Virologic Outcome Measures in HIV Clinical Trials: A Methodological Study

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Introduction

HIV viral load is an important prognostic indicator and surrogate measure of treatment response.

The viral threshold used to define virologic failure or success varies throughout the HIV literature:

- the World Health Organization defines virologic failure as a plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months on ART; [1]
- the British HIV association defines failure as single confirmed plasma HIV RNA above 200 copies/mL.[2]

Variations in definitions of virologic success or failure may preclude the comparison of trials and prevent pooling of trial data.[3] Likewise, missing data in HIV clinical trials threatens the internal validity, introducing error, and decreasing the power of the trial.[4] As such, we sought to explore the role of virologic outcomes in the levels of missing data.

Objectives

The aim of this paper is to review viral load thresholds used to define virologic failure as well as the trial characteristics associated with lower thresholds and missing outcome data.

Methods

We conducted a methodological review of published HIV randomized controlled trials (RCT) using a search (2009-2019) of PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials.

We used logistic regression to determine the factors associated with a virologic threshold ≤ 50 copies/mL and linear regression to determine the factors associated with missing outcome data.

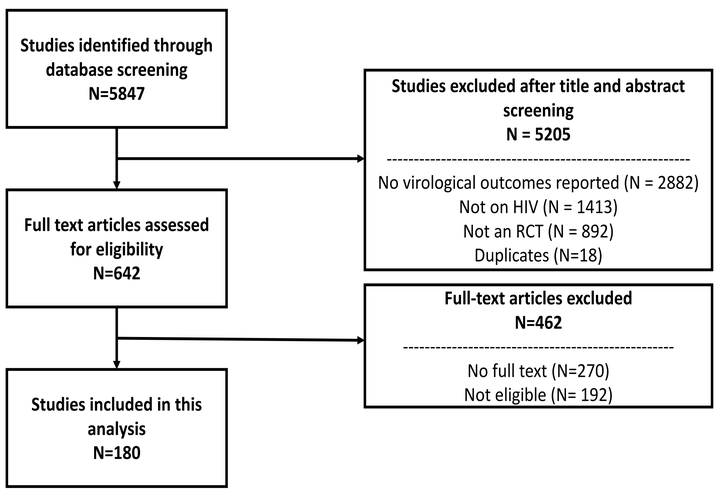

Figure 1: Flow of Studies

Results

Table 1: Characteristics of included studies

Variable	Statistic
Overall	180
Year of publication: median (q1;q3)	2016 (2015 – 2017)
Income level: n (%)	
High	98 (54.4)
Upper middle	11 (6.1)
Lower middle	18 (10)
Low	10 (5.6)
Mixed	43 (23.9)
Funding: n (%)	
Industry	54 (39.4)
Government or private	83 (60.6)
Intervention type: n (%)	
Pharmacological	151 (83.9)
Non-pharmacological	29 (16.1)
Number of sites: n (%)	
Single centre	40 (22.4)
Multi-centre	139 (77.7)
Number randomized: median (q1;q3)	243 (101 – 491)
Percent missing: median (q1;q3)	9.0 (3.1 – 16.0)
Virologic outcome as primary outcome: n (%)	130 (73.5)
Outcome type: n (%)*	
Change in viral load	33 (18.3)
Virologic success	89 (49.4)
Virologic failure	59 (32.8)
Virologic rebound	9 (5)
Other	6 (3.3)
Thresholds used (copies/ml): n(%)**	
>50	50 (28.0)
≤50	96 (53.3)
No threshold used	32 (17.8)
Number of time points required for confirmation of virologic outcome: n(%)	
1	119 (66.9)
>1	59 (33.1)
Time to event outcome (yes): n(%)	16 (9.0)
Q=quartile; SD=standard deviation	

*Study may have more than one outcome; **Study may have more than one virologic threshold

Table 2: Univariate and multivariate logistic regression analyses to detect factors associated with viral threshold of 50 or less

	Model 1: Multivariate Analysis		Model 2: Multivariate Analysis	
	aOR (95% CI)	P	aOR (95% CI)	P
Year of Publication	0.92 (0.6-1.30)	0.632	-	-
Source of funding (Industry)[a]	**5.25 (1.71-16.12)**	**0.004**	**6.39 (2.18-18.74)**	**0.001**
Number of sites (Multicenter)[b]	1.34 (0.42-4.22)	0.622	-	-
Income level (High)[c]	**2.70 (1.02-7.17)**	**0.046**	2.46 (0.976-6.20)	0.056
Intervention Type (Pharmaceutical)[d]	2.62 (0.61-11.20)	0.194	-	-
Number of Patients Randomized	1.00 (1.00-1.00)	0.528	-	-

P < 0.05 indicates statistical significance. CI: confidence intervals; Reference variables: Government and Private source[a]; Single Center[b]; Mixed, Middle, or Low Income[c]; Non-Pharmaceutical Intervention[d]; Model 1: Multivariable Analysis: Pseudo R^2 = 0.21.; P = 0.001; AIC = 1.112; Model 2: Multivariable Analysis: Pseudo R^2 = 0.16.; P < 0.001; AIC = 1.078

Results

Table 3: Univariate and multivariate linear regression analyses to detect factors associated with percentage of missing outcome data

	Univariate Analysis		Multivariable Analysis	
Percentage of Missing Data	Coef. (95% CI)	P	Coef. (95% CI)	P
Year of Publication	0.56 (-0.96 – 2.10)	0.469	-0.03 (-1.98 – 1.92)	0.978
Source of funding (Industry)[a]	-1.56 (-6.78 – 3.66)	0.556	2.65 (-3.41 – 8.70)	0.388
Intervention Type (Pharmaceutical)[b]	-1.74 (-7.25 – 3.77)	0.534	**-11.86 (-21.09 – -2.63)**	**0.012**
Number of sites (Multicenter)[c]	0.16 (-4.75 – 4.79)	0.995	4.73 (-1.99 – 11.45)	0.166
Income level (High)[d]	-1.25 (-5.32 – 2.81)	0.544	-0.55 (-6.15 – 5.05)	0.845
Outcome Type (Virologic Failure)	1.98 (-2.32 – 6.29)	0.365	3.02 (-2.61 – 8.66)	0.289
Viral Threshold < 50	-4.08 (-8.85 – 0.76)	0.098	-2.76 (-9.30 – 3.79)	0.405
Length of Follow Up (Weeks)	0.09 (-0.17 – 0.36)	0.496	-0.12 (-0.54 – 0.30)	0.561
Number of Patients Randomized	-0.00 (-0.00 – 0.00)	0.355	0.00 (0.00 – 0.00)	0.116
Number of Viral Load Measurement Timepoints (More than 1)[f]	-0.91 (-5.38 – 3.56)	0.688	2.23 (-3.82 – 8.28)	0.466

CL: confidence limits; Reference variables: Government and Private[a]; Non-Pharmaceutical[b]; Single Center[c]; Mixed, Middle, or Low Income[d]; Outcome type: Not virologic failure[e] One-time timepoint[f] Multivariable model: R2 = 0.11 P = 0.28

Conclusions

Country income level, **source of funding** and **type of intervention** were associated with choice of virologic thresholds and this may in part explain heterogeneous virologic outcomes. Furthermore, trials of **pharmaceutical interventions** were associated with lower levels of missing data. The development and acceptance of formal guidelines on virologic outcome reporting in randomized controlled trials are needed.

References

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