

Outcome of adults receiving second line therapy in Medecins Sans Frontières-supported projects in resource limited settings

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Rationale

- Despite a considerable rate of success of antiretroviral therapy (ART) in resource limited settings (RLS), a substantial proportion of patients on ART fail to suppress viral load (VL) to undetectable levels
- Detection of failure in resource-limited settings (RLS) is based on clinical criteria, or decline in CD4 count, as viral load (VL) measurements are not routinely available
- Continuing ART while viremia is detectable, selects resistance mutations which may limit the success of subsequent regimens
- *This is of particular concern when future treatment options are limited*

Objectives

- ✓ To describe characteristic of patients who required a second-line PI-containing regimen
- ✓ To investigate results of these regimens
- ✓ To identify factors associated with death, and loss of follow-up

Methods (1)

Data collection:

- 80393 patients from 50 MSF-supported ART projects in 22 countries, between October 2001 and 2006
 - 60% females, 94% ART-naive
 - Median CD4 count at initiation (cells/ μ l): 109 [IQR 44-182]
 - Median follow-up (months): 10 [IQR 3-20]
- Data collected through FUCHIA software (Epicentre, Paris) and censored at last visit (up to December 2006)
- Definition of failure:
 - Return of CD4 cell count to pre-therapy baseline or below, or > 50% fall
 - Onset or recurrence of WHO Stage 3 or 4 conditions
- **Definition of « Second line regimen »**
 - PI-containing regimen after at least 6 months of an NNRTI first-line regimen in a naïve patient*
 - AND at least one change in the NRTI component (concomitant to the switch to PI)

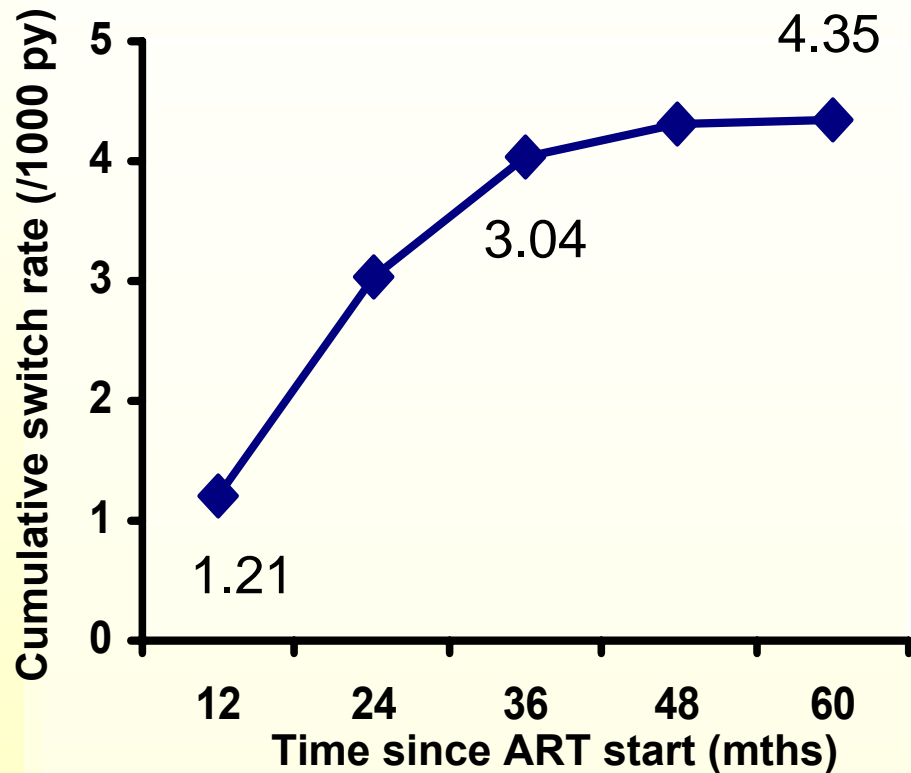
*women who received a PMTCT regimen were still considered to be naive when starting a first line NNRTI-regimen

Methods (2)

Analysis:

- Survival analysis (Kaplan-Meier method) used to plot the probability that patients switched to a second line regimen remain alive and on therapy
- Factors associated with progression to death /LTFU were analyzed using Poisson regression models
- Immunological success defined by a > 50 CD4 cell count increase within the first 6 months after second line regimen initiation

Cumulative rate of switch to second line



At:	Py	Nb switched
6 mths	29410	0
12 mths	49514	60
24 mths	72130	219
36 mths	79400	319
48 mths	80827	348
60 mths	80986	352

Overall switch rate: 4.4/1000py

These 352 patients were included in the analysis

Patients on second line therapy

Characteristics at switch (n=352)

Women	200 (57%)	
Median age [IQR] yr	35 [29-41]	
Median BMI [IQR] kg/m ²	20 [18-22]	(n=303)
Median nadir CD4 count [IQR]	37 [13-87]	(n=350)
Median CD4 count [IQR]	99 [38-202]	(n=228)
Median VL copies/ml	44000 [16406-166197]	(n=65)
Median duration of first line [IQR] mths	20 [14-28]	
Median follow-up on second line [IQR] mths	7 [2-20]	

Reasons for switch

CD4 <50/mm³	72/228 (32%)	
New WHO stage 3/4	109 (31%)	
CD4 value ≤ CD4 at ART initiation	60 (33%)	(n=184)

* All first line include 2NRTI (d4T/AZT+3TC) +NNRTI

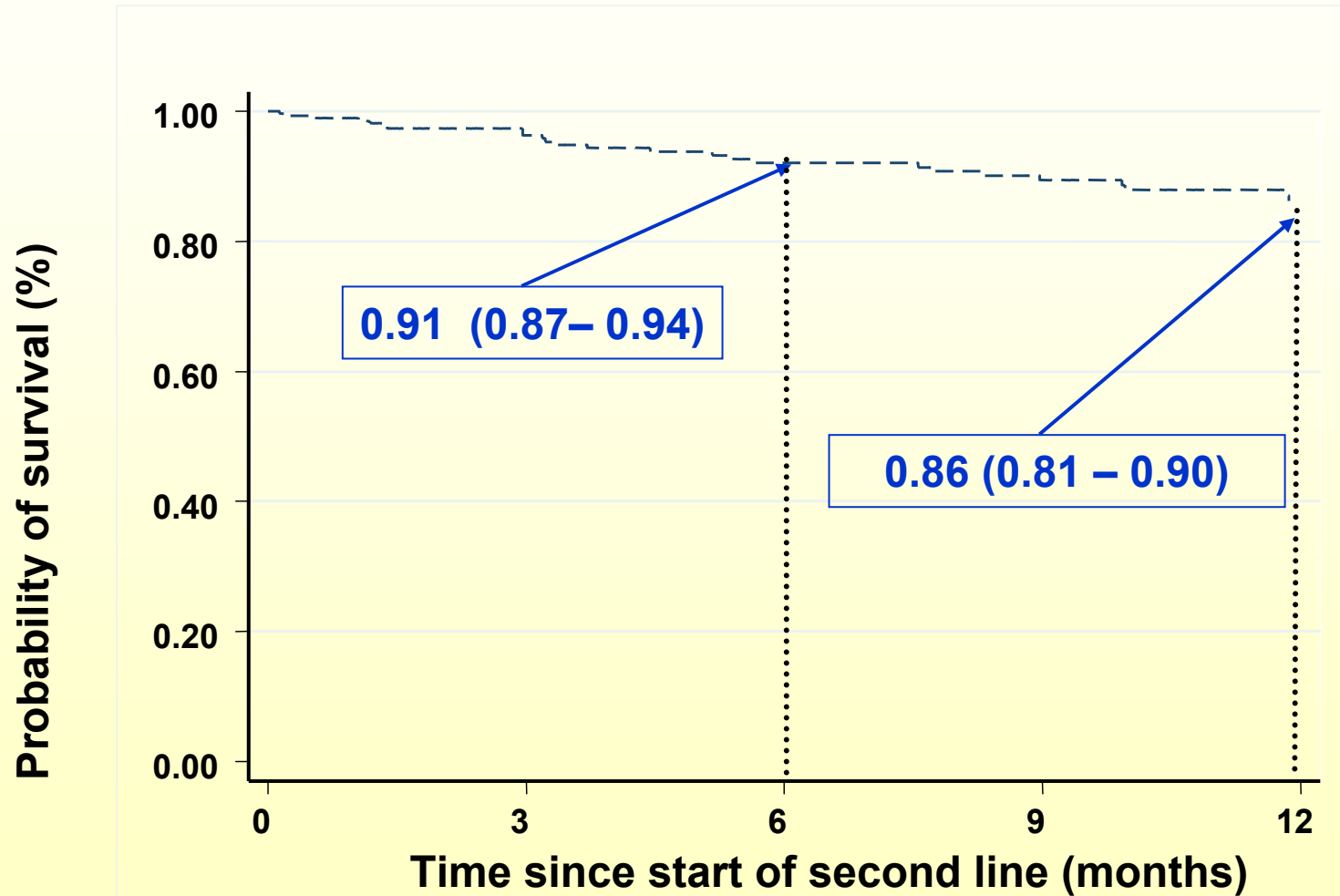
Second line regimen

Second line drugs	n	%
PI component		
LPV/r	163	46
Nelfinavir	166	47
Other	23	7
NRTI component		
AZT + ddl	119	34
ABC + ddl	70	20
TDF-based	71	20
AZT + 3TC only	44	13
Other ddl-based	17	5
Other ABC-based	22	6
Other	9	3
Total	352	100

NRTI component: one change (n=131, 37%), two changes (n=221, 63%)

Probability of survival on second line (n= 352)

Deaths & LTFU at 6 and 12 months (95% CI)



Population at risk	249	201	165	142
Number of events	9	13	6	4

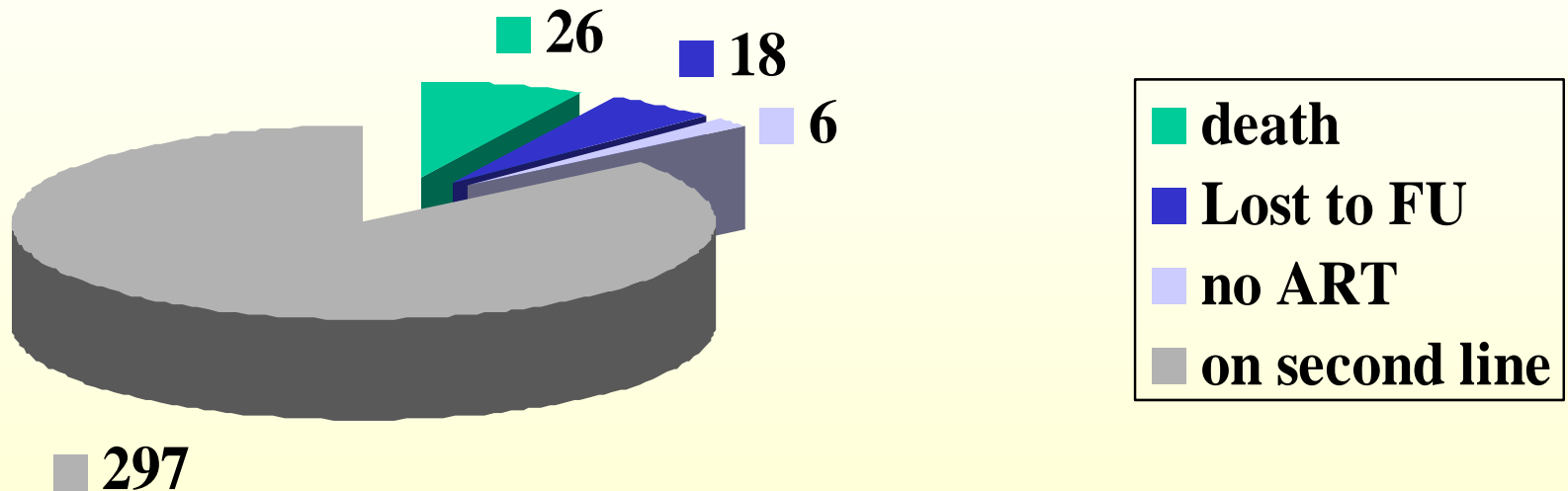
Factors associated with progression to death

Baseline parameter	Univariate ¹		Multivariate ²	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Females	0.76 (0.44-1.32)	0.33	0.89 (0.51-1.55)	0.68
Age				
<26 years	1.03 (0.56-1.89)	0.98	1.11 (0.44-2.79)	0.98
26-35 years	1.11 (0.44-2.77)		1.01 (0.55-1.87)	
BMI <17 (kg/m ²)	1.55 (0.58-4.15)	0.38	1.57 (0.60-4.15)	0.36
WHO stage 3/4 at ART initiation	2.69 (0.82-8.84)	0.10	2.47 (0.75-8.12)	0.14
WHO stage 3/4 (3 months bef. switch)	0.88 (0.46-1.71)	0.72	0.72 (0.37-1.44)	0.36
CD4 count nadir <50 cells/mm ³	2.11 (1.15-3.89)	0.02	1.86 (0.95-3.64)	0.004
CD4 count <50 cells at switch	2.56 (1.19-5.51)	0.04		
ART component				
Change in NRTI (1 versus 2)	1.09 (0.60-1.98)	0.77	0.99 (0.54-1.82)	0.98
Use of boosted PI	1.29 (0.38-4.38)	0.68	1.13 (0.33-3.89)	0.85
Type of PI	0.87 (0.23-3.22)	0.83	0.94 (0.25-3.49)	0.93

1. Poisson regression model adjusted for project;

2. Poisson regression model adjusted for project and CD4 count <50 cells/mm³ at switch

Treatment outcome



Median months at LTFU: 9 [3 - 15]

Median months at death: 6 [3 - 9]

	Median gain CD4	% increase CD4>50 / mm ³
6 months	+ 81 (IQR 37-136)	68.2 % (n=66)
12 months	+ 131 (IQR 37-196)	74.6 % (n=55)

Discussion (1)

- **Very low rate of second line regimen (4.4/1000 py) but continuous increase over the years**

- **Limitations:**

- 1) Unknown proportion of patients who should have been on second line based on virological criteria.

Data from SA suggest that at 5 years 20% of patients are on a second line regimen¹. By contrast, first line regimen last less than one year in a cohort study in the US²

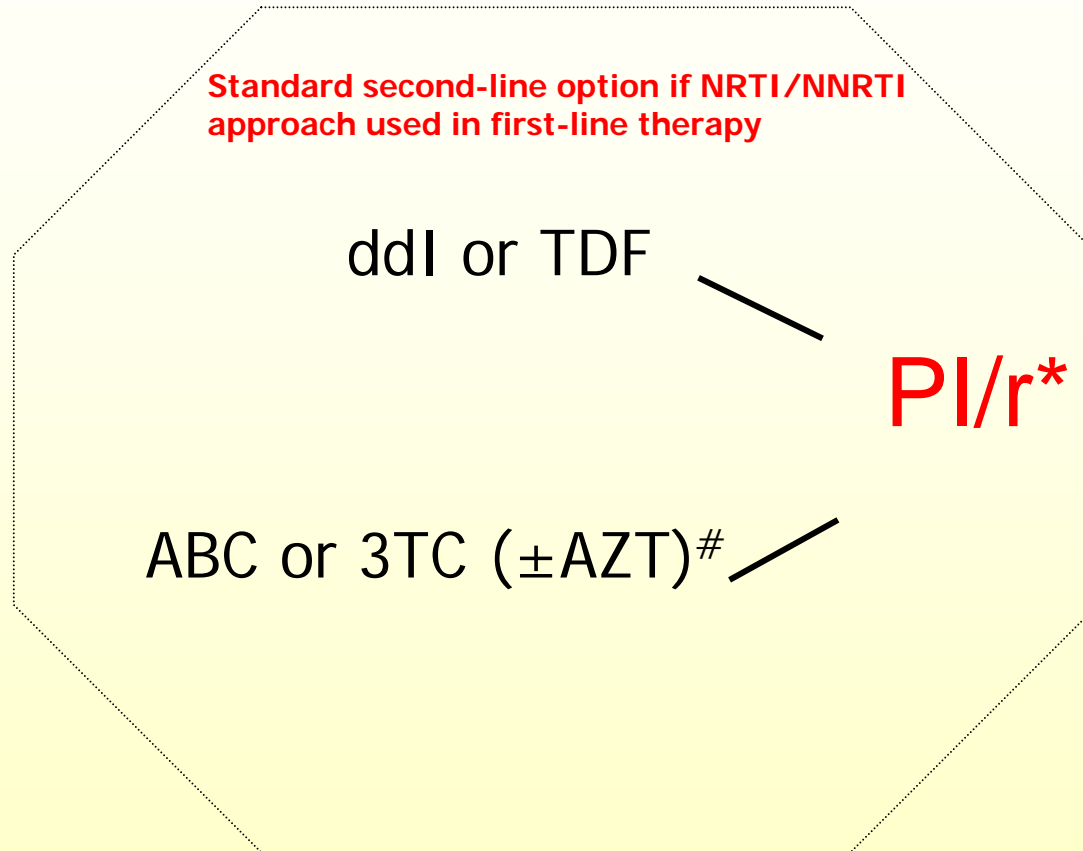
- 2) No virological confirmation of failure – definition of failure may vary according to diagnostic and lab facilities

- **Reasons for the low rate of second line**

- 1) **Accessibility of 2nd-line** (availability, affordability, increased pill burden, refrigeration)

- 2) **Second line = last resort**

WHO guidelines: Second line ARV drugs in adults and adolescents



None of the second line drugs recommended by WHO are currently available in RLS

Discussion (2)

- **Short term efficacy of PI second line regimen**
 - 91% survival at 6 months, 86% at 12 months: preliminary results, larger sample and longer FU needed, selection bias possible (first line: 90% survival at 1 year, MSF cohort*)
 - This analysis doesn't include patients entering the programs with previous ART experience
 - 52% non-boosted PI
 - Treatment changes driven by clinical symptoms or CD4 drop
 - NRTI recycling is frequent (42% thymidine analogue)*

How routine use of VL would have impacted on these results?

Conclusions

- Very low rate of second-line regimens, which are used late, after a likely prolonged period of high viremia
- With follow-up of 7 month (median), second line regimen are nonetheless effective, as judged by the CD4 count, despite delayed switch, and frequent use of nelfinavir
- The cost of second line drugs is still prohibitive and the availability of WHO recommended second line regimens (TDF, heat stable boosted PI) is not ensured
- No further options are currently available for these patients.

Acknowledgments

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