

RETROSPECTIVE MATCHING ANALYSIS OF INDUCTION/MAINTENANCE HIV TREATMENT STRATEGIES

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Induction-maintenance strategy

- initiate HAART - potent multiclass regimen (PI/NNRTI + 2 NRTIs)
- switch from PI/NNRTI to 3rd NRTI once viral replication satisfactorily under control
- aim to maintain viral suppression whilst minimizing chances of longer-term toxicities

How can we examine the effectiveness of such a strategy?



New treatment vs standard treatment:

Observational data

Need to deal with non-randomization of patients to treatment options

- inverse proportional weighting
- propensity scores
- retrospective matching

Focus of analysis

How would our cases have fared if they had been given standard treatment?

PRE-HAART

HAART

POST-MATCHING



treatment history

matching
(baseline)

follow-up

clinic

Rx history

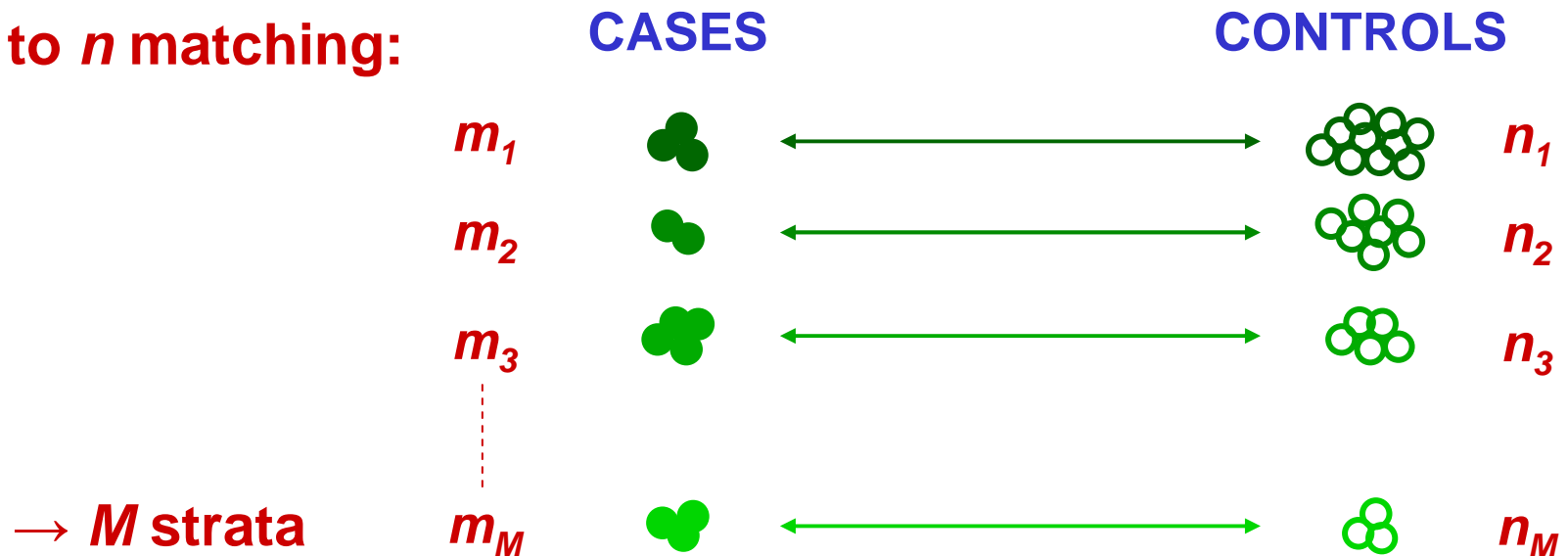
PI/NNRTI
time on HAART
calendar year
CD4 count

matching
variables

Retrospective matching of controls to cases

- stratification, matching on set of discrete/continuous variables
- aims to achieve a balance in prognostic factors

m to *n* matching:

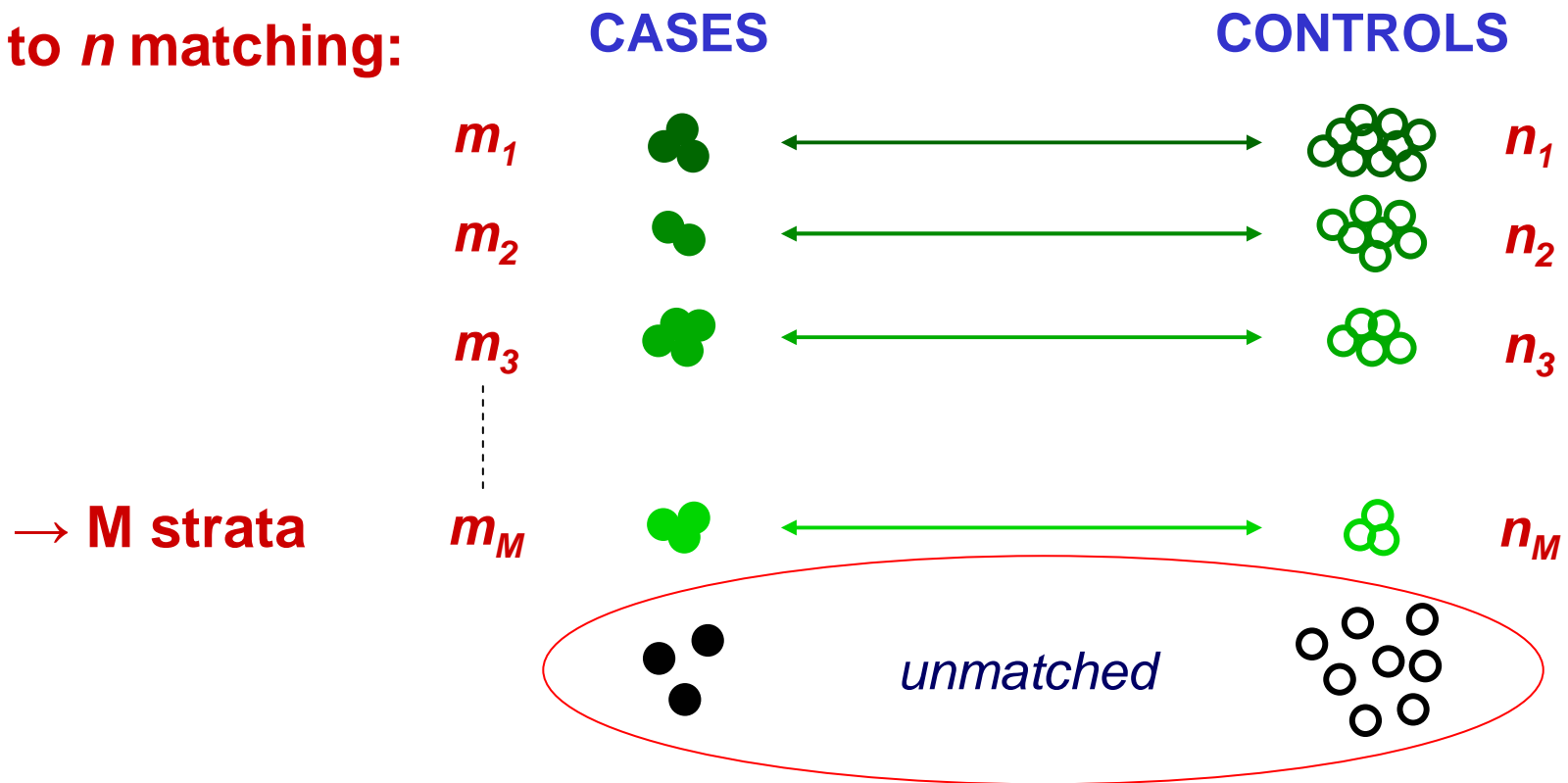


- typically $m_j < n_j$
- increasing M with increasing total sample size

Retrospective matching of controls to cases

- stratification, matching on set of discrete/continuous variables
- aims to achieve a balance in prognostic factors

m to *n* matching:



- would like to emulate randomized trial but there are limitations



How would our cases have fared if they had been given the standard treatment?

Analyses need to take account of matched groupings

Stratified Cox model

- examines consistency across strata of proportional treatment hazards

Weighted Cox/Kaplan-Meier analyses

- downweight individual contributions to achieve a balance across the strata in the contributions to the analyses.

Weighted Kaplan-Meier curve - balanced contributions from each stratum*:

$$\hat{S}^w(t) = \prod_{u:u \leq t} \left(1 - \Delta \hat{\Lambda}^w(u) \right) = \prod_{u:u \leq t} \left(1 - \frac{\sum_{j=1}^M \delta_j(u) / n_j}{\sum_{j=1}^M R_j(u) / n_j} \right)$$

$\delta_j(u)$: # events in stratum j at time u

$R_j(u)$: # in risk set in stratum j at time u

n_j : total # in stratum j

**eg Winnet & Sasieni, JAMA, 2002;*

Galimberti, Sasieni & Valsecchi, Stats in Medicine, 2002

Following counting process arguments (and ignoring extra variation induced by randomness of strata):

$$\text{Var}(\hat{S}(t)) \approx \hat{S}(t)^2 \text{Var}(\hat{\Lambda}(t)) \approx \hat{S}(t)^2 \sum_{s \leq t} \sum_{j=1}^M \frac{\delta_j(s)/n_j}{n_j \left(\sum_{j'=1}^M R_{j'}(s)/n_{j'} \right)^2}$$

OR

$$\text{Var}(\hat{S}(t)) \approx \hat{S}(t)^2 \sum_{s \leq t} \sum_{j=1}^M \frac{\delta_j(s)/n_j}{n_j \left(\sum_{j'=1}^M R_{j'}(s)/n_{j'} \right) \left(\sum_{j'=1}^M R_{j'}(s)/n_{j'} - \delta_j(s)/n_j \right)}$$

i.e. utilizing Tsiatis or Greenwood analogues with adjustments
of $1/n_j$

Weighted Kaplan-Meier curve

- Very easily constructed in any package that allows down-weighting of individuals
- However, the limiting form of the weighting function depends explicitly on the limiting censoring distributions of the strata:

$$\frac{\delta_j(u)/n_j}{\sum_{j'=1}^M R_{j'}(u)/n_{j'}} \rightarrow \frac{S_j(u)(1-F_j^c(u))\lambda_j(u)}{\sum_{j'=1}^M S_{j'}(u)(1-F_{j'}^c(u))}$$

Note: $\hat{\Lambda}^w(t) \neq \frac{1}{M} \sum_{j=1}^M \tilde{\Lambda}_j(t) = \frac{1}{M} \sum_{j=1}^M \sum_{u:u \leq t} \frac{\delta_j(u)}{R_j}$

WKM AUC test statistic for 2-sample comparison:

$$\int_0^T (\hat{S}_1^w(t) - \hat{S}_2^w(t)) dt$$

- need to be able to realistically assume that

$$F_{1j}^c = F_{2j}^c \text{ for all } j, \text{ so that } S_1^w = S_2^w$$

under null hypothesis of equality of underlying
survival distributions



Weighted Cox analyses

- weight individual contributions so that each stratum contributes equally to the analysis
- fit weighted Cox model, Rx group as covariate
 - robust Wald test, clustered by strata
- powerful when hazards are approx. proportional
- enables modelling of both group effect and strata effects

2 sample comparisons

$S_{1j} = S_{2j}$ with piecewise linear hazards:

$$\lambda_j(t | \alpha_j) = \alpha_j I(t \leq 2) + 0.02 \alpha_j I(t > 2)$$

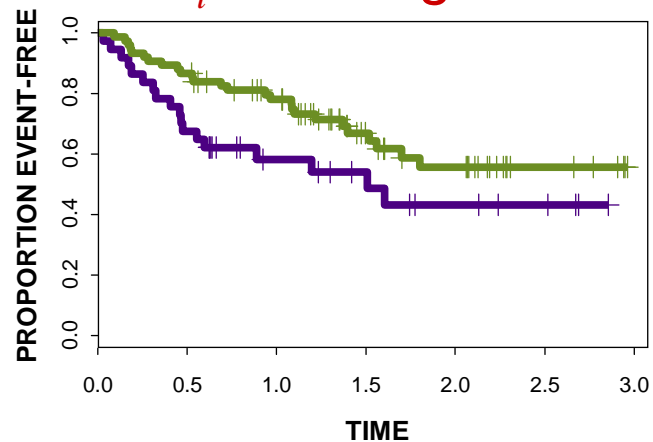
$\alpha_j \sim U(0.05, 1)$ and ordered for $j=1..M$

$F_{1j}^c = F_{2j}^c$, variable across strata

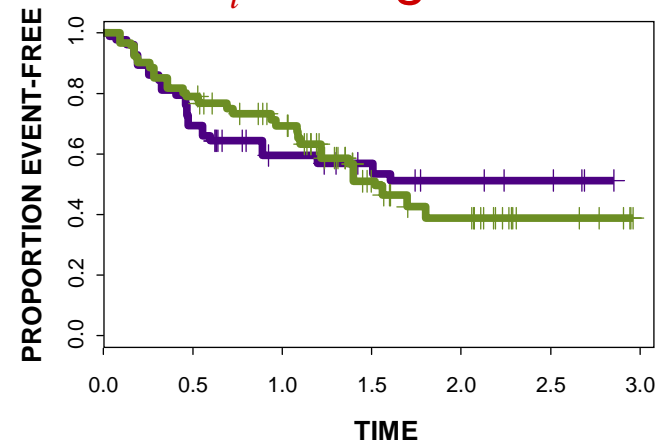
$n_{1j} \sim 1 + \text{Pois}(0.2)$ and *ordered* for $j=1..M$

$n_{2j} \sim 1 + \text{Pois}(2)$ and *reverse ordered* for $j=1..M$

\hat{S}_i : unweighted



\hat{S}_i^w : weighted

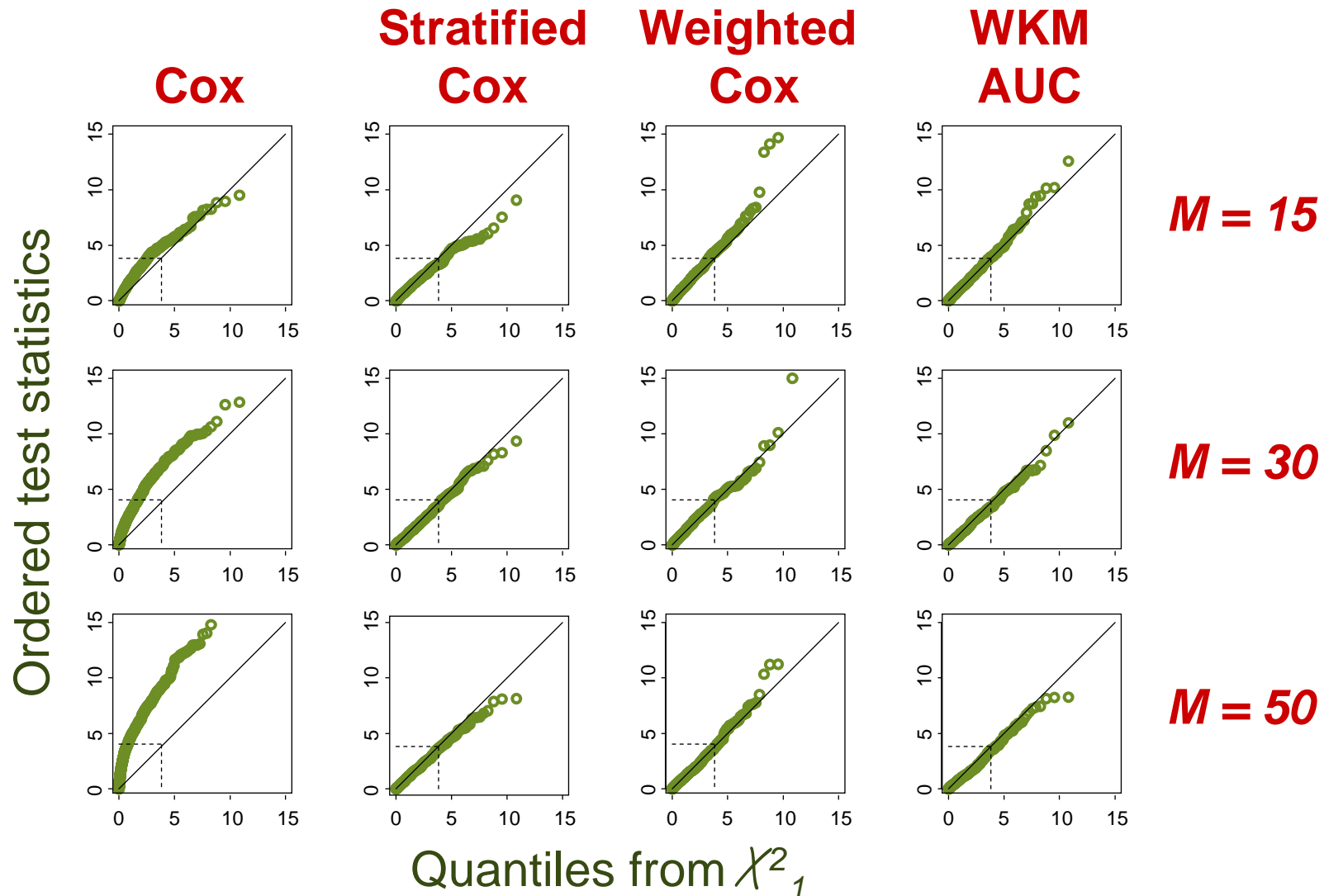


example

Simulation results

Sample 1 : mean $n_j = 1.4$, 55% censoring

Sample 2 : mean $n_j = 3.6$, 42% censoring



Application revisited

>3 months viral suppression on a PI/NNRTI regimen, $n = 685$

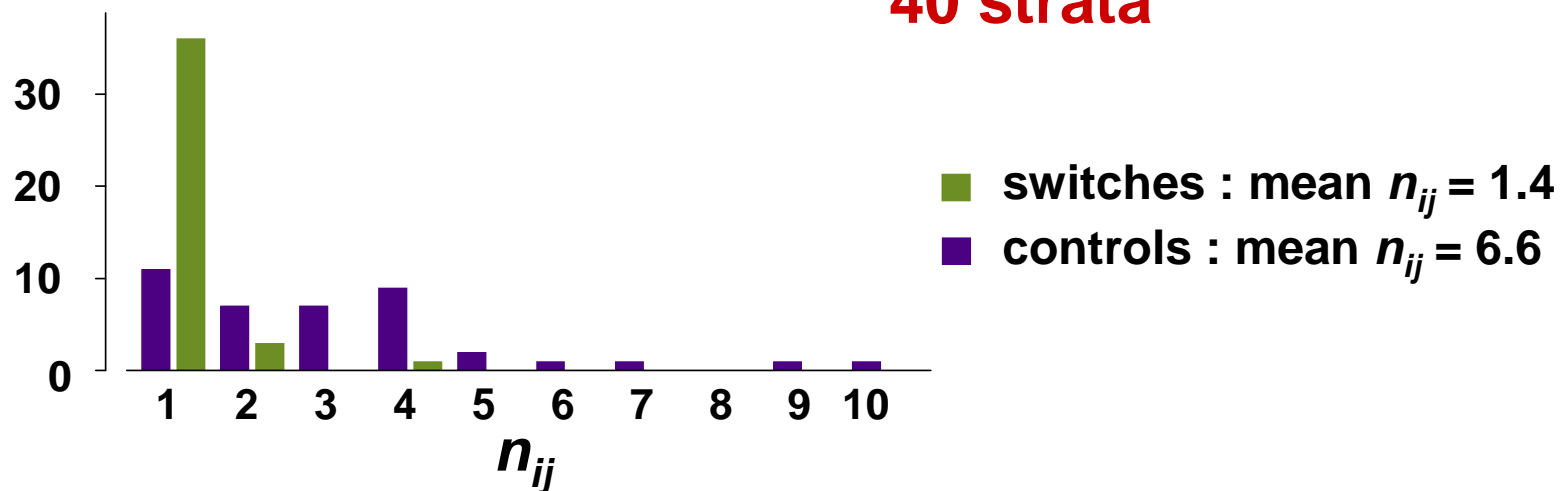
initiating defined induction-maintenance
strategy (PI/NNRTI \rightarrow 3-NRTI)
 $n = 56$

not matched
 $n = 16$

matched controls
identified
 $n = 46$

selected as matched
controls
 $n = 124$

40 strata



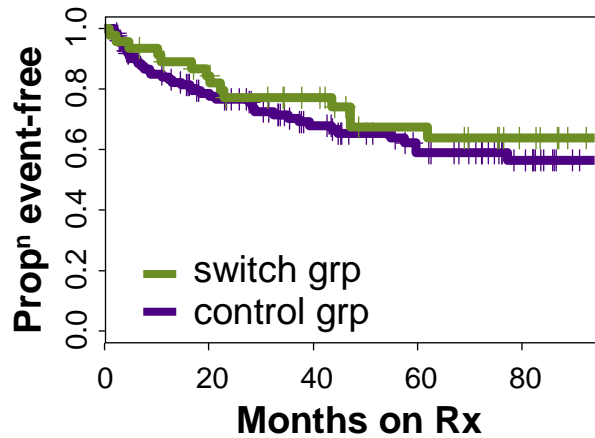
Analyses

Time to losing viral suppression

UNWEIGHTED

Cox
 $p = 0.4$

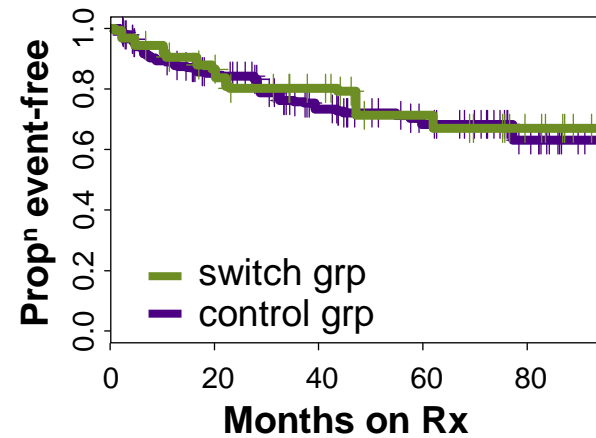
KM AUC
 $p = 0.4$



WEIGHTED

robust Cox
 $p = 0.4$

WKM AUC
 $p = 0.9$

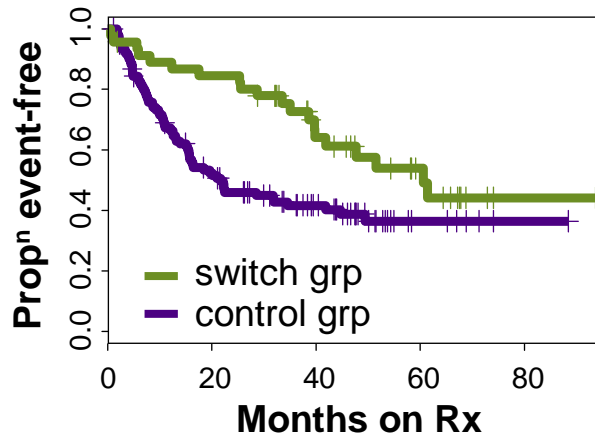


Time to changing regimen class

UNWEIGHTED

Cox
 $p = 0.008$

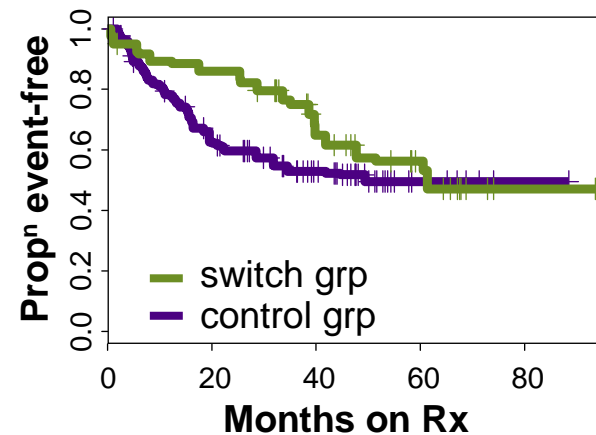
KM AUC
 $p = 0.0002$



WEIGHTED

robust Cox
 $p = 0.02$

WKM AUC
 $p = 0.04$

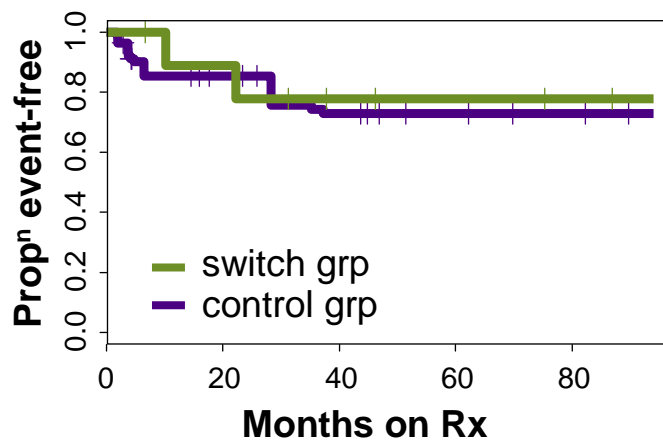


Time to losing viral suppression

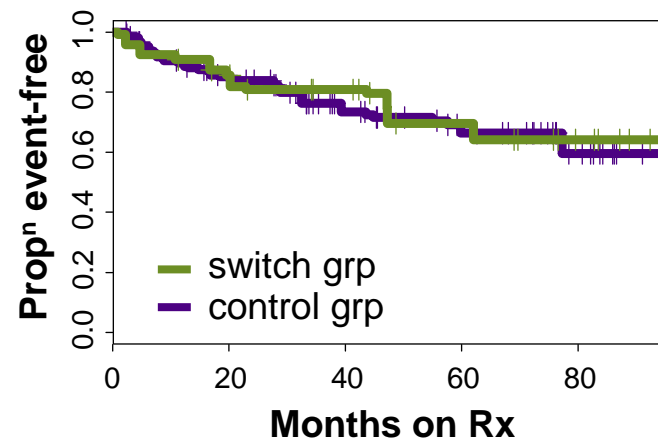
- loss of viral suppression associated with higher CD4 at HAART initiation ($p=0.002$) and prior Rx experience (ie mono or dual NRTI prior to HAART) ($p=0.01$), but not with switching from PI/NNRTI ($p>0.3$)

Matching time : months since start of HAART

≤ 24 mths (10 strata)



> 24 mths (30 strata)

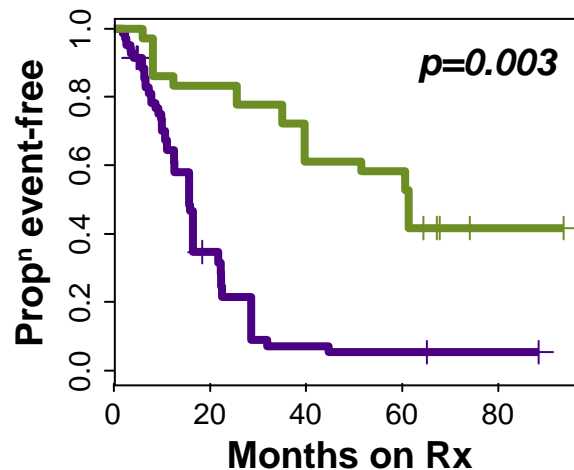


Time to changing regimen class

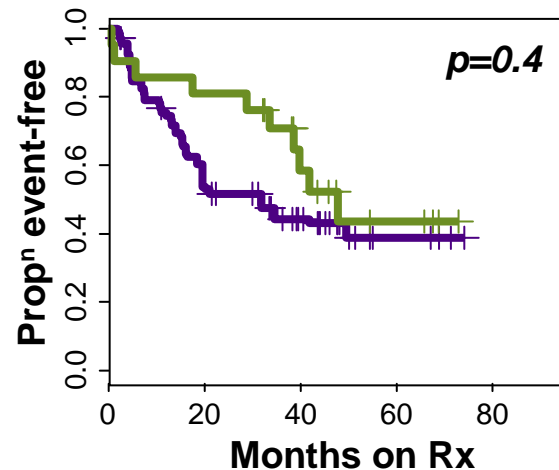
- changing regimen class more likely for those on a PI ($p=0.0006$) and/or matched in earlier years ($p<0.0001$), particularly in control group.

Year of matching:

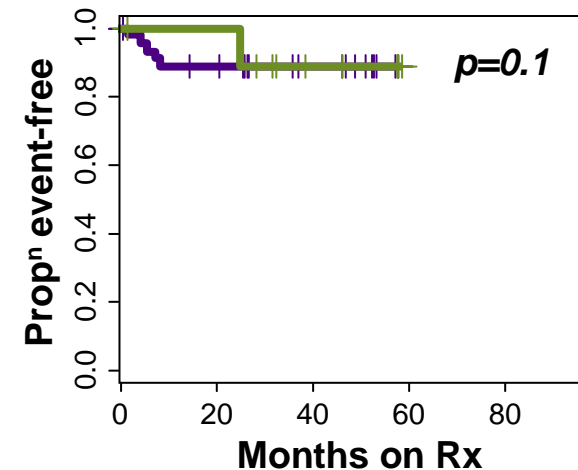
1999-2000



2001-2002



2003-2005



— switch grp — control grp

Retrospective matching

- provides an upfront means of ensuring like is compared with like
- does not depend on model fitting - gives transparency
- lends itself to easy visual representation of the comparison

- Appropriate analysis tools available
 - comparisons of the WKM curves – useful when hazards are non-proportional
 - weighted Cox modelling – readily applied using standard software