

Late treatment failures in CSF in patients on long-term maintenance ART with ritonavir-boosted PI monotherapy

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BACKGROUND

Combination antiretroviral treatment (cART) with 3 drugs is the recommended treatment for the majority of HIV infected patients. To keep HIV replication controlled, lifelong HIV-therapy is necessary. The benefit of triple therapy regimen is obvious, nevertheless patients on long term cART risk side effects, particularly mitochondrial toxicity, metabolic effects and lipodystrophy. These concerns and high costs of cART have stimulated the search for alternative treatment strategies to limit drug exposure.

HIV monotherapy with ritonavir-boosted PIs (rb-MT) remains a potentially attractive treatment strategy for simplification in HIV infected individuals. However, based on the poor penetration of protease inhibitor into the central nervous system, long-term safety in particular with respect to HIV-RNA-suppression in CNS needs to be confirmed.

STUDY AIMS and HYPOTHESIS

This observational study evaluates long-term monotherapy-maintenance failure (plasma or CSF) in patients fully suppressed for at least 12 months on rb-MT.

Hypothesis:
Failure during rb-MT occurs early or never

METHODS and STUDY DESIGN

Study design

- Analysis of prospectively gathered data on patients who did participate in one of three monotherapy trials (Indinavir/r (1), ATARITMO (Atazanavir/r)(2), MOST (Lopinavir/r) (3))

Subjects

- Study participants from these studies, who remained successfully suppressed (< 50 copies/ml) in CSF and/or plasma during the entire trial, were offered the possibility to continue on long-term mono-maintenance.
- While on rb-MT, patients were asked to provide CSF samples in yearly / two-yearly intervals.
- Ethical approval and informed consent were obtained for all study participants.

Inclusion criteria

- Patients who maintained HIV-RNA suppression in plasma on rb-MT for at least one year
- Patients demonstrating HIV-RNA > 200 copies/ml in CSF discontinued rb-MT and resumed triple therapy ("CSF-failure")
- Patients with plasma HIV-RNA values > 50 copies/ml discontinued rb-MT and resumed triple therapy ("Plasma-failure")

Statistics

- Descriptive statistics were applied.
- Kaplan Meier survival analysis was used to demonstrate proportion of patients remaining on rb-MT over time.

RESULTS

Patient characteristics and CSF evaluations

- Until May 2010, **27 patients** have initiated rb-MT within one of the three trials and remained fully suppressed on rb-MT for at least 1 year
- Medium follow-up time is **4.8 years** (1.1-8.4)
- 23/27 (85%) patients** consented to a spinal tap with a total of 56 examinations (average: 2.4 per patient).
- The demographic data are depicted in *Table 1*.

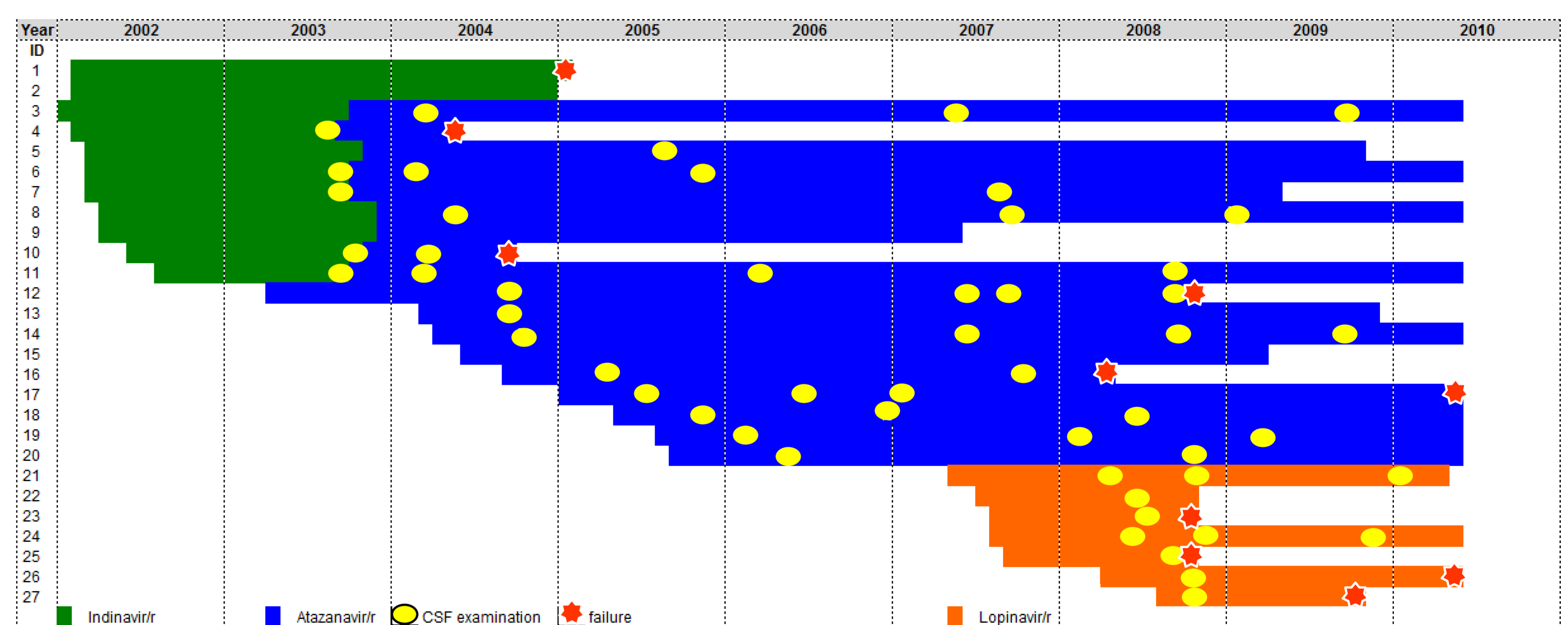
Table 1: Study population

Parameter	HIV + patients (n=27)
sex (male)	70%
median age at start rb-MT (range)	42 (32 – 74) years
median CD4 nadir (range)	215 (20-470) /µl

Treatment history and time on monotherapy

Some of the patients participated in the first (Indinavir/r) and the second monotherapy (Atazanavir/r) trial. Time on and kind of monotherapy, CSF examinations and failures are plotted for all patients in *Fig 1*.

Fig 1: Treatment history and time on monotherapy



Characteristics of treatment failures

- 9/27 (33%) patients (2 women, 7 men) failed according to the predefined characteristics. 3/9 failures occurred in CSF only (*Table 2*).
- Plasma failure occurred after a median follow up time of 2.1 years (range: 1.1 - 2.9, *Fig 2*)
- CSF-failure occurred after a median follow up time of 2.3 years (range: 1.1 - 5.6, *Fig 3*)

Fig 2: Time w/o plasma failure

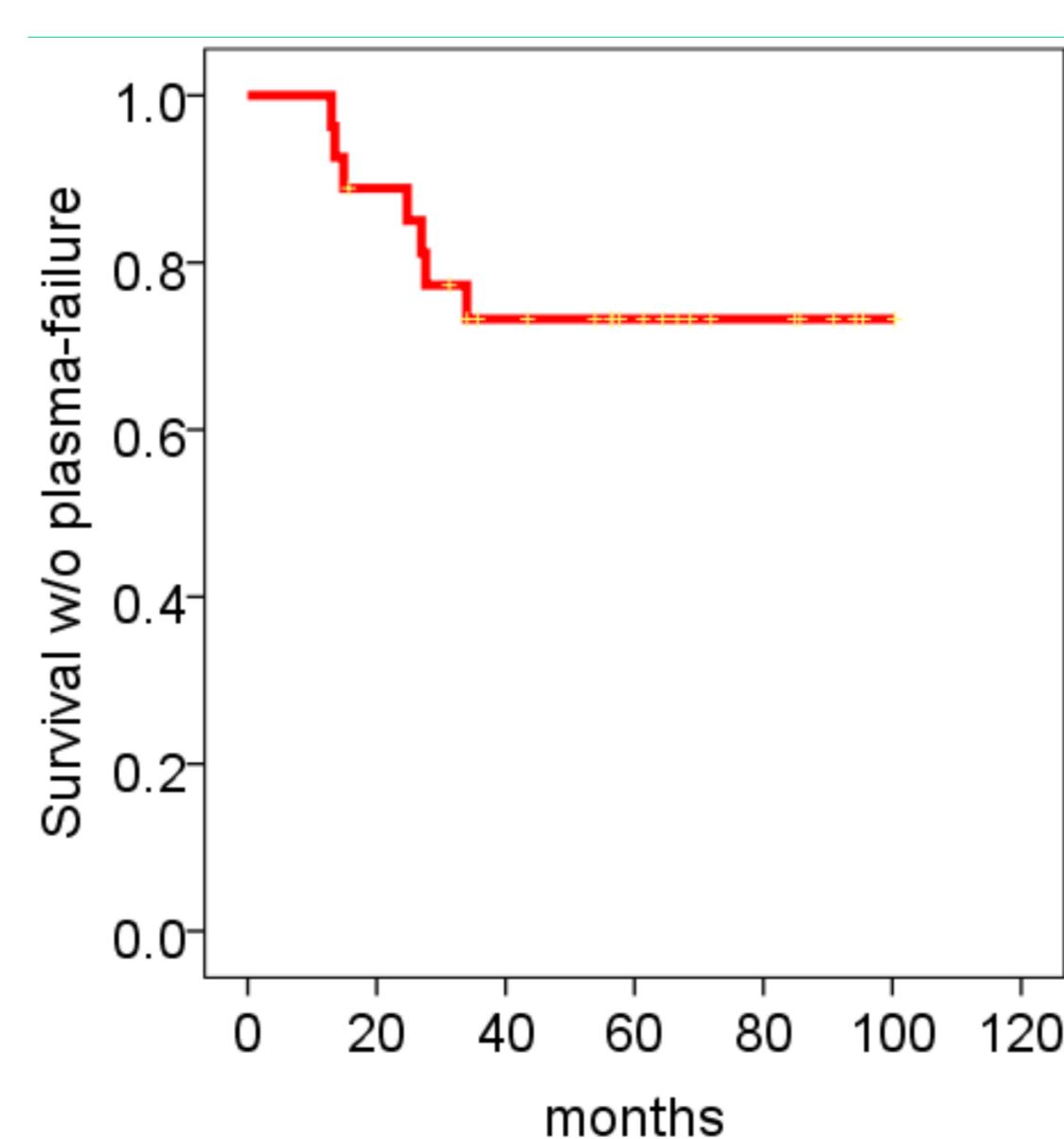


Fig 3: Time w/o CSF failure

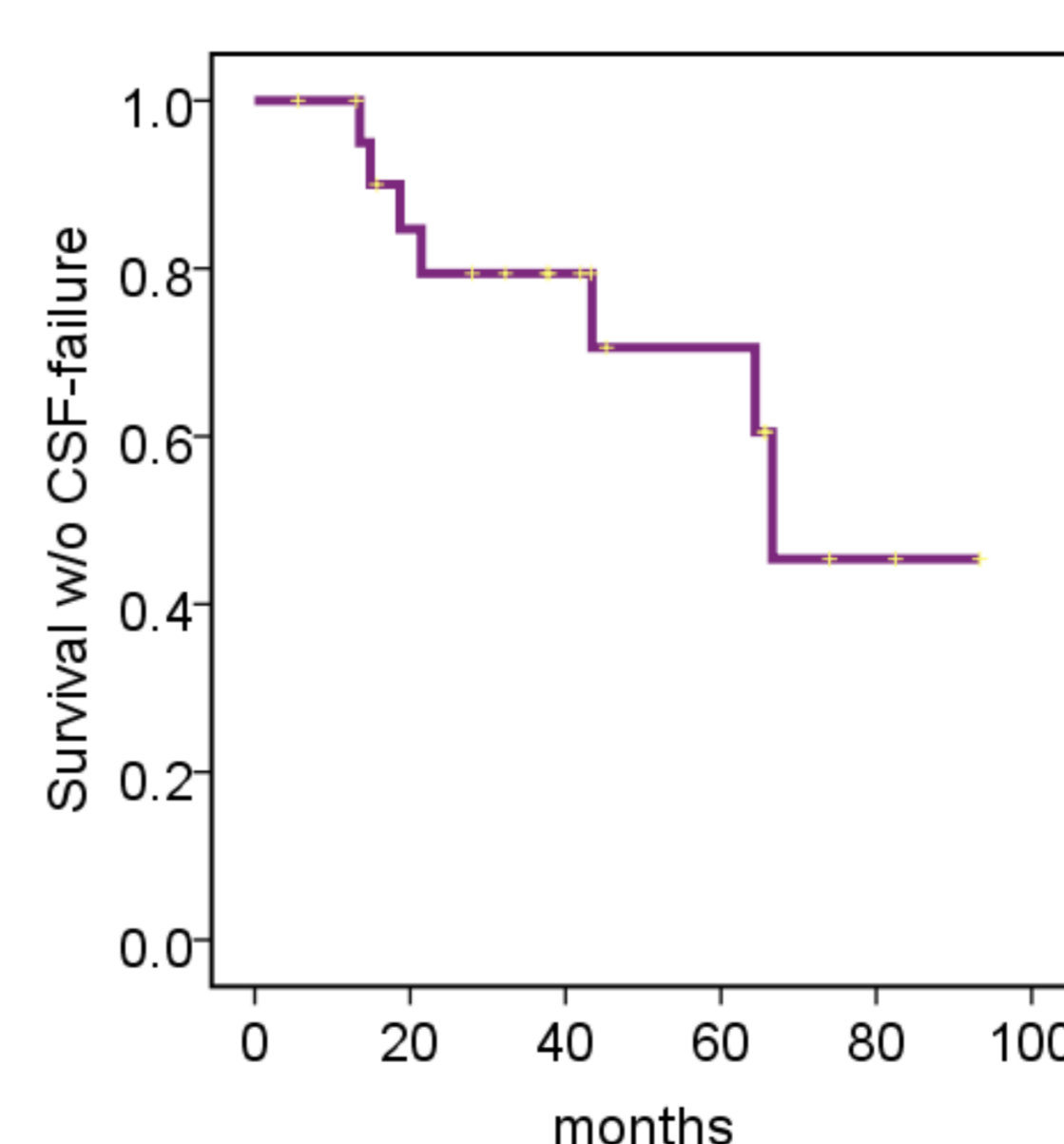


Table 2: Outcome

Parameter	HIV + (n=27)
Plasma AND CSF failure	n=4
Plasma failure only	n=2
CSF failure only	n=3
Plasma failure (no spinal tap)	n=1
Continued w/o failure	n=9
Stopped w/o failure	n=7
Drop out w/o failure	n=1

Reasons for stopping without failure were:

- denial of further spinal taps
- hyperlipidemia
- kidney stones under treatment with ATV/r
- pregnancy
- patient wish

DISCUSSION

- Contrary to our clinical impression (see hypothesis), patients on rb-MT continue to develop virological failures even after 12 months of successful HIV-RNA suppression.
- Association between failure and low CD4 nadir was previously reported (3, 4).
- Isolated treatment failure in CSF appears to be a relevant concern (one third of failures!) and can occur after years of successful maintenance.
- rb-MT may still remain a valid long-term treatment strategy for selected patients.
- Predictive markers of long-term failure of rb-MT still need to be determined (5).

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CONCLUSION

- Even after 12 months of full HIV-RNA suppression, 1/3 of patients may still develop failure in plasma or CSF (median follow up time of 5 years).
- As long as predictors of CSF-failures are not known, rb-MT should be discouraged in patients who do not consent to some monitoring of CSF levels.