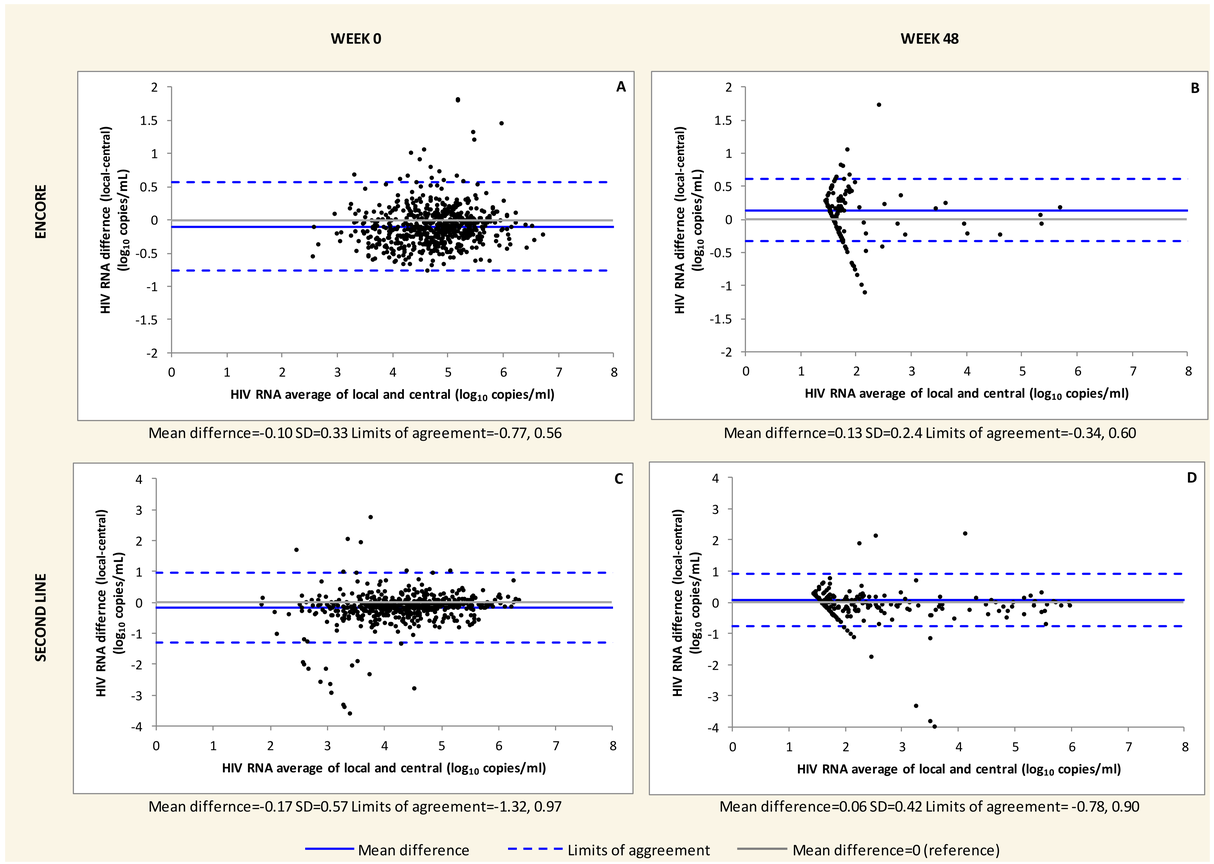


Figure HIV RNA $\log_{10}$ copies /mL: difference (local - central) versus average of values with limits of agreement, by trial and study week.(SD = standard deviation of the mean difference).

Trial outcomes
In both ENCORE and SECOND-LINE the primary studies found the experimental arm to be non-inferior to the control arm using central pVL measures. The point estimates and confidence interval determined using local measures alone were qualitatively similar to central results in both studies (Table).

Agreement
At week 0 mean pVL was greater than 4 $\log_{10}$ copies in both trials on both measures. At this time point for both trials local measures were on average marginally lower than central measures (Figure 1 A, C). There was no discernible pattern to the distribution of data points outside the limits of agreement, nor between the average and difference between measures, for either trial.

At week 48 mean pVL was less than 2 $\log_{10}$ copies in both trials on both measures. For both trials local measures were on average marginally higher than central measures, which can be at least partially explained by difference in lower limits of detection. These data form an arrow shape at lower average pVLs. This distribution is an artefact of the lower bounds of detection for the pVL assays. Very few data points lie outside the limits indicating agreement.

Conclusions

The comparison of primary endpoints revealed **no difference** in interpretation of trial outcomes based on the use of local or central pVL measures. These data indicate that in a clinical trial setting, where the outcome of interest is pVL within routine limits of detection, **central laboratory testing is not warranted.**

Acknowledgements
This study was funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales Australia