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Modeling Sequential Adverse Events of HIV/AIDS: Transition-Specific Parametric Multi-state Model

Zelalem Dessie[1] , Temesgen Zewotir[1], Henry Mwambi[1] and Delia North[1]

[1]University of KwaZulu-Natal, South Africa

Abstract

Background: HIV infected ART naive patients may experience many intermediate events including between-event transition throughout the duration of their follow up. Through modeling these transitions, we can get a deeper understanding of HIV disease process and progression and factors that influence disease process and progression pathway. In this work, we present transition-specific parametric multi-state models to describe HIV disease process and progression.

Methods: The data is from an ongoing prospective cohort study conducted amongst adult women who were HIV-infected in Kwazulu-Natal, South Africa. Participants were enrolled into the acute HIV Infection phase, and then followed up during chronic infection and up to ART initiation.

Results: Transition specific distributions for multi-state models, including a variety of accelerated failure time (AFT) and proportional hazards models (PH), were presented and compared in this study. The analysis revealed that women enrolling with lower CD4 count (sever and advanced diseasing stage) had a far lower chance on immune recovery, and a considerably higher chance of immune deterioration compared to those women enrolling with a CD4 count greater than 350 (mild and normal diseasing stage). Our analyses also revealed that middle age, higher educational levels, higher scores for red blood cell counts, higher mononuclear scores, higher granulocytes scores and higher physical health score, all had a significant effect on a shortened time to immunological recovery, while women with many sex partners, higher viral load and larger family size had a significant effect on accelerating time to recurrence.

Conclusion: Multi-state modelling of transition specific distributions offers a flexible tool for the study of demographic and clinical characteristics affects on entire disease progression pathway. It is hoped that the article will help applied researchers to familiarize with the models and including interpretation of results.

Background

- AIDS which is caused by HIV has been the major problem worldwide.
- The disease being one without any cure is still accountable for social, health and economic crises in many developing countries.
- Despite the decline in the HIV mortality, a better understanding of patient trajectories and the entire progression pathway, is of great importance in order to improving survival of HIV infected patients.

Background Continued

- Multi-state is very useful for giving a better understanding of HIV disease process and progression over time.
- Most methodological developments have generally focused on semi-parametric as the fundamental framework of the multi-state model.
- The basis of this paper is the modeling of time to sequential adverse events of HIV/AIDS, using transition specific parametric distributions for multi-state models

Data

- CAPRISA 002, 004 and 008 massive datasets
- They are ongoing prospective cohort study in KZN, Durban, South Africa.

Factor Analyses of Clinical Parameters

White blood cell parameters	Rotated Factors		
	1. Granulocytes comp	2. Mononuclear comp	3. Eosinophils comp
Leucocyte	**0.925**	0.282	0.146
Neutrophils	**0.936**	-0.158	0.022
Lymphocytes	0.226	**0.838**	-0.109
Monocytes	**0.635**	0.417	-0.032
Eosinophils	0.085	0.058	**0.947**
Basophils	-0.035	**0.616**	0.339

Red Blood cell Parameters	Rotated Factors	
	1. Hb and Haematocrit Comp	2. Red blood cell indices Comp
RBC counts	**0.946**	-0.130
Hb	**0.886**	0.439
Haematocrit	**0.919**	0.366
MCV	0.075	**0.953**
MCH	0.024	**0.825**
MCHC	0.201	**0.521**
RDW	-0.382	**-0.592**

Blood Chemistry items	Rotated Factors	
	1. Liver Abnormality Comp	2. Electrolyte Comp
Chloride	-0.023	**0.455**
Alkaline	0.174	0.032
ALT(GPT)	**0.829**	-0.073
AST (GOT)	**0.967**	-0.122
Sodium	0.103	**0.994**
Calcium	-0.020	**0.213**
LDH	0.052	**-0.769**
Total protein	-0.009	**0.670**

Proc factor .....

- ✓ White blood cell parameters
  - ➢ F1:Granulocytes comp
  - ➢ F2:Mononuclear comp
  - ➢ F3:Eosinophils comp

  81%
- ✓ Red blood cell parameters
  - ➢ F1:H&H comp
  - ➢ F2:RBC indices comp

  77%
- ✓ Blood Chemistry
  - ➢ F1: Liver abnormality comp
  - ➢ F2: Electrolyte comp

  85%

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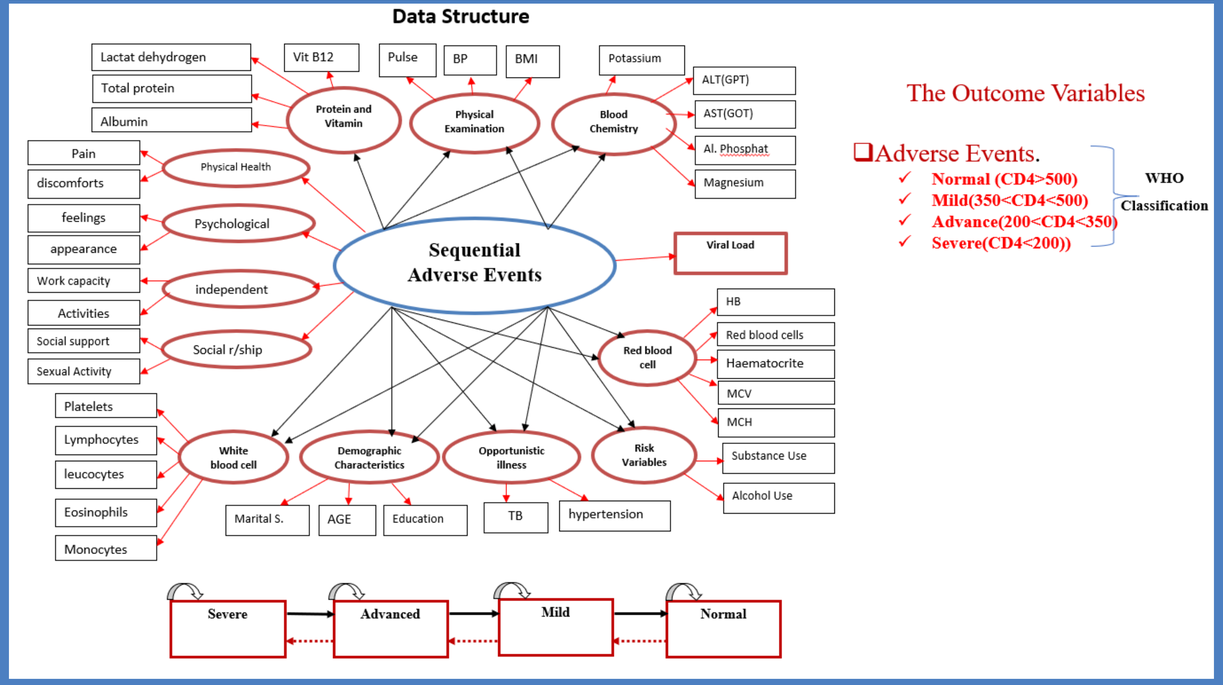
Data Continued



The Outcome Variables

- Adverse Events.
  - ✓ Normal (CD4>500)
  - ✓ Mild(350<CD4<500)
  - ✓ Advance(200<CD4<350)
  - ✓ Severe(CD4<200))

WHO Classification

Multi-State Model

- The transitions are to be modelled by a four-state multi-state model.
- Transition probabilities between two states i and j relative to the given process history, are defined as

$$P_{ij}(s,t) = P(Y(t) = j | Y(s) = i, H_s) \quad for\ i,j \in S\ and\ s,t \in T$$

Multi-State Model Continued

$$h_{ij}(t) = \lim_{\delta t \to 0} \frac{P(Y(t+\delta t) = j | Y(s) = i)}{\delta t}$$

- Alternatively, we can describe the model indexing by transition. Therefore, for the kth transition from state ak to state bk, we have

$$h_k(t) = \lim_{\delta t \to 0} \frac{P(Y(t+\delta t) = b_k | Y(s) = a_k)}{\delta t}$$

- We provide a variety of distributional choices including the Exponential, Weibull, Log-logistic, Log-normal and Generalized Gamma distribution
- A multistate model can be specified by a combination of transition-specific survival models.
- The most convenient way to do this is through the stacked data notation, where a patient has a row of data for each transition that they are at risk for, using start and stop notation.
- We provide a variety of distributional choices including the Exponential, Weibull, Log-logistic, Log-normal and Generalized Gamma distribution.
- For example we used:-
  - The PH representation of kth transition the Weibull model

$$h_k(t;X) = \lambda\gamma t^{\gamma-1} \exp(X_k\beta_k),$$

  - The AFT representation of kth transition the Weibull model

$$h_k(t;X) = \frac{1}{\sigma} t^{\frac{1}{\sigma}-1} \exp\left(\frac{-\mu - X_k\alpha_k}{\sigma}\right)$$

- The implementation was carried out using:-

Proc NLMIXED.....

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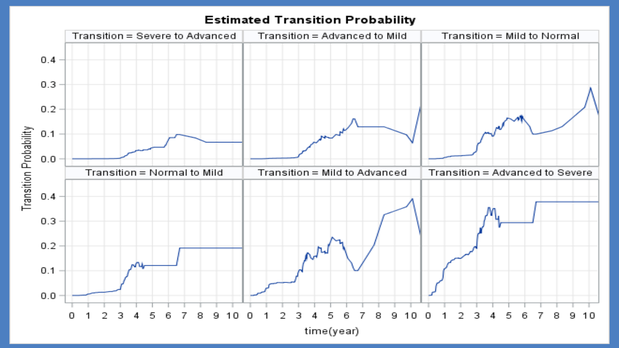
Multi-State Model Continued

❑ We also calculated and plotted the transition probabilities using :- %PTRANSIT Macro and PROC SGPANEL .....

Results and discussion

Estimated Transition Probability



✓Women enrolling with lower CD4 count (sever and advanced diseasing stage) had a far lower chance on immune recovery

✓It has a higher chance of immune deterioration compared to those women enrolling with a CD4 count greater than 350 (mild and normal diseasing stage)

Model Selection

Transition	Criteria	Exp.	Weibull	Log-logistic	Log-Normal	Gen-Gamma
1	AIC	341.37	322.52	375.61	**321.32**	323.16
	BIC	426.98	411.29	470.90	**410.09**	415.09
2	AIC	1606.12	1538.31	**1524.84**	1528.19	1527.79
	BIC	1741.73	1678.95	**1665.48**	1668.82	1673.46
3	AIC	2185.01	**2109.77**	2117.94	2114.48	2117.64
	BIC	2335.51	**2265.84**	2265.01	2270.55	2289.44
4	AIC	2021.85	1880.14	**1867.61**	2114.48	1868.15
	BIC	2168.97	2032.71	**2020.17**	2270.56	2026.17
5	AIC	1992.44	1841.26	**1822.15**	1887.68	1824.26
	BIC	2143.07	1997.47	**1978.35**	2040.24	1986.04
6	AIC	690.28	638.59	**633.21**	636.67	637.12
	BIC	825.39	778.69	**773.32**	776.78	782.23

✓ The best fitting model for transition 1 was found to be the Log-Normal model

✓ The best fitting model for transition 2, 4, 5 and 6 was found to be the Log-logistic model

✓ The best fitting model for transition 5 and 6 was found to be the Weibull model

Results Continued

Transition-Specific Parametric Multi-state Results

Variables	Transition 1: Severe to Advanced	Transition 2: Advanced to Mild	Transition 3: Mild to Normal	Transition 4: Normal to Mild	Transition 5: Mild to Advanced	Transition 6: Advanced to Severe
Viral Load	-0.23(-0.49, 0.03)	**0.07(0.03, 0.17)***	**0.10(0.01, 0.19)****	**-0.35(-0.43, -0.26)***	**-0.35(-0.43, -0.26)***	**-0.39(-0.55, -0.23)***
Anemia: Yes	**0.54(0.13, 0.95)***	0.10(-0.09, 0.29)	0.14(-0.05, 0.33)	-0.02(-0.18, 0.14)	-0.13(-0.27, 0.02)	-0.29(-0.55, -0.04)
TB: No	**-0.22(-0.31, -0.14)***	0.12(-0.22, 0.46)	**-0.66(-1.13, -0.20)***	-0.16(-0.62, 0.29)	-0.25(-0.53, 0.03)	-0.10(-0.73, 0.52)
Marital Status: Married	0.14(-0.37, 0.65)	0.12(-0.10, 0.33)	0.06(-0.16, 0.29)	-0.02(-0.23, 0.19)	**0.33(0.16, 0.51)***	0.06(-0.29, 0.41)
Marital Status: Many Partners	**0.54(0.40, 0.68)***	0.13(-0.24, 0.49)	0.04(-0.37, 0.46)	-0.17(-0.53, 0.18)	0.44(-0.12, 0.76)	0.35(-0.18, 0.88)
Education:9-10 Grade	-0.14(-0.86, 0.58)	0.05(-0.25, 0.35)	-0.09(-0.41, 0.23)	**0.46(0.17, 0.75)***	0.08(-0.16, 0.32)	-0.20(-0.58, 0.19)
Education: ≥ 11Grade	-0.03(-0.65, 0.60)	0.06(-0.21, 0.32)	-0.16(-0.45, 0.12)	**0.30(0.02, 0.57)***	0.26(-0.05, 0.47)	0.30(-0.06, 0.65)
Age_Cat:21-39	-0.18(-0.74, 0.39)	-0.21(-0.44, 0.01)	-0.05(-0.26, 0.16)	-0.11(-0.30, 0.08)	-0.06(-0.24, 0.12)	0.02(-0.30, 0.35)
Age_Cat:>40	**0.16(0.03, 0.29)****	-0.52(-0.99, 0.06)	-0.46(-0.81, 0.10)	-0.16(-0.49, 0.17)	0.20(-0.15, 0.56)	0.43(-0.30, 1.16)
Sex while Drunk :No	**-0.10(-0.18, -0.02)***	0.19(-0.06, 0.44)	-0.02(-0.31, 0.26)	-0.06(-0.29, 0.18)	0.18(-0.05, 0.41)	**0.38(0.03, 0.72)***
Independence Score	0.02(-0.05, 0.09)	0.001(-0.03, 0.02)	-0.02(-0.04, 0.001)	**0.08(0.06, 0.10)***	**0.02(0.002, 0.04)***	**0.04(0.001, 0.09)***
Social relationship	0.01(-0.10, 0.10)	0.004(-0.03, 0.03)	0.06-(0.03, 0.08)	**0.03(0.01, 0.06)***	**0.02(0.004, 0.04)***	**0.05(0.01, 0.10)***
Physical Health Score	**-0.13(-0.23, -0.03)***	-0.01(-0.05, 0.04)	**-0.11(-0.16, -0.06)***	-0.18(-0.23, 0.13)	-0.04(-0.08, 0.001)	-0.02(-0.09, 0.04)
Psychological Score	0.10(-0.01, 0.20)	0.08(-0.04, 0.13)	0.10(-0.06, 0.14)	**0.16(0.11, 0.20)***	**0.08(0.04, 0.11)***	**0.07(0.00, 0.14)***
Liver Abn Comp	0.001(-0.18, 0.18)	**0.11(0.03, 0.20)****	-0.05(-0.13, 0.02)	0.04(-0.03, 0.10)	0.01(-0.06, 0.08)	-0.02(-0.11, 0.08)
RBC indices	0.07(-0.11, 0.25)	0.09(-0.001, 0.17)	-0.07(-0.15, 0.001)	0.03(-0.04, 0.10)	**0.08(0.01, 0.14)****	0.01(-0.11, 0.13)
Granulocytes comp	-0.01(-0.22, 0.20)	**-0.12(-0.20, -0.04)***	-0.08(-0.15, 0.001)	0.07(-0.001, 0.13)	0.08(-0.02, 0.15)	0.01(-0.11, 0.13)
Mononuclear comp	-0.18(-0.38, 0.03)	**-0.19(-0.25, -0.12)***	**-0.27(-0.34, -0.19)***	0.21(-0.13, 0.28)	**0.29(0.21, 0.36)****	**0.27(0.13, 0.42)****

Example of Interpretation:-

❑The viral load of a women in the study increases, the time from advanced to mild stages of the disease decelerated by a factors of 0.90 ($Time\ Ratio = e^{-\alpha} = e^{-0.11} = 0.90$)

❑The time from mild to normal diseasing stages of non TB co-infected women, was accelerated by a factors of 1.68 ($e^{-\alpha} = e^{0.52} = 1.68$), as compared to TB co-infected

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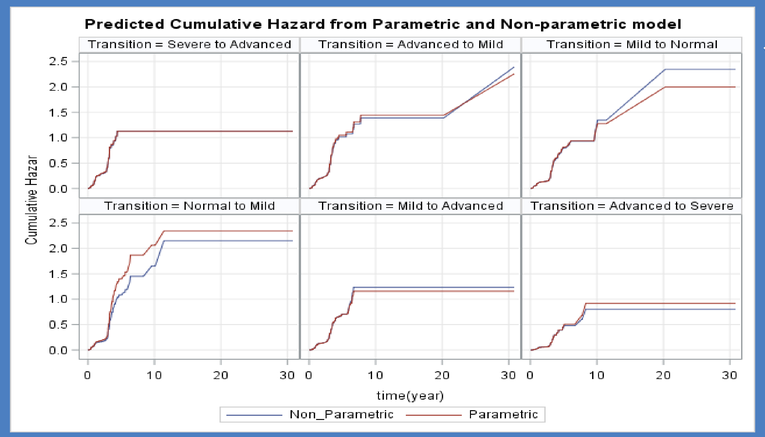
Results Continued

Model Diagnosis



- ✓ These comparisons showed the overall good performances of parametric transition specific multi-state model in terms of fit for the transition probabilities

Conclusion

- ❑ We have presented the use of transition specific distributions for multi-state models, allowing a wide variety of parametric distributional choices, including the combination of the PH model and AFT models.
- ❑ Women enrolling with lower CD4 count (sever and advanced diseasing stage) had a far lower chance on immune recovery compared to those women enrolling with a CD4 count greater than 350 (mild and normal diseasing stage)
- ❑ Women enrolling with lower CD4 count had higher chance of immune deterioration compared to those women enrolling with a CD4 count greater than 350.

Future Direction

- ✓ In future work, we plan to conduct complex statistical models such as multivariate structural equation model of ordinal clinical state, viral load and QOL of a patient on some relevant factor, covariates and latent variables

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