Tests of BDL Bias and Variance - v.1a

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Purpose

This file will test the determination of bias and variance when calculating viral loads and other variables that are subject to detection limits. For HIV-1 patients, the objective of antiretroviral treatment is to make their plasma RNA viral load zero.

However, there is a practical limit below which the assays cannot distinguish between the presence of virus and having no virus (the zero objective). This is called the "detection limit" and patients who achieve this level are said to have a viral load "BDL", below detection limit. One of the most important consequences of exactitude in measuring true lack of the presence of virus is the phrase "undetectable = untransmittable" [G. C. Chang *et al*. [1]][2]. This frees, at least emotionally, the individual from concern about transmitting the virus to a partner.

There have been various strategies to deal with calculations of viral load in a panel of patients. One has been to eliminate the cases from the calculation, another has been to treat the viral level of those patients who are BDL as 0, assuming they are really without any virus. Still another strategy has been to assign a value equal to the detection limit. Others have used a value of half the detection limit, i.e., half of the difference between the detection limit and zero.

Name	Strategy	Value Assigned to "BDL"
censor	eliminate case	no value
zero	treat as zero	0
dl	treat as detection limit	detection limit
halfdl	treat as half of detection limit	detection limit/2

This study was inspired by a blog post by Nikolas Siccha, "Lower Limits of Detection or Quantification".[3] He develops a Bayesian model to explore the pharmacodynamics of drugs that cause the measurement of interest to fall below detection limits. As it deals with the dynamics over time of a drug's presence and efficacy in a patient, his question is more complex than the question I would like to address here.

! Important

What is the relationship between the true value of viral load below detection limit and the strategies used to estimate it and how does that effect analyses of the viral load of a sample or population?

Method

I will create a panel of 1,000 PLWH artificially with estimates of their viral load at a baseline and after 48 simulated weeks of antiretroviral treatment (ART) when some of them will have viral loads reduced to BDL, which I will define here as 50 copies per mL.[1] According to a 2009 clinical trial (STARTMRK) of Raltegravir, a 1st generation integrase inhibitor, 86.1% of the RTG arm of naive patients had viral loads BDL by week 48. [4] Likewise, a clinical trial (SINGLE) of a second generation integrase inhibitor, Dolutagravir, showed 88% of the DTG arm with viral loads below detection limit by week 48. [5] For my panel, I will use a proportion of 85% of patients achieving true viral loads between 0 and 50 by the 48 week mark. 85% is a bit more conservative than either of the real trials, but consistent with their results.

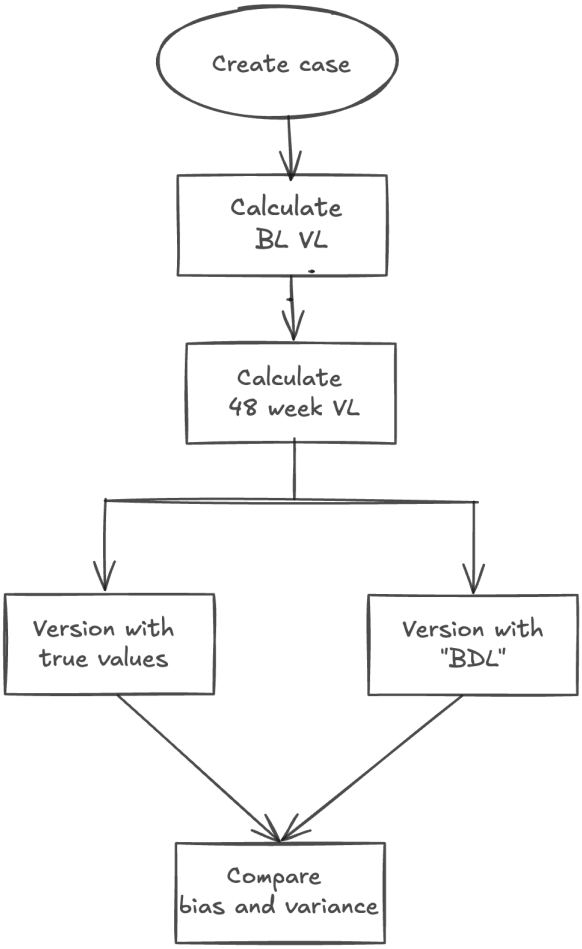
The baseline viral loads will be determined by calculating 1,000 normal variates from a truncated normal distribution with a mean of 900 copies per mL and a standard deviation of 1,000 copies. Since values below detection limit make no sense for this simulation, these values will be removed by using the truncated normal distribution.[6]

The 48 week data will be reduced dramatically (and unrealistically)[2] by 97.5% and the number of values below 50 copies per mL will be calculated. I will then create a second version substituting the true values below the detection limit with BDL. Using the four strategies outlined in Table 1, I will then compare the bias and variance of each of these strategies for substituting the true value of the viral load. Finally, I will propose a method for imputing values that is commonly applied in studies using the R statistical language.

The flow chart below shows a schematic of the workflow of this study.

[1] While 50 copies was a common level for detection limit until 2024, since then it has been reduced to 30 or 20 copies depending on the measurement technology used. I am using 50 here as the purpose is to explore the bias and variance of samples rather than to test the detection limit itself.

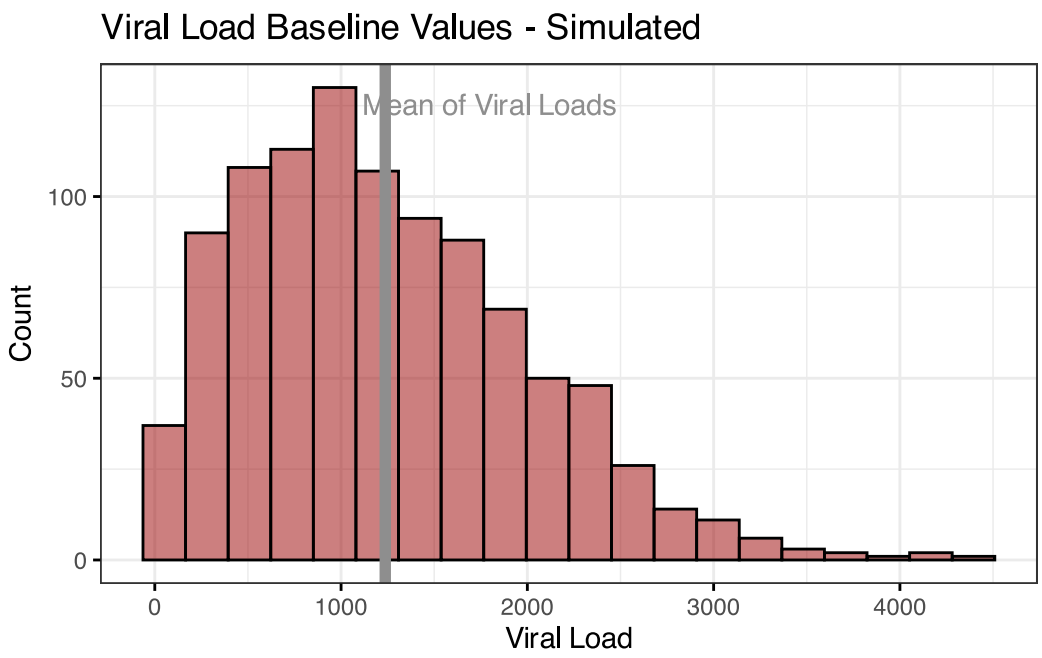
[2] While unrealistic, this large reduction is useful to give us a number of values BDL that can be tested against the 4 strategies.



Baseline

```
Descriptive Statistics
bl
N: 1000

                     bl
------------- ---------
         Mean   1237.22
      Std.Dev    753.15
          Min     51.00
       Median   1116.50
          Max   4395.00
          IQR   1058.25
           CV      0.61
```

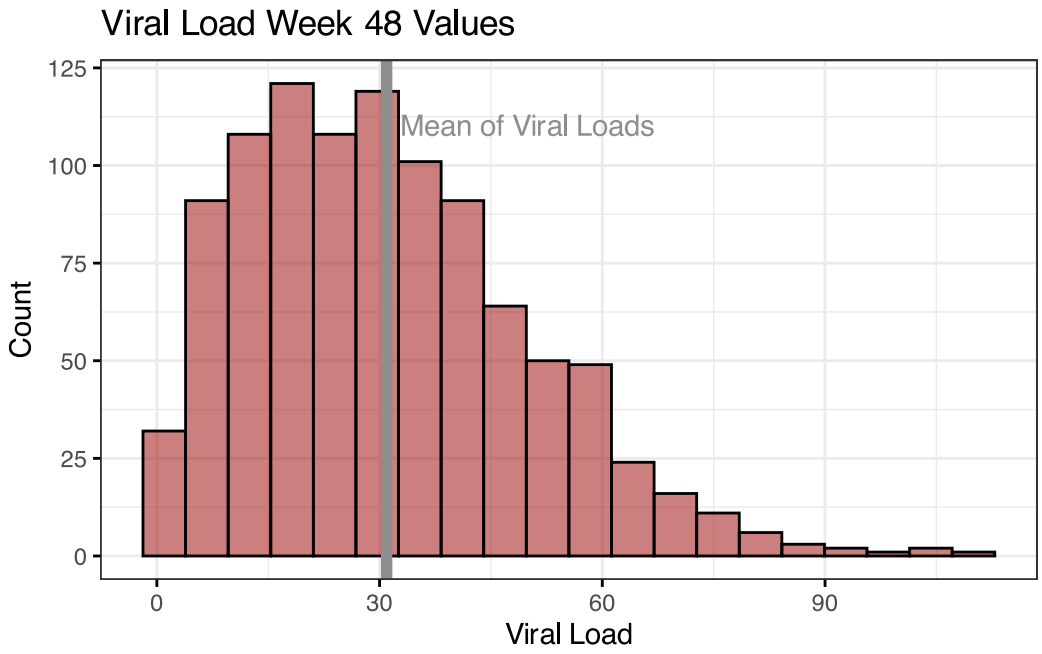


Week 48 Viral Load

We will calculate the viral load at 48 weeks to be 97.5% less than the original viral load.

```
Descriptive Statistics
bldf$w48
N: 1000

                  w48
------------- --------
         Mean    30.95
      Std.Dev    18.84
          Min     1.00
       Median    28.00
          Max   110.00
          IQR    27.00
           CV     0.61
```



To give you an idea of what we have now, here are the first 10 cases in our dataset. While we know the true values of the viral load, the assay itself will only give us a BDL signal instead of the value. This occurs 835 times out of the 1,000 cases. The question is what can we do about it and what does that do to the distribution of viral loads that we are trying to use to make an inference about HIV-1 treatment strategies.

	Week 48	
Baseline	True Value	BDL
2,271	57	57
335	8	bdl
1,263	32	bdl
1,533	38	bdl
1,304	33	bdl
794	20	bdl
2,412	60	60
805	20	bdl
2,918	73	73
837	21	bdl

Bibliography

[1] G. C. Chang *et al.*, “Brief Report: Undetectable HIV-1 Viral Load Among Virally Suppressed People Living With HIV: Implications for Undetectable Equals Untransmittable (U=U) in Resource-Limited Settings Using Dried Spot Testing,” *Journal of Acquired Immune Deficiency Syndromes (1999)*, vol. 100, no. 4, pp. 289–293, Dec. 2025, doi: 10.1097/QAI.0000000000003745.

[2] C. Combescure *et al.*, “How reliable is an undetectable viral load?,” *HIV medicine*, vol. 10, no. 8, pp. 470–476, Sep. 2009, doi: 10.1111/j.1468-1293.2009.00714.x.

[3] N. Siccha, “Lower limits of detection or quantification.” [Online]. Available: https://www.generable.com/post/lloqs?utm_source=substack&utm_medium=email

[4] J. L. Lennox *et al.*, “Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial,” *Lancet (London, England)*, vol. 374, no. 9692, pp. 796–806, Sep. 2009, doi: 10.1016/S0140-6736(09)60918-1.

[5] S. L. Walmsley *et al.*, “Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection,” *The New England Journal of Medicine*, vol. 369, no. 19, pp. 1807–1818, Nov. 2013, doi: 10.1056/NEJMoa1215541.

[6] O. Mersmann, H. Trautmann, D. Steuer, and B. Bornkamp, *Truncated Normal Distribution*. 2023. [Online]. Available: https://github.com/olafmersmann/truncnorm