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STATISTICAL POWER TO DETECT DRUG TOXICITY IN HIV CLINICAL TRIALS

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AIMS: Conclusions on drug safety are often made from HIV clinical trials without prior analysis of the power to detect treatment effects on various adverse events. Toxicity can be measured either from continuous data (for example, mean/median change in laboratory parameters) or categorical data (for example, Grade 3 or 4 (serious or life-threatening) events).

METHODS: Estimates of the variability of laboratory parameters and clinical toxicities were taken from published clinical trials. The sample sizes required for 80% power and 5% significance level to detect a treatment effect on toxicity were calculated using standard parametric techniques, for change from baseline in continuous data and for a doubling in the incidence of given clinical toxicities. The summary statistic Area Under the Curve Minus Baseline (AUCMB) was also used to examine power for continuous data, using lipids data from the FOCUS trial.

RESULTS: For total cholesterol, the estimated sample size for detection of a 0.5 mmol/l (18 mg/dl) difference between treatment groups was 159 per arm, compared with 435 per arm to detect a 5% versus 10% incidence of Grade 3 or 4 hypercholesterolaemia between arms. Similar results were obtained with analysis of other lipid parameters and with haemoglobin. For events with very low incidence (for example, hypersensitivity, pancreatitis and lactic acidosis) sample sizes per arm with 80% power to detect a doubling ($x-y\%$) in incidence between two treatments were 1826 for 1–2% incidence, 1141 for 2–4% incidence, 749 for 3–6% incidence and 553 for 4–8% incidence. From the FOCUS trial, the standard deviation of change for fasting cholesterol was reduced by 20%, and for triglycerides by 40%, by using AUCMB, instead of mean change, to define

response. A 20% (40%) lower standard deviation equates to a 36% (64%) lower sample size to detect the same effect size.

CONCLUSIONS: Most HIV clinical trials are too small to detect differences in the incidence of individual Grade 3 or 4 toxicities between treatment arms. Laboratory toxicities should be analysed by treatment arm using change from baseline as a continuous measure to maximise statistical power. Use of summary statistics such as AUCMB may further increase power for continuous data.

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