Multi-class Discriminative Classification Model on Antiretroviral Therapy Reaction and Failure Developed on the Unique Records of the Akwa Ibom HIV Database

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Introduction

- HIV has no known cure, but the infected patient is treated with highly active antiretroviral therapy (HAART) [3], mainly for the purpose of suppressing the viral load (the amount of HIV in the blood stream) and prolonging the life expectancy of the patient (Ekpenyong, Etebong, and Jackson 2019, 1).

-Current antiretroviral therapy does not cure HIV infection but allows a person's immune system to get stronger. This helps them to fight other infections (World Health Organization, n.d.)

- machine learning

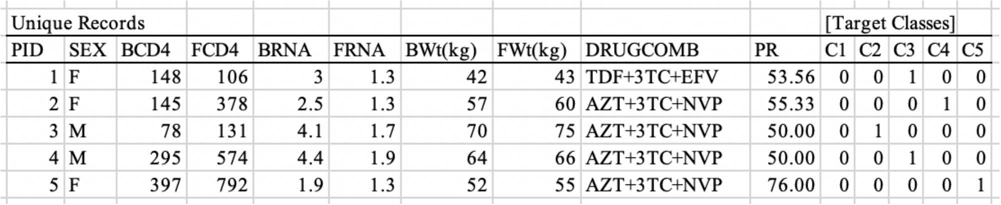
This undertaking is part of the capstone in the Professional Certificate Program in Data Science of Harvard Online. The corresponding R Markdown and R files are in the GitHub of nsmacaspac.

Unique Records of the Akwa Ibom HIV Database

In a previous study on patient response to antiretroviral therapy, Ekpenyong, Etebong, and Jackson (2019, 3) used a database of patients who received treatment for HIV from thirteen health centers in Akwa Ibom, Nigeria, between 2015 and 2018. Two years later, they published the processed dataset (Ekpenyong et al. 2021b, Appendix) with minor oversight in the accompanying article, which were easily reconciled through the 2019 study and were appropriately referenced throughout this project. The processed dataset is composed of an Individual Treatment Change Episodes table with a column for each antiretroviral drug administered and a concatenated Unique Records table with the drugs combined into a column for each antiretroviral therapy of three drugs administered. For the purpose of this project, we utilize only the Unique Records table.

The Unique Records table was imported with the corresponding read_xlsx function in the language R. The dataset is composed of 1,056 patient records, each with 15 columns: patient identification, sex, baseline CD4 count, follow-up CD4 count, baseline RNA load, follow-up RNA load, baseline weight, follow-up weight, drug combination, and patient response and drug reaction classifications 1 to 5 (fig. 1).

The immunological marker CD4 count is given in cells per cubic millimeter (Ekpenyong et al. 2021a, 8). The viral RNA load is expressed in times 10^2 copies (Ekpenyong, Etebong, and Jackson 2019, 10). The weight ranges from 4.7 to 125 kg on account of the presence of pediatric patients (Ekpenyong, Etebong, and Jackson 2019, 2). The three-drug combinations of antiretroviral therapy are a complementary mix of nucleoside reverse transcriptase inhibitors tenofovir (TDF), lamivudine (3TC) and zidovudine (AZT), and non-nucleoside reverse transcriptase inhibitors efavirenz (EFV) and nivarapine (NVP) given in the first 6 months of treatment (Ekpenyong et al. 2021a, 8).



Unique Records										[Target Classes]				
PID	SEX	BCD4	FCD4	BRNA	FRNA	BWt(kg)	FWt(kg)	DRUGCOMB	PR	C1	C2	C3	C4	C5
1	F	148	106	3	1.3	42	43	TDF+3TC+EFV	53.56	0	0	1	0	0
2	F	145	378	2.5	1.3	57	60	AZT+3TC+NVP	55.33	0	0	0	1	0
3	M	78	131	4.1	1.7	70	75	AZT+3TC+NVP	50.00	0	1	0	0	0
4	M	295	574	4.4	1.9	64	66	AZT+3TC+NVP	50.00	0	0	1	0	0
5	F	397	792	1.9	1.3	52	55	AZT+3TC+NVP	76.00	0	0	0	0	1

Figure 1: First rows of the Unique Records table of the Akwa Ibom HIV Database.

Patient response and drug reaction were quantified and classified in the 2019 study using expert domain knowledge and the advanced method of interval type-2 fuzzy logic system (Ekpenyong, Etebong, and Jackson 2019, 4, 7). The drug reaction classification uses a binary system to indicate very high interaction (C1), high interaction (C2), low interaction (C3), very low interaction (C4), and no interaction (C5; Ekpenyong, Etebong, and Jackson 2019, 11). A low response rate signifies high to very high drug interactions and treatment failure, whereas a high response rate denotes low to no drug interactions (Ekpenyong, Etebong, and Jackson 2019, 10, 13).

Tidy Dataset

The dataset was rendered into tidy format to prepare it for preprocessing. The fifteen columns were renamed consistently with their aforementioned descriptions, with vhi_tf corresponding to very high interaction_treatment failure and ni corresponding to no interaction. Missing values were not detected.

```
colnames(dataset) <- c("id", "sex", "bcd4", "fcd4", "brna", "frna", "bweight", "fweight", "therapy", "r
head(dataset, n = 5)
##   id sex bcd4 fcd4 brna frna bweight fweight     therapy response vhi_tf hi_tf
## 1  1   F  148  106  3.0  1.3      42      43 TDF+3TC+EFV 53.56199      0     0
## 2  2   F  145  378  2.5  1.3      57      60 AZT+3TC+NVP 55.33422      0     0
## 3  3   M   78  131  4.1  1.7      70      75 AZT+3TC+NVP 50.00000      0     1
## 4  4   M  295  574  4.4  1.9      64      66 AZT+3TC+NVP 50.00000      0     0
## 5  5   F  397  792  1.9  1.3      52      55 AZT+3TC+NVP 76.00000      0     0
##   li vli ni
## 1  1   0  0
## 2  0   1  0
## 3  0   0  0
## 4  1   0  0
## 5  0   0  1
```

The brna and frna columns were multiplied by 10^2 to simplify the unit from times 10^2 copies to just copies. This aligns them with the unit used for viral RNA load in the WHO definition of HIV (World Health Organization, n.d.).

The vhi_tf, hi_tf, li, vli, and ni columns were verified to have only one value per row. Hence, the binary system was relabeled as vhi_tf to ni using the case_when function and merged under a newly defined dreaction column. This brought down the number of columns to eleven.

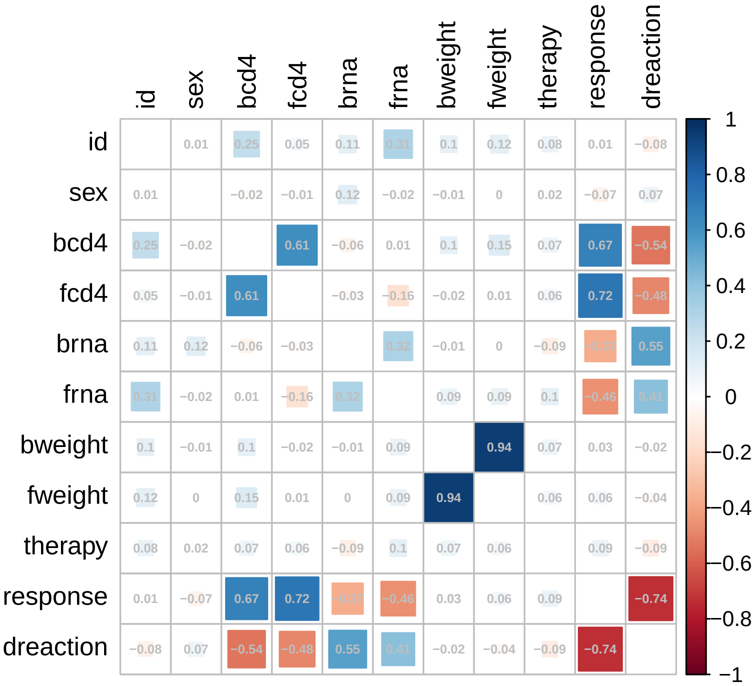
```
dataset1 <- dataset |>
  mutate(brna = brna*10^2) |>
  mutate(frna = frna*10^2) |> # simplifies the unit from times 10^2 copies to just copies
  mutate(dreaction = case_when(vhi_tf == 1 ~ "vhi_tf",
                               hi_tf == 1 ~ "hi_tf",
                               li == 1 ~ "li",
                              vli == 1 ~ "vli",
                              ni == 1 ~ "ni")) |> # relabels drug reactions as vhi_tf to ni and merges
  select(-vhi_tf, -hi_tf, -li, -vli, -ni)
head(dataset1, n = 5)
##   id sex bcd4 fcd4 brna frna bweight fweight     therapy response dreaction
## 1  1   F  148  106  300  130      42      43 TDF+3TC+EFV 53.56199        li
## 2  2   F  145  378  250  130      57      60 AZT+3TC+NVP 55.33422       vli
## 3  3   M   78  131  410  170      70      75 AZT+3TC+NVP 50.00000     hi_tf
## 4  4   M  295  574  440  190      64      66 AZT+3TC+NVP 50.00000        li
## 5  5   F  397  792  190  130      52      55 AZT+3TC+NVP 76.00000        ni
```

Preprocessed Dataset

The sex, therapy, and dreaction variables of the dataset were changed from character to numeric class using the factor and as.numeric functions to allow for numerical data examination. All eleven variables showed good data variability.

??? DISTRIBUTION

The correlation coefficients across variables were calculated and visualized using the cor and corrplot functions (fig. 2; Wei and Simko 2021).



	id	sex	bcd4	fcd4	brna	frna	bweight	fweight	therapy	response	dreaction
id		0.01	0.25	0.05	0.11	0.31	0.1	0.12	0.08	0.01	−0.08
sex	0.01		−0.02	−0.01	0.12	−0.02	−0.01	0	0.02	−0.07	0.07
bcd4	0.25	−0.02		0.61	−0.06	0.01	0.1	0.15	0.07	0.67	−0.54
fcd4	0.05	−0.01	0.61		−0.03	−0.16	−0.02	0.01	0.06	0.72	−0.48
brna	0.11	0.12	−0.06	−0.03		0.32	−0.01	0	−0.09	−0.37	0.55
frna	0.31	−0.02	0.01	−0.16	0.32		0.09	0.09	0.1	−0.46	0.41
bweight	0.1	−0.01	0.1	−0.02	−0.01	0.09		0.94	0.07	0.03	−0.02
fweight	0.12	0	0.15	0.01	0	0.09	0.94		0.06	0.06	−0.04
therapy	0.08	0.02	0.07	0.06	−0.09	0.1	0.07	0.06		0.09	−0.09
response	0.01	−0.07	0.67	0.72	−0.37	−0.46	0.03	0.06	0.09		−0.74
dreaction	−0.08	0.07	−0.54	−0.48	0.55	0.41	−0.02	−0.04	−0.09	−0.74	

Figure 2: Matrix of the correlation coefficients between variables.

Patient response and drug reaction highly correlated with each other, having an absolute coefficient of 74% (fig. 2). This was expected as they refer to similar information. Hence, only the dreaction variable was retained as an outcome for the purpose of this project.

On the other hand, CD4 count was negatively correlated with drug reaction (-48% and -54%) whereas RNA load was positively correlated with it (41% and 55%), while having minimal correlation with each other (fig. 2). This meant that the bcd4, fcd4, brna and frna variables contained distinct information relevant to drug reaction and were kept as predictors.

The preprocessed dataset was streamlined to contain only these pertinent predictors and outcome for faster classification modeling. The dreaction variable was changed from character to factor class as required for outcomes in classification models.

```
dataset2 <- dataset1 |>
  select(bcd4, fcd4, brna, frna, dreaction) |> # keeps CD4 count and RNA load as predictors and drug re
  mutate(dreaction = factor(dreaction, c("ni", "vli", "li", "hi_tf", "vhi_tf")))
head(dataset2, n = 5)
##   bcd4 fcd4 brna frna dreaction
## 1  148  106  300  130        li
## 2  145  378  250  130       vli
## 3   78  131  410  170     hi_tf
## 4  295  574  440  190        li
## 5  397  792  190  130        ni
```

Predictors

The predictors CD4 count and RNA load are measures of immune system health and HIV status, respectively (Ekpenyong, Etebong, and Jackson 2019, 10; World Health Organization, n.d.). They are crucial markers of drug reaction and treatment failure that can be obtained from simple laboratory tests in settings with limited resources for the costly HIV genotyping to determine drug resistance (Isaakidis et al. 2010, 7; Revell et al. 2010, 605).

The interactions of these predictors with drug reaction were further visualized using ggplot2 functions (fig. 3). The plots showed a general increase in CD4 count and decrease in RNA load at follow-up. This indicated the robustness of the immune system of most patients in suppressing the HIV and positive patient response to the treatment (Ekpenyong, Etebong, and Jackson 2019, 10).

However, the plots also exhibited patients who retained a low CD4 count and high RNA load at follow-up (fig. 3). They were the same cases classified as with high drug interaction and treatment failure.

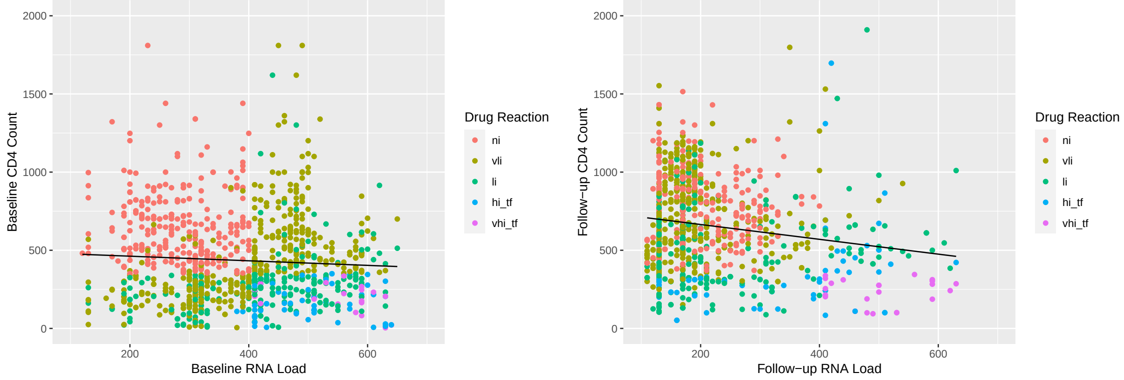


Figure 3: Scatterplots of CD4 count, RNA load, and the corresponding drug reaction at baseline and follow-up.

Classification Models

In the final dataset with the bcd4, fcd4, brna, and frna variables as predictors and the dreaction variable as outcome, there were only 1,056 observations. The dataset was split into 80% train set and 20% test set using the createDataPartition function to maximize the data available for both training and testing. The function additionally preserved the distribution of the five outcome classes of the dreaction variable: ni, vli, li, hi_tf, and vhi_tf (Kuhn 2019).

```r
set.seed(20, sample.kind = "Rounding") # if using R 3.6 or later
# set.seed(20) # if using R 3.5 or earlier
# for reproducibility during assessment
train_index <- createDataPartition(dataset2$dreaction, p = 0.8, list = FALSE)
train_set <- dataset2[train_index,]
test_set <- dataset2[-train_index,]
```

Classification models introduced in the program that can possibly accommodate the nonlinear nature of the decision boundaries of the outcome classes (similar to what was observed in fig. 3) were successively trained on the train set with the train function. We discuss them in the following subsections. The streamlined dataset allowed for the use of the default resampling method of the function that is bootstrapping for twenty-five times, which would have been time-consuming otherwise. Thereafter, the models were evaluated for the accuracy of their outcome prediction in the test set.

k-Nearest Neighbor Classification

-discriminative classification model(Haugh 2017)

- we find the k nearest neighbors of x and use majority voting of these neighbors to classify x … and that maximizes the accuracy (Irizarry 2002)
- kNN is easier to adapt to non-linear dimensions (Irizarry 2002)
- accuracy, proportion of predicted correctly (Irizarry 2002)
- check sensitivity and specificity to remove the clouding by the prevalence of our assessment (Irizarry 2002)
- ask if the prevalence of the outcome is expected to be the same in future data; is the sample biased? (Irizarry 2002)

The optimal model was tuned at 3 nearest neighbors.

Its predicted drug reaction was obtained using the predict function. This was compared with the observed drug reaction in the test set utilizing the confusionMatrix function, which resulted in an accuracy of 88%. This level of accuracy came with good sensitivity and specificity for most outcome classes, but the model had a low true positive detection rate for the class hi_tf.

```r
set.seed(30, sample.kind = "Rounding") # if using R 3.6 or later
# set.seed(30) # if using R 3.5 or earlier
knn_model <- train(dreaction ~ ., train_set, method = "knn", tuneGrid = data.frame(k = seq(3, 9, 1))) #
knn_model
## k-Nearest Neighbors
##
## 847 samples
##   4 predictor
##   5 classes: 'ni', 'vli', 'li', 'hi_tf', 'vhi_tf'
##
## No pre-processing
## Resampling: Bootstrapped (25 reps)
## Summary of sample sizes: 847, 847, 847, 847, 847, 847, ...
## Resampling results across tuning parameters:
##
##   k  Accuracy  Kappa
##   3  0.804     0.719
##   4  0.797     0.710
##   5  0.799     0.711
##   6  0.797     0.709
##   7  0.796     0.707
##   8  0.798     0.710
##   9  0.798     0.710
##
## Accuracy was used to select the optimal model using the largest value.
## The final value used for the model was k = 3.

knn_dreaction <- predict(knn_model, test_set)
head(knn_dreaction)
## [1] hi_tf  li     vhi_tf li     vli    vli
## Levels: ni vli li hi_tf vhi_tf

confusionMatrix(knn_dreaction, test_set$dreaction)$overall["Accuracy"]
## Accuracy
##     0.88
confusionMatrix(knn_dreaction, test_set$dreaction)$byClass[, 1:2]
##               Sensitivity Specificity
## Class: ni           0.932       0.967
## Class: vli          0.893       0.920
## Class: li           0.854       0.957
## Class: hi_tf        0.615       0.995
## Class: vhi_tf       1.000       0.990
```

Recursive Partitioning and Regression Trees Model

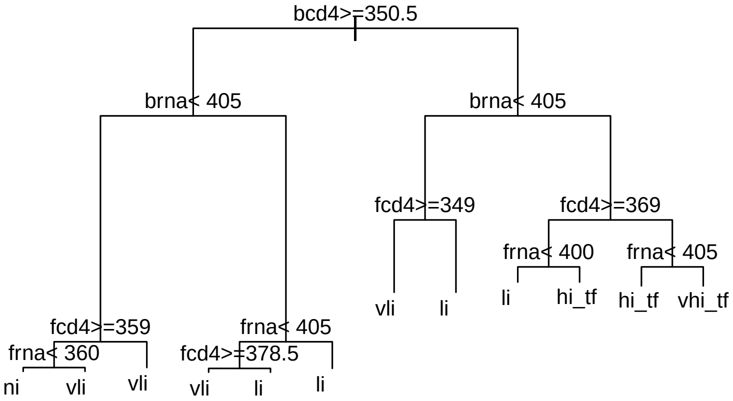
-discriminative classification model (Haugh 2017)

The model was optimized at a complexity parameter of 0. It was visualized as shown with the plot and text functions for easy interpretation (Irizarry 2002).

The accuracy of its outcome prediction was at 97.6%, higher than that from the k-Nearest Neighbor Classification and with high sensitivity and specificity for all outcome classes.

```
set.seed(40, sample.kind = "Rounding") # if using R 3.6 or later
# set.seed(40) # if using R 3.5 or earlier
rpart_model <- train(dreaction ~ ., train_set, method = "rpart", tuneGrid = data.frame(cp = seq(0, 0.1,
rpart_model
## CART
##
## 847 samples
##   4 predictor
##   5 classes: 'ni', 'vli', 'li', 'hi_tf', 'vhi_tf'
##
## No pre-processing
## Resampling: Bootstrapped (25 reps)
## Summary of sample sizes: 847, 847, 847, 847, 847, 847, ...
## Resampling results across tuning parameters:
```

```
##
##   cp    Accuracy  Kappa
##   0.00  0.961     0.944
##   0.01  0.959     0.942
##   0.02  0.950     0.929
##   0.03  0.923     0.890
##   0.04  0.907     0.866
##   0.05  0.898     0.853
##   0.06  0.888     0.838
##   0.07  0.875     0.819
##   0.08  0.866     0.805
##   0.09  0.856     0.790
##   0.10  0.839     0.763
##
## Accuracy was used to select the optimal model using the largest value.
## The final value used for the model was cp = 0.
plot(rpart_model$finalModel, margin = 0.05) # margin adjusts the plot size
text(rpart_model$finalModel, cex = 0.8) # cex adjusts the label size
```



```
rpart_dreaction <- predict(rpart_model, test_set)

confusionMatrix(rpart_dreaction, test_set$dreaction)$overall["Accuracy"]
## Accuracy
##    0.976
confusionMatrix(rpart_dreaction, test_set$dreaction)$byClass[, 1:2]
##                Sensitivity Specificity
## Class: ni            0.966       1.000
## Class: vli           1.000       0.984
## Class: li            0.958       0.994
## Class: hi_tf        0.923       0.990
## Class: vhi_tf       1.000       1.000
```

Rborist Model

-discriminative classification model (Haugh 2017)

- The goal is to improve prediction performance and reduce instability by averaging multiple decision trees (Irizarry 2002)
- A disadvantage of random forests is that we lose interpretability. An approach that helps with interpretability is to examine variable importance. varImp function to know which predictors are used the most (Irizarry 2002)

The optimal model was tuned at 4 predictors to test for a given split and a minimum node size of 1. The baseline RNA load is the most important predictor.

Its predicted drug reaction had an accuracy of 99%, higher than those from the k-Nearest Neighbor Classification and the Recursive Partitioning and Regression Trees model. This accuracy was accompanied by excellent sensitivity and specificity for all outcome classes.

```
## Random Forest
##
## 847 samples
##   4 predictor
##   5 classes: 'ni', 'vli', 'li', 'hi_tf', 'vhi_tf'
##
## No pre-processing
## Resampling: Bootstrapped (25 reps)
## Summary of sample sizes: 847, 847, 847, 847, 847, 847, ...
## Resampling results across tuning parameters:
##
##   predFixed  minNode  Accuracy  Kappa
##   1          1        0.964     0.949
##   1          2        0.965     0.950
##   1          3        0.964     0.948
##   1          4        0.963     0.947
##   2          1        0.975     0.964
##   2          2        0.975     0.964
##   2          3        0.975     0.964
##   2          4        0.975     0.964
##   3          1        0.977     0.967
##   3          2        0.977     0.967
##   3          3        0.977     0.967
##   3          4        0.977     0.966
##   4          1        0.977     0.968
##   4          2        0.977     0.968
##   4          3        0.977     0.967
##   4          4        0.977     0.967
##
## Accuracy was used to select the optimal model using the largest value.
## The final values used for the model were predFixed = 4 and minNode = 1.
## Rborist variable importance
```

```
##
##      Overall
## brna   100.0
## fcd4    44.9
## bcd4     7.5
## frna     0.0
## Accuracy
##     0.99
##               Sensitivity Specificity
## Class: ni           1.000        1.00
## Class: vli          1.000        1.00
## Class: li           0.958        1.00
## Class: hi_tf        1.000        0.99
## Class: vhi_tf       1.000        1.00
```

Quadratic Discriminant Analysis

-generative classification model (Haugh 2017)

-The quadratic discriminant analysis is generally preferred due to greater flexibility of the decision boundaries (Haugh 2017)

The accuracy of its outcome prediction was at 76.1%, lower than those from the k-Nearest Neighbor Classification, the Recursive Partitioning and Regression Trees model, and the Rborist model. The accuracy came with good specificity, but the model had mediocre true positive detection rates for the classes li and hi_tf.

```
## Quadratic Discriminant Analysis
##
## 847 samples
##   4 predictor
##   5 classes: 'ni', 'vli', 'li', 'hi_tf', 'vhi_tf'
##
## No pre-processing
## Resampling: Bootstrapped (25 reps)
## Summary of sample sizes: 847, 847, 847, 847, 847, 847, ...
## Resampling results:
##
##   Accuracy  Kappa
##   0.727     0.601
## Accuracy
##    0.761
##               Sensitivity Specificity
## Class: ni           0.814       0.980
## Class: vli          0.798       0.800
## Class: li           0.646       0.870
## Class: hi_tf        0.615       1.000
## Class: vhi_tf       1.000       0.995
```

Multi-class Discriminative Classification Model

- discriminatuve classification model (Haugh 2017)
- results of model performances

- the model with the best predictions on new data
- Two RF models were trained using .8000 TCEs without the use of genotypes, one with comprehensive and one with simplified treatment history information. Both models predicted virological response for 400 independent test cases with an accuracy of 82%. The models were able to identify alternative regimens (involving the same restricted range of drugs) that they predicted would have reduced viral load to below 50 copies/mL in almost half of the cases of actual treatment failure.11 They identified regimens that were predicted to be more effective than those that failed in almost all cases. A secondary analysis of the input variables used for these models revealed that the baseline viral load was by far the most important variable (considerably more so than CD4 counts, for example) for the models in making these predictions. These studies suggest that with viral load monitoring in place, computational models could play an important future role in optimizing antiretroviral therapy in resource-limited settings. (Revell et al. 2010, 606)

Conclusion

- therapy is not a predictor.

-it must be noted that, due to the limited resources in the Nigerian environment, only 5 drugs combined into 3 therapies were possible (Ekpenyong, Etebong, and Jackson 2019, 3)

- meaningful decisions on antiretroviral therapy administration
- it shall aid physicians on more proactive detection of acute interaction as well as early referrals of patients with failed treatments, for immediate change in treatment episode (Ekpenyong, Etebong, and Jackson 2019, 2)

References

Ekpenyong, Moses E., Mercy E. Edoho, Ifiok J. Udo, Philip I. Etebong, Nseobong P. Uto, Tenderwealth C. Jackson, and Nkem M. Obiakor. 2021a. “A Transfer Learning Approach to Drug Resistance Classification in Mixed HIV Dataset.” *Informatics in Medicine Unlocked* 24: 100568. https://doi.org/10.1016/j.imu.2021.100568.

Ekpenyong, Moses E., Philip I. Etebong, and Tenderwealth C. Jackson. 2019.”Fuzzy-Multidimensional Deep Learning for Efficient Prediction of Patient Response to Antiretroviral Therapy.” *Heliyon* 5: e02080. https://doi.org/10.1016/j.heliyon.2019.e02080.

Ekpenyong, Moses E., Philip I. Etebong, Tenderwealth C. Jackson, and Edidiong J. Udofa. 2021b.”Processed HIV Prognostic Dataset for Control Experiments.” *Data in Brief* 36: 107147. https://doi.org/10.1016/j.dib.2021.107147.

Haugh, Martin. 2017. “IEOR E4525: Machine Learning for OR & FE (Columbia University).” Accessed August 15, 2023. http://www.columbia.edu/~mh2078/ML_ORFE.html.

Irizarry, Rafael A. 2002. *Introduction to Data Science: Data Analysis and Prediction Algorithms with R.* http://rafalab.dfci.harvard.edu/dsbook/.

Isaakidis, Petros, Marie-Eve Raguenaud, Vantha Te, Chhraing S. Tray, Kazumi Akao, Varun Kumar, Sopheak Ngin, Eric Nerrienet, and Rony Zachariah. 2010. “High Survival and Treatment Success Sustained After Two and Three Years of First-line ART for Children in Cambodia.” *Journal of the International AIDS Society* 13: 11. https://doi.org/10.1186/1758-2652-13-11.

Kuhn, Max. 2019. “The caret Package.” Last modified March 27, 2019. https://topepo.github.io/caret/.

Revell, A. D., D. Wang, R. Harrigan, R. L. Hamers, A. M. J. Wensing, F. DeWolf, M. Nelson, A.-M. Geretti, and B. A. Larder. 2010. “Modelling Response to HIV Therapy Without a Genotype: An Argument for

Viral Load Monitoring in Resource-Limited Settings." *Journal of Antimicrobial Chemotherapy* 65: 605-607. https://doi.org/10.1093/jac/dkq032.

Wei, Taiyun, and Viliam Simko. 2021. "An Introduction to corrplot Package." Last modified November 18, 2021. https://cran.r-project.org/web/packages/corrplot/vignettes/corrplot-intro.html.

World Health Organization, n.d. "HIV." Accessed July 21, 2023. https://www.who.int/health-topics/hiv-aids#tab=tab_1.