Evaluating Durability of First Line Antiretroviral Therapy with a Multi-state model

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Study objective

- To assess the rate of first line antiretroviral treatment modifications and compare durability of available first line ARVs

- To assess reasons for first line antiretroviral treatment modifications

- To investigate the rate of toxicity related treatment modification and identify robust treatments toward toxicity.

The Jimma HARRT Study

Description of the cohort

- Data for this study were obtained from a large outpatient HIV clinic in Jimma, South west Ethiopia.

- The hospital gives free ART service for people living in Jimma town and the neighbors

- HIV infected patients are started on ART when they manifest signs and symptoms of WHO Stage III or their CD4 count falls below 200 (modified to 350 after 2010)

- Those who start ART have a regular follow-up which includes clinical and immunological monitoring

The Jimma HARRT Study

Study population

- All patients initiating ART who were ART naive, aged 18 years or older and had an ART treatment start date in between Junary 1, 2007 to end of December, 2011 were eligible for this analysis

- The data was closed for analysis on the end of Augest, 2013

- 1453 patients were eligible but169 excluded because they were not followed up for more than 1 month.

- This left 1284 subjects for analysis.

The Jimma HARRT Study

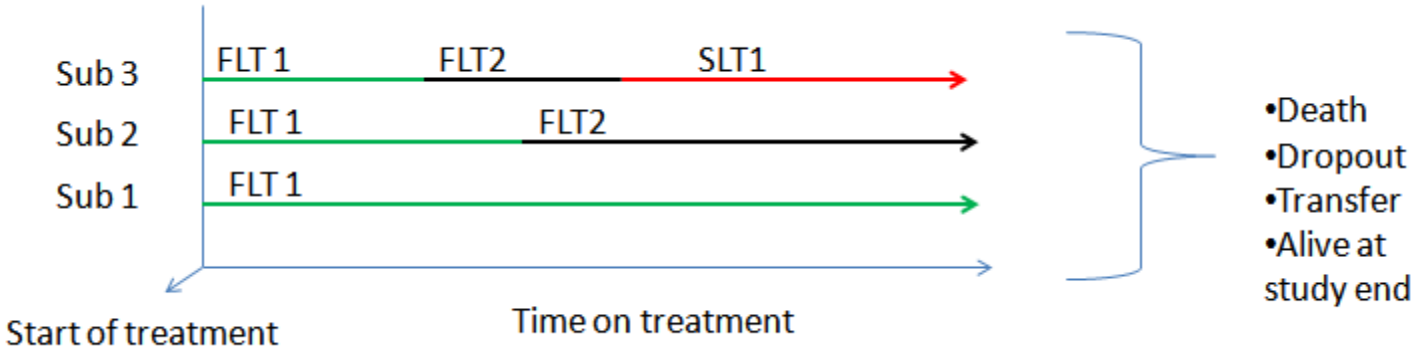
Baseline characteristics of study subjects.

Characteristics		n(%)
Gender (n(%))	Male	439(34.19)
	Female	845(68.81)
WHO Stage(n(%))	SI	372(28.97)
	SII	398(30.99)
	SIII	419(32.63)
	SIV	95(7.41)
Treatment at start(n(%))	d4T+3TC+NVP	526(40.96)
	d4T+3TC+EFV	67(5.22)
	AZT+3TC+NVP	185(14.41)
	AZT+3TC+EFV	82 (6.39)
	TDF+3TC+EFV	401(31.23)
	TDF+3TC+NVP	23(1.79)
Age (Median (IQR))		30 (26-35)
Baseline CD4 (Median (IQR))		137(78-201)
Status at the end(n(%))	Dead	52(4.05)
	Drop	197(15.34)
	Transfer	127(9.89)
	Under follow up	908(70.72)

The Jimma HARRT Study

Study outcome

- Primary outcome: time-to-treatment change
  - ➢ Treatment change: changing one or two drugs without initiating a second-line ART therapy.

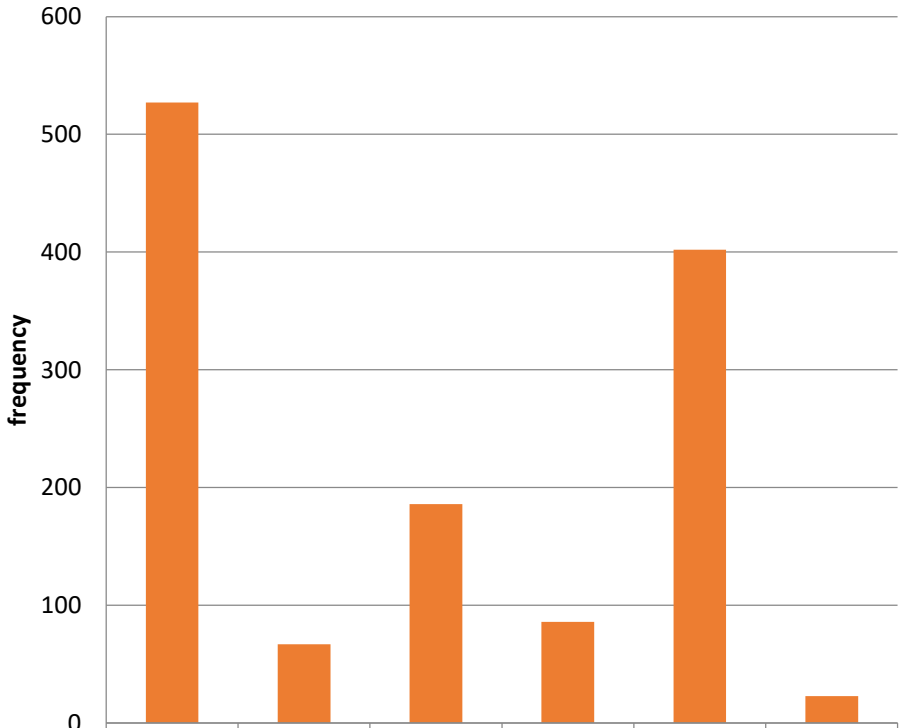


- Person-time of the study subject ended at the earliest of initiation on second-line therapy, discontinuation of treatment, dropout, death, transfer or closure of the data set for analysis set(may 25, 2013).

The Jimma HARRT Study

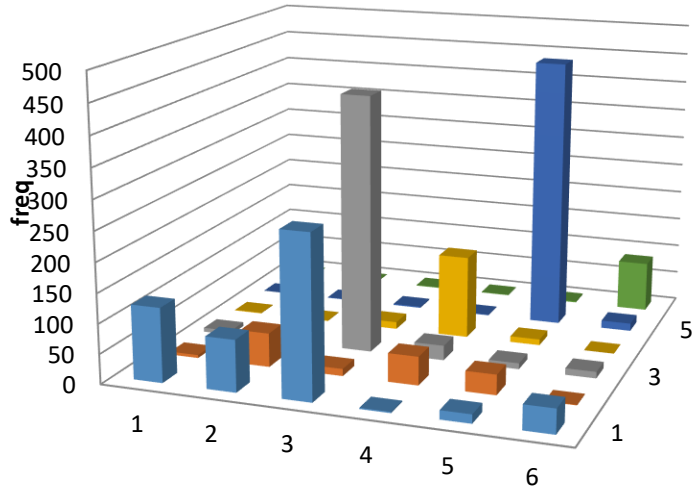
Study outcome

At start



	1	2	3	4	5	6
Freq	527	67	186	86	402	23

At the end

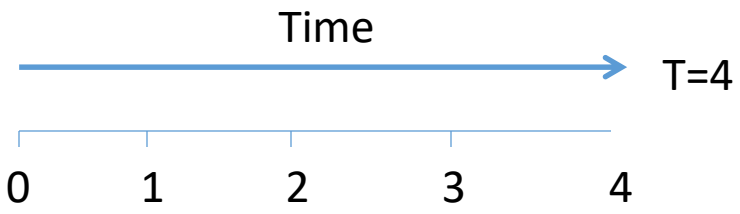


	1	2	3	4	5	6
1	125	87	271	2	15	41
2	5	57	12	48	34	1
3	7	0	431	25	10	11
4	1	1	12	140	10	0
5	0	1	2	1	456	13
6	0	0	1	1	2	85

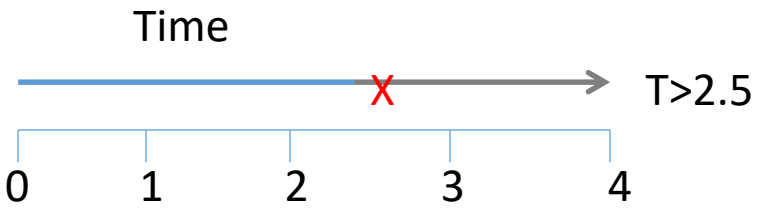
1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

Basics of survival analysis

- Our Interest: To model the time-to treatment modification and describe the treatment course of patients under HAART
- **Observations**: time to event continuous random variable $T > 0$



- **Censoring**: some observations cannot be observed, the only available information being a lower bound.



- Standard methods not valid.

Modeling Survival Data

- Because of this peculiarity, instead of modeling the density $f(t)$ of T, the hazard is considered

$$a(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid T \ge t)}{\Delta t} = \frac{f(t)}{S(t)} = -\frac{d}{dt}\log(S(t))$$

With, $$S(t) = \int_t^{\infty} f(u)du = P(T \ge t) = 1 - F(t)$$

- The basic regression model for the hazard is the Proportional Hazards (PH) Model (Cox, 1972)

$$a(t \mid X) = a_0(t)\exp(\beta^t X)$$

- Survival analysis: methods for analyzing time to a single event

- Patient under HAART may experience recurrent treatment switching episodes

Multi-state Models (MSM)

- Multi-state models describe random movements of individuals among a finite number of states
  - ➢ transition: change of state
  - ➢ state structure species states and possible transitions
    - absorbing state: further transitions cannot occur, e.g., death
    - transient state: not absorbing
- Important targets
  - ➢ Transition intensities
    - Estimation of instantaneous risk of state i to j transition at time t
  - ➢ Assessing covariate effect on the hazard of transition
  - ➢ Transition probability
    - Quantifying the probability of being in state j at time t when in state i at time $s < t$

Multi-state Models (MSM)

Inference: Markov models

- Important class of models which satisfy Markov assumption: transition probability only depends on current state not on history
- Non-parametric model: we ignore the influence of covariates
  - Let X(t) denote the state occupied at time t
  - The instantaneous risk of a transition from state g into state h at time t is

$$\alpha_{gh}(t) = \lim \frac{P(X(t+\Delta t) = h \mid X(t) = g)}{\Delta t}$$

and, cumulative hazard

$$A_{gh}(t) = \int_0^t a_{gh}(u)du$$

$$\hat{A}_{gh}(t) = \sum_{t_i < t} dN_{gh}(t_i) \Big/ Y_g(t_i)$$

Nelson-Aalen estimator

Multi-state Models (MSM)

Inference: Markov models

- The transition probabilities $P(s,t)$ matrix has elements,

$$P_{gh}(s,t) = P(X(t) = h \mid X(s) = g)$$

denoting the transition probability from state g tot state h in time interval (s; t].

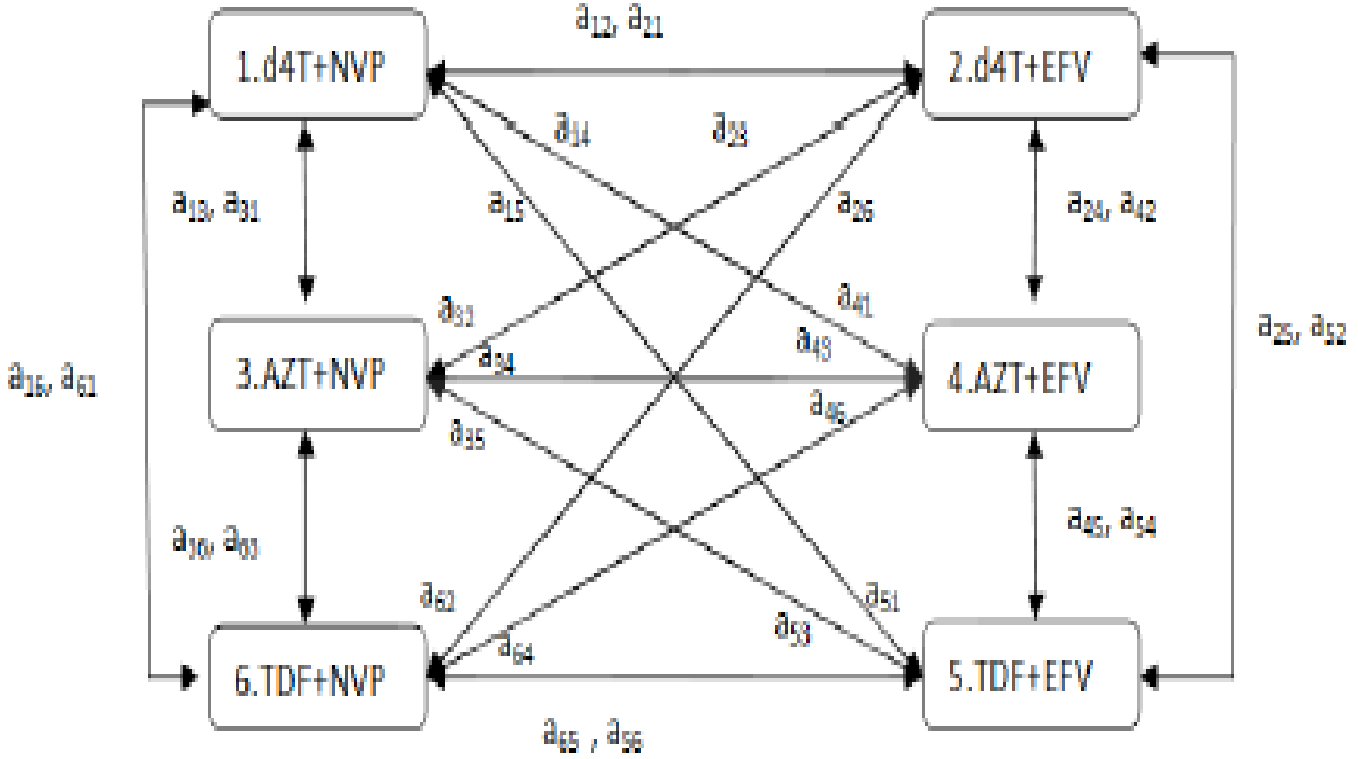
- The transition probability matrix is estimated as

$$\hat{P}(s,t) = \prod_{u \in (s,t]} (I + \Delta \hat{A}(u)) \text{ , u} \in \text{(s, t]}$$

Aalen-Johanson estimator

Application to HARRT study

Model formulation



Proposed Six-state multi state model for treatment change: note 3TC is present in all states

Application to HARRT study

Important targets

- probability of staying in treatment g for a patient who start therapy with treatment g

$$\hat{P}_{gg}(s,t) = \exp\left(-\int_s^t \sum_{g \neq h} a_{gh}(u)du\right)$$

$\hat{P}_{gg}(s,t)$ can be used to compare treatments durability

- Probability of switching main treatment(NNRTI)
  - P_{12} for state 1, P_{34} for state 3, P_{56} , for state 5
  - P_{21} for state 2, P_{43} for state 4, P_{65}, for state 6

Application to HARRT study

Important targets

- Probability of changing backbone(NRTI)
  - $P_{13} + P_{16}$ for state 1 $P_{35} + P_{36}$ for state 3 $P_{54} + P_{52}$ for state 5
  - $P_{24} + P_{25}$ for state 2 $P_{42} + P_{45}$ for state 4 $P_{63} + P_{61}$ for state 6

- Probability of changing both backbone and main treatment at the same time.
  - $P_{14} + P_{15}$ for state 1 $P_{32} + P_{35}$ for state 3 $P_{53} + P_{51}$ for state 5
  - $P_{23} + P_{26}$ for state 2 $P_{41} + P_{46}$ for state 4 $P_{64} + P_{62}$ for state 6

Result

Observed transition (all cause)

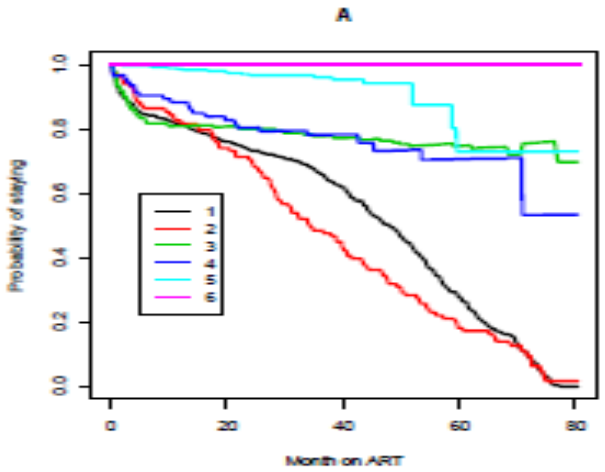
	1	2	3	4	5	6	no event	total entering
1	-	87(0.16)	271(0.50)	2(0.004)	15(0.028)	41(0.08)	125(0.23)	541
2	5(0.03)	-	12(0.08)	48(0.31)	34(0.22)	1(0.006)	57(0.36)	157
3	7(0.014)	0(0.00)	-	25(0.052)	10(0.021)	11(0.023)	431(0.89)	484
4	1(0.006)	1(0.006)	12(0.073)	-	10(0.061)	0(0.000)	140(0.853)	164
5	0(0.000)	1(0.002)	2(0.004)	1(0.002)	-	13(0.027)	456(0.964)	473
6	0(0.000)	0(0.000)	1(0.011)	1(0.011)	2(0.022)	-	85(0.955)	89

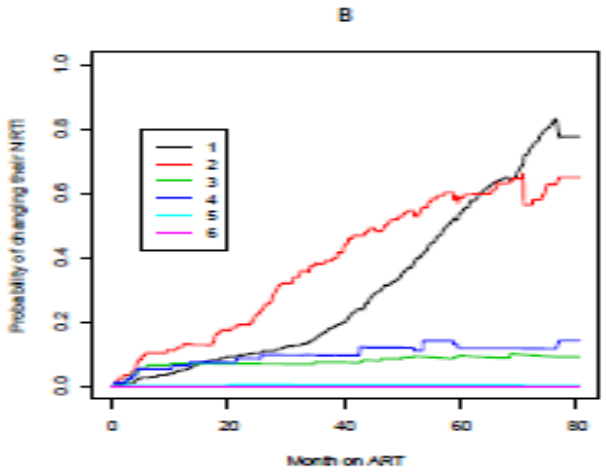
1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

Result

Estimated transition probabilities (All cause)

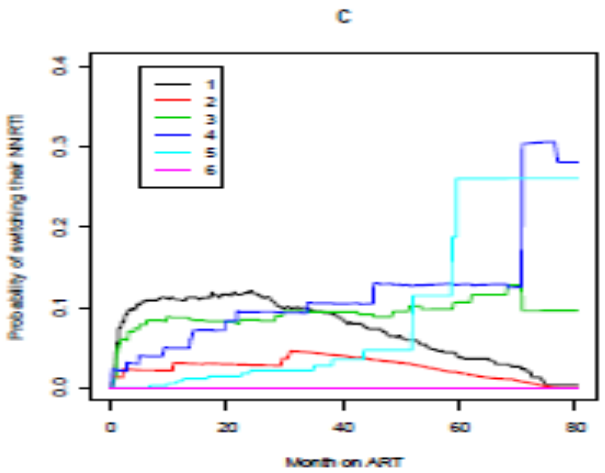
Probability of staying

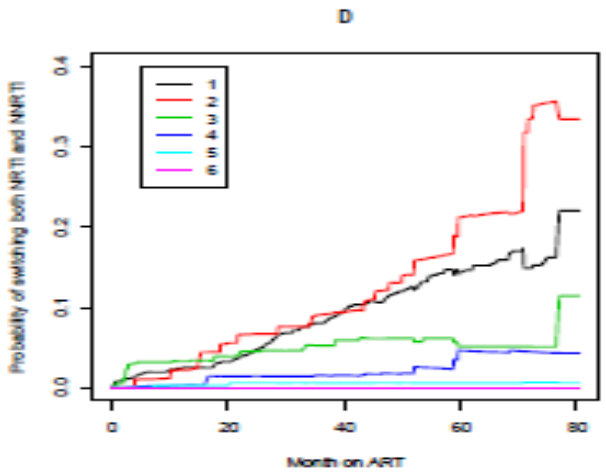




Probability of changing NRTI

Probability of changing NNRTI





Probability of changing NRTI and NNRTI

1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

Result

Reason for treatment change

	1	2	3	4	5	6	Total
Drug out of stock	0(0.00)	0(0.00)	3(5.56)	0 (0.00)	0 (0.00)	0(0.00)	3(0.48)
Hepatitis	0(0.00)	0(0.00)	1 (1.85)	0 (0.00)	0(0.00)	0(0.00)	1(0.16)
New TB	68(16.35)	3(3.00)	15 (27.78)	0 (0.00)	1(5.88)	1(25.00)	88(14.31)
Phaseout	106(25.48)	18 (18.00)	0(0.00)	0 (0.00)	0(0.00)	0(0.00)	124(20.16)
Pregnancy	1(2.40)	6 (6.00)	0 (0.00)	5 (20.83)	11(64.70)	1(25.00)	24(3.9)
Toxicity/side effect	198(47.59)	56(56.00)	29 (53.70)	13 (54.17)	3(17.65)	2(50.00)	301(48.94)
Treatment failure	2(4.1)	1 (1.00)	1 (1.85)	0 (0.00)	0 (0.00)	0(0.00)	4(0.65)
others	41 (9.86)	16 (16.00)	5 (9.26)	6 (25.00)	2 (11.76)	0(0.00)	70(11.38)
Total change	416	100	54	24	17	4	615

1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

Result

Time-to-treatment change due to toxicity

Outcome

- Time-to-treatment change due to toxicity
- Treatment changes for other reasons were censored

Observed transition

	1	2	3	4	5	6	no event	total entering
1	-	15(2.77)	142(26.25)	2(0.36)	6(1.10)	33(6.09)	343(63.40)	541
2	2(1.27)	-	5 (3.18)	25 (15.92)	22(14.01)	1(0.63)	102(64.96)	157
3	7(1.44)	0(0.00)	-	6(1.24)	7(1.45)	9(1.85)	455(94.00)	484
4	0(0.00)	1(0.60)	5 (3.05)	-	7(4.26)	0(0.00)	151(92.07)	164
5	0(0.00)	1(0.21)	0 (0.00)	0(0.00)	-	2(0.42)	470(99.36)	473
6	0(0.00)	0(0.00)	1 (1.12)	1(1.12)	0(0.00)	-	87(97.75)	89

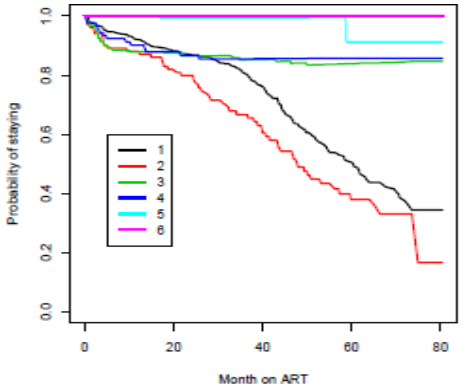
1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

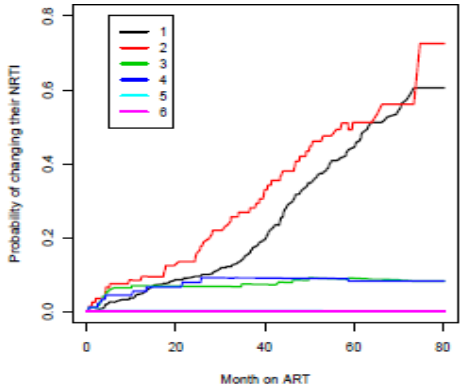
Result

Time-to-treatment change due to toxicity

Estimated transition probabilities

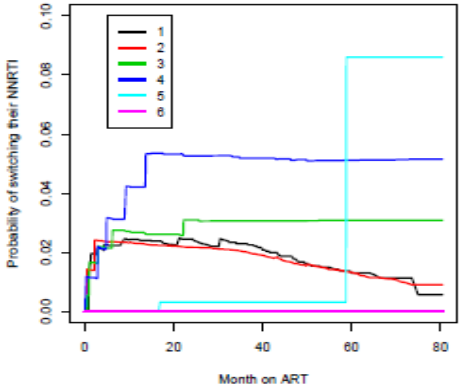
Probability of staying

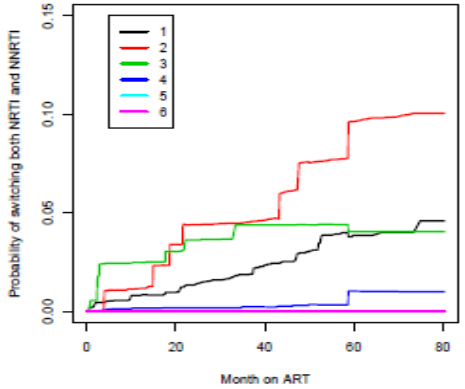




Probability of changing NRTI

Probability of changing NNRTI





Probability of changing NRTI and NNRTI

1: d4T+NVP 2: d4T+EFV 3: AZT+NVP 4: AZT+EFV 5: TDF+EFV 6: TDF+NVP

Concluding remark

Public health point of view

- All cause treatment modification:
  - Regimens containing d4T have the lowest probability of staying, higher probability of changing NRTI alone and higher probability of changing both the NRTI and NNRTI at the same time.
  - Regimens that contain AZT have a relatively higher probability of changing NNRTI alone
- Treatment modification due to toxicity:
  - Regimens containing d4T have the lowest probability of staying, higher probability of changing NRTI alone, lowest probability of changing NNRTI due to toxicity
  - Relatively, treatment combinations that contain AZT had higher probability of switching the main treatment keeping their backbone

Concluding remark

Statistical point of view

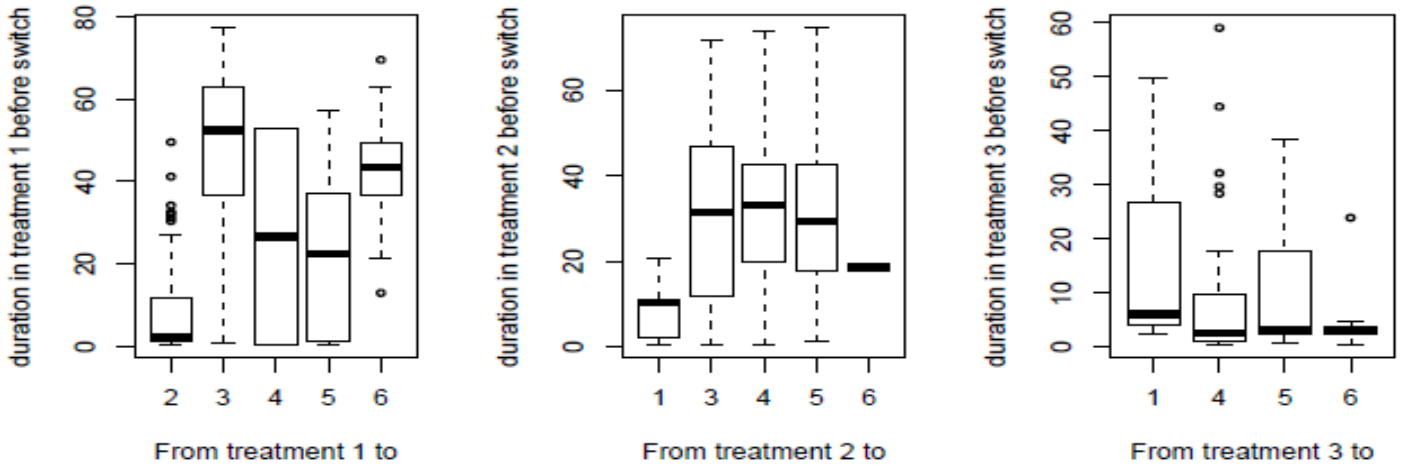
- Multi-state models allow for a very flexible approach that can model almost any kind of longitudinal failure time data

- Using the proposed Multi-state model we predict probabilities of for important events which have public health implication

- The assumed Markov property simplifies our probability calculations,

Future work

- Relaxing Markov assumption
  - ➢Markov models ignore past history and may be inappropriate in many application



  - ➢Semi-Markov model accounts the “time spent in preceding state" for transition probability from present state
    - Disadvantage: computation

Future work

- Assessing covariate effect on transition intensities and transition probability, such as CD4 rate of change
  - ➢ Cox's proportional hazards model: covariate act multiplicatively on the intensity
  - ➢ Difficulties: covariates may have different effect for each transition
    - If there are 3 possible transition and a covariate with only two levels, this will lead to 6 transition-specific covariates
- Censoring: covariates may affect censoring mechanism and transition process leading to dependent censoring
  - ➢ Nelson-Aalen and Aalen-Johansen estimators not valid
- Subject variation in transition intensities not fully explainable by observed covariates

Selected references

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Thank you