Success and Failure at 24 Months of HAART in a Resource-poor Setting: Observational Cohort of 416 HIV-treated Patients,IDD,KSFH

Presented by Dr. Prak Narom

Justification

- Important need to document long-term outcomes of patients on HAART in southern countries
  - Success/Failure immuno-clinical criteria (simplified follow-up) ?
  - Adherence evolution ?
  - Type and severity of side-effects ?
  - Apparition and type of viral resistances ?
- Observational cohorts / clinical trials

MSF HIV/AIDS Programme in Phom Penh, Cambodia

- Opened in 1997
- Integrated with the infectious disease department of the P.B. N. Sihanouk hospital
- HAART available for free since June 2001
- Counselling / psychosocial assistance
- Use of generic ARVs and Fixed Dose Combination (FDC)
- HAART Initiation according to WHO recommendations (CD4 < 200 cells/ml or WHO stage IV)
- Simplified biological follow-up: no viral loads available
- End of Dec 2005: 2,500 among them 104 children, started HAART

Objectives of the M24 Study

Main objective

- *Retrospective cohort analysis* of patients who started ARV 24 ± 2 months ago and followed without viral load monitoring

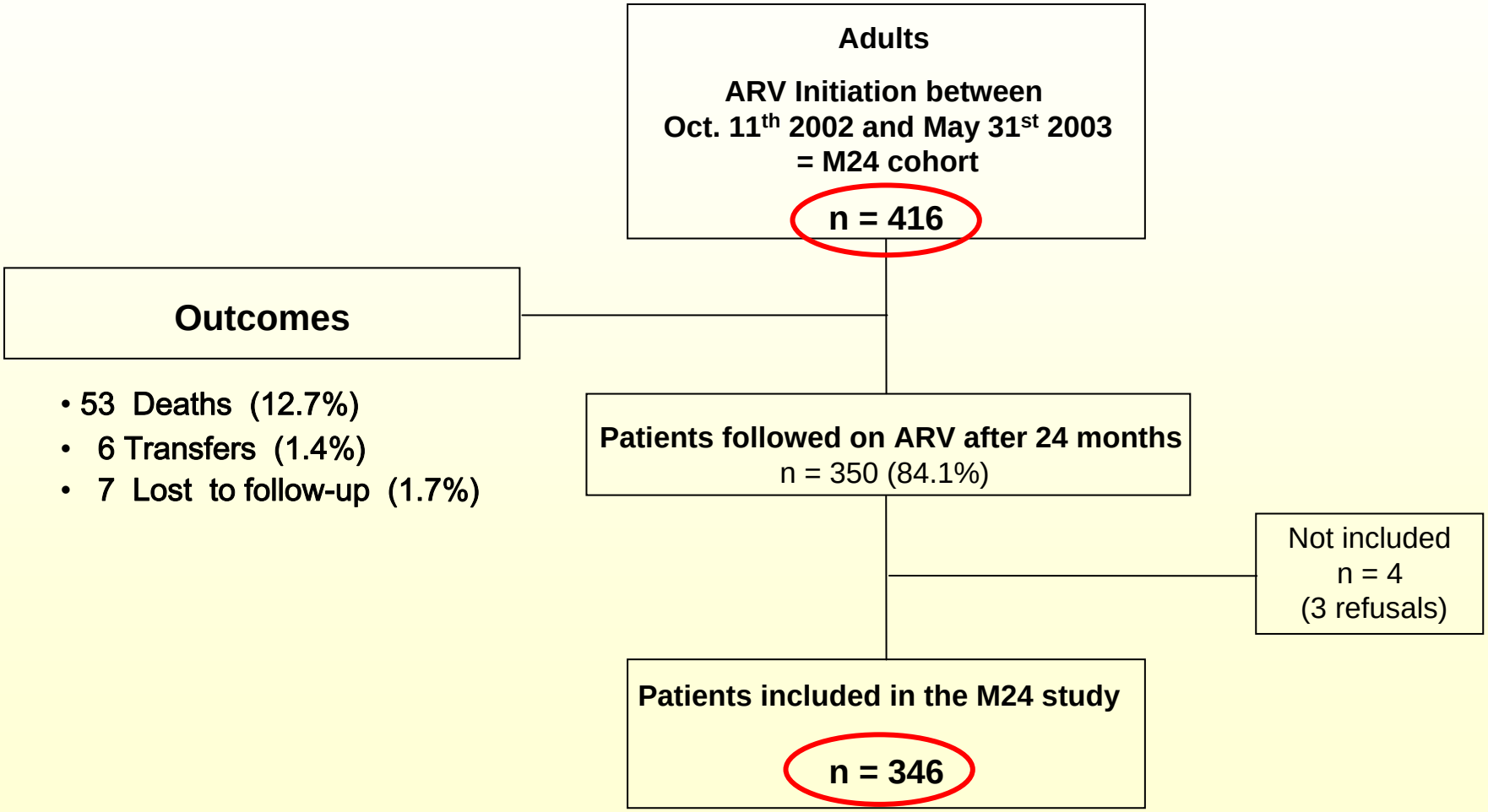
Secondary objectives

- Description of *success/failure clinico-immunological criteria* at 24 months and at 6, 12 and 18 months
- Identification of the *reasons for virological failure* at 24 months
- Description of *resistance mutations to ARV* observed at 24 months
- Analysis of the *observance* of the patients still on ARV at 24 months
- Evaluation of *ARV side-effects* during the 24 months of treatment
- *Pharmacological* analysis of ARV at 24 months

Methods

- Descriptive Analysis
  - Clinical information routinely collected in the FUCHIA© software, clinico-biological and observance questionnaries
  - Retrospective analysis of adults who started HAART 24 ± 2 months ago (M24 cohort)
- Survival analysis (Kaplan Meier)
- Virological evaluation
  - Exhaustive inclusion of adults still on ARV (Dec. 2004 – April 2005)
  - Viral loads measured using real-time PCR
  - RT HIV-1 Genotyping of samples with more than 400 copies/ml
- Analysis of clinico-immunological factors associated with virological failure (logistic regression)
- Pharmacological evaluation

Patients of the M24 cohort



Characteristics at ARV initiation

M24 Cohort (N = 416), April 2005, Cambodia

Men	247	59.2 %
Median age (years)	33.6	(IQR*: 30.1 – 38.2)
Without ARV background (naives)	397	95.2 %
Advanced clinical stage		
WHO stage III	192	46.0 %
WHO stage IV	204	48.9 %
Body Mass Index <18 kg/m^2	161 / 387	41.6 %
<15 kg/m^2	40 / 387	10.3 %
CD4 cells/ml (median)	13	(IQR: 3 – 62)
< 50 cells/ml	270 / 383	70.5 %
Initial ARV treatment		
3TC / d4T / EFV	337	80.8 %
3TC / d4T / NVP	64	15.3 %
Median time of follow-up (months)	23.8	22.8 – 24.0

* IQR: Inter-Quartile Range

Immunological Restoration

M24 Cohort (N = 416), April 2005, Cambodia

	Day 0	6 months	12 months	18 months	24 months
CD4 (median cells/ml)	13	134	193	240	269
(IQR*)	(3 – 62)	(90 – 198)	(139 – 263)	(160 – 324)	(193 –374)
% with CD4 **					
< 50 cells/ml	70.5	6.7	0.9	1.3	1.0
< 200 cells/ml	99.0	75.6	52.8	35.5	26.7
CD4 gain (median cells/ml)	-	+ 102	+ 154	+ 194	+ 234
(IQR)	-	(63 – 141)	(96 – 218)	(131 – 278)	(153 – 319)

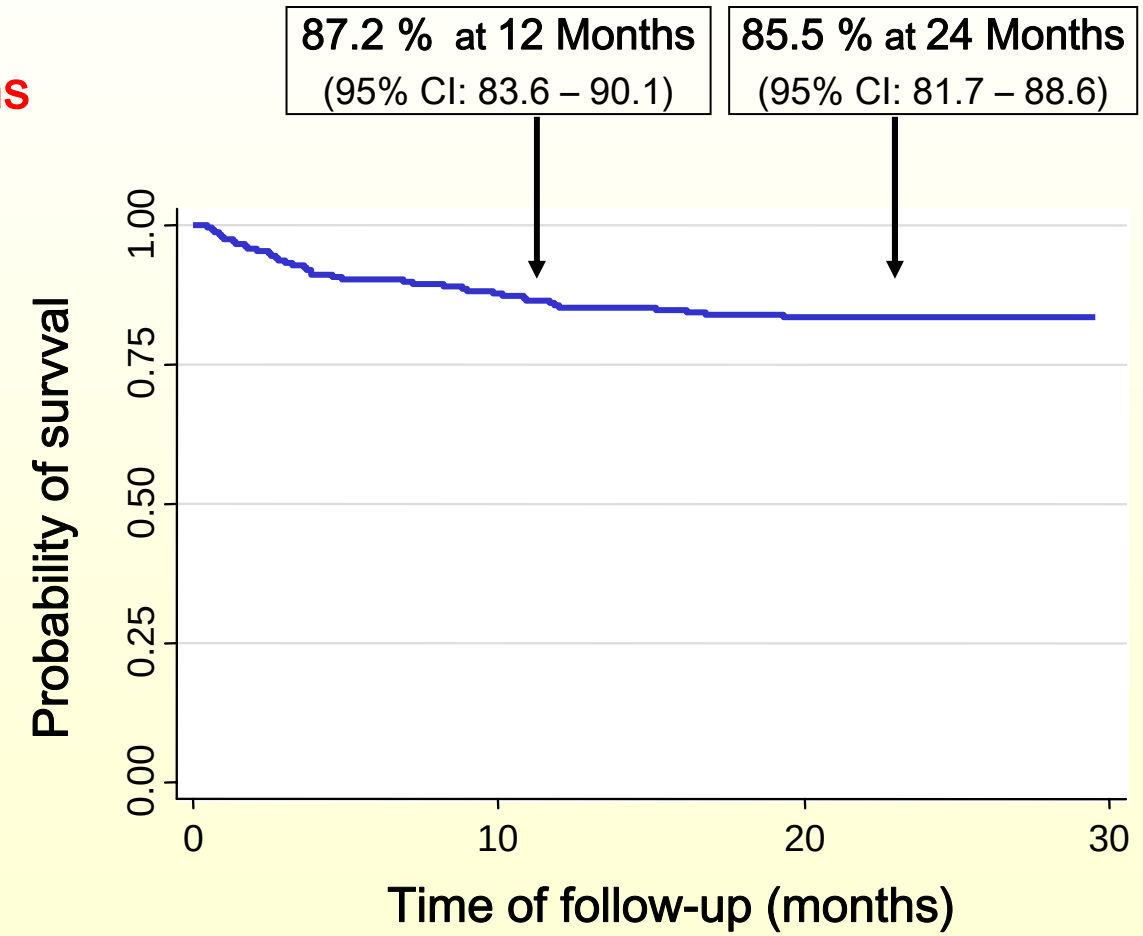
* IQR: Inter-Quartile Range

** Among available CD4

Survival Analysis

M24 Cohort (N= 416)

66 % of the deaths within the first 6 months

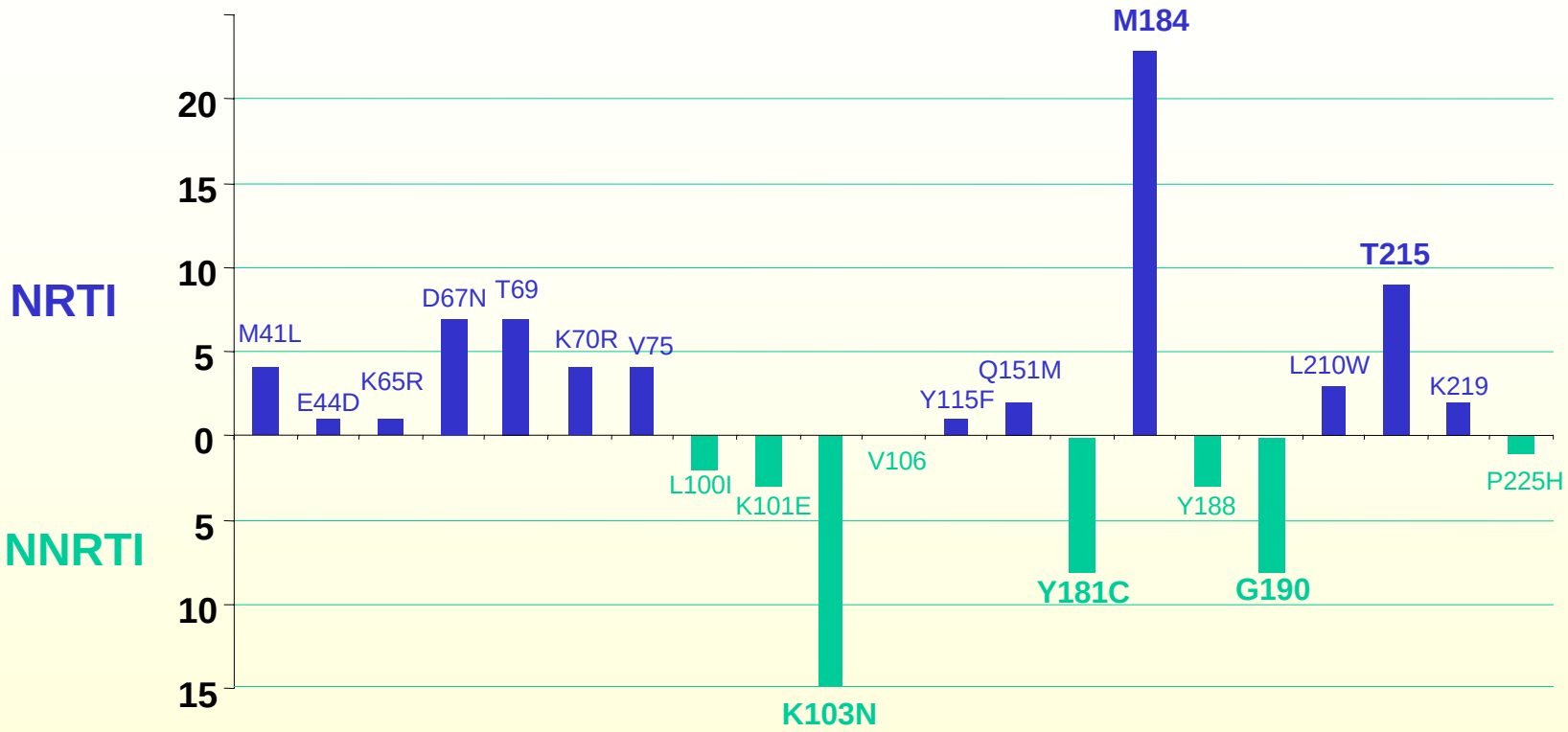


Plasma Viral Loads of Patients included in the M24 study

(N= 346)

Viral Loads (copies /ml)	N	%	CI 95%	Cumulative %
< 40	276	79.8	75.1 – 83.9	79.8
[40-400[	30	8.7	6.0 – 12.3	88.4
[400-1,000[	9	2.6	1.3 – 5.1	91.0
[1,000-5,000[	7	2.0	0.9 – 4.1	93.0
[5,000-30,000[	9	2.6	1.3 – 5.1	95.7
> 30,000	15	4.3	2.5 – 7.2	100.0
Total	346	100.0		

HIV RT Genotyping
(N=39*)

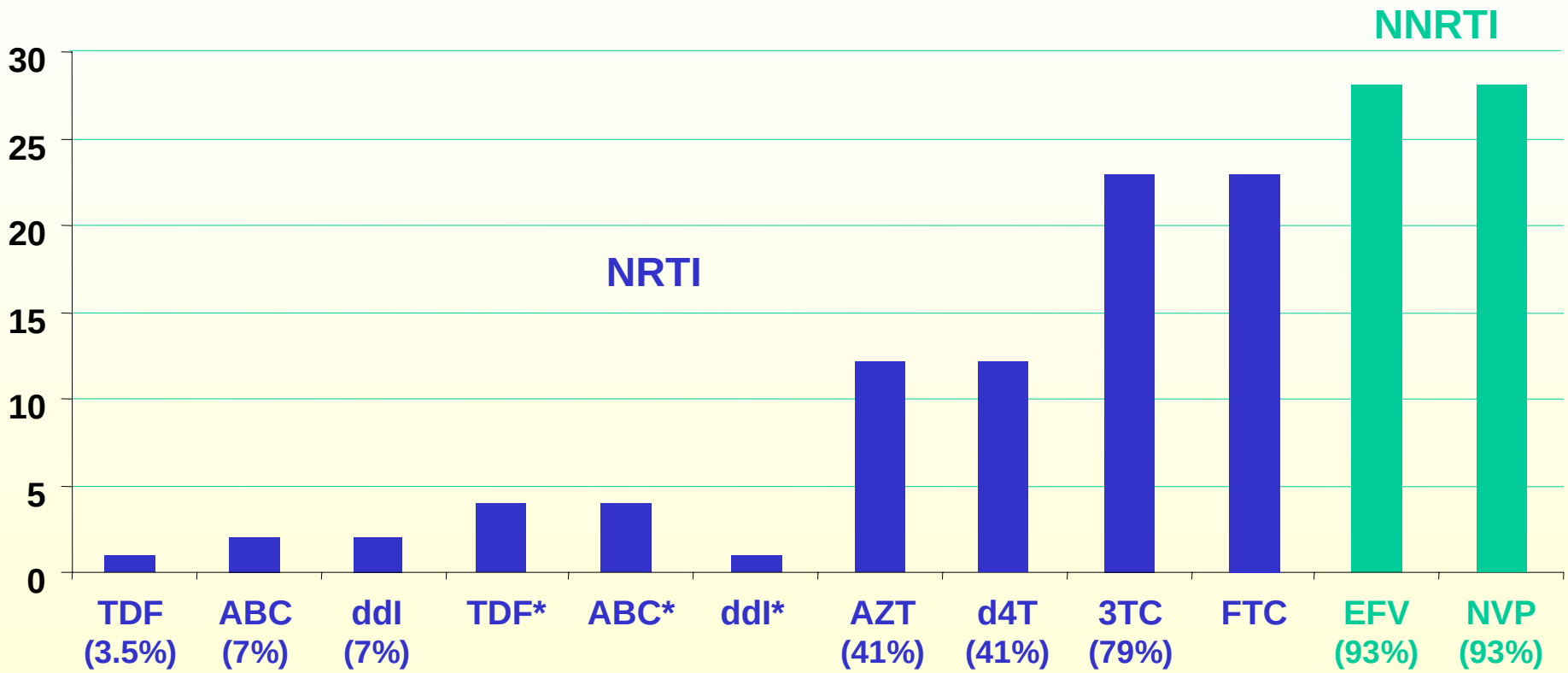


- No mutations 10/39 (25.6 %)
- NRTI mutations 23/39 (59 %)
- NNRTI mutations 28/39 (71.8 %)

* One sample could not be amplified

ARV Resistance Distribution

(according to ANRS algorithms, N=29)



- Multi-resistance to AZT / d4T / 3TC / NVP/EFV 12/29 (41 %)

* Intermediate resistance

Sensibility to proposed 2nd lines

(M24 failures, n=29)

2nd line proposed :	3 "S"	2 "S"	1 "S" (KAL)	Intakes/ Day	Cost USD
DDI+AZT+KAL	**16 (55%)**	**11 (38%)**	**2 (7%)**	**3**	**856**
DDI+3TC+KAL	**6 (21%)**	**20 (69%)**	**3 (10%)**	**3**	**783**
DDI+ABC+KAL	**23 (80%)**	**3 (10%)**	**3 (10%)**	**3**	**1597**
TDF+AZT+KAL	16 (55%)	9 (31%)	4 (14%)	2	936
TDF+3TC+KAL	**6 (21%)**	**18 (62%)**	**5 (17%)**	**2**	**863**
TDF+ABC+KAL	22 (76%)	3 (10%)	4 (14%)	2	1687
ABC+AZT+KAL	16 (55%)	8 (28%)	5 (17%)	2	1533
ABC+3TC+KAL	6 (21%)	17 (58%)	6 (21%)	2	1460

Sensibility to potential 2nd line regimen

(M24 failures with RT mutations, n=29)

2nd line proposed	Sensitive to *3 molecules*	Intakes /Day	Cost USD
ddI+ABC+KAL	**23 (80%)**	3	1597
TDF+ABC+KAL	**22 (76%)**	2	1687
ddI+AZT+KAL	16 (55%)	3	856
TDF+AZT+KAL	16 (55%)	2	936
ABC+AZT+KAL	16 (55%)	2	1533
ddI+3TC+KAL	6 (21%)	3	783
ABC+3TC+KAL	6 (21%)	2	1460
TDF+3TC+KAL	6 (21%)	2	863

A scenario according to discussed 2nd line regimen in Cambodia (no ABC), june 2006

(M24 failures with RT mutations, n=29)

	2nd line proposed	Number of patients
1	(ddI or TDF) + AZT + KAL	16 (55%)
2	(ddI or TDF) + 3TC + KAL	*6* (21%)*
0	No initial choice	13 (45%)
3	*Tritherapy:* ddI + TDF$ + KAL	**10** (34%)
4	*Bitherapy:* (ddI or TDF) + *(3TC)* + KAL	***13*** (45%)

* All also sensitive to 1

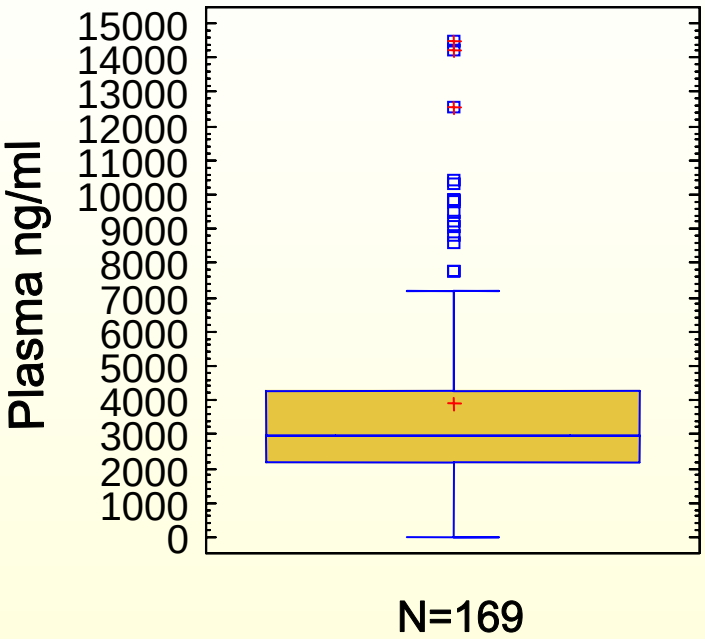
$ Not recommended association unless strict surveillance

Many patients already had severe mitochondrial toxicity or AZT-induced anemia precluding the use of ddI and AZT

Importance of ABC availibility for second line regimen

NNRTI plasma concentrations
(12h post-dose for EFV and trough for NVP)

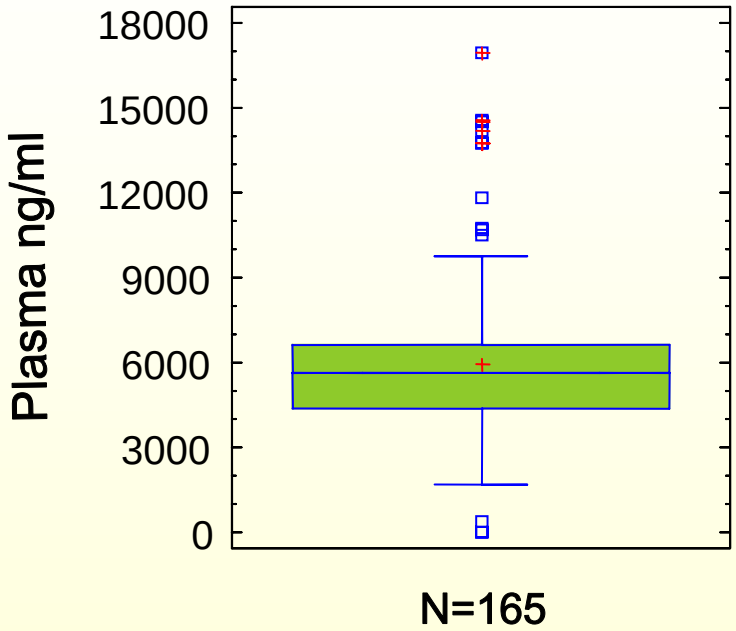
EFV



Median : 2946 ng/mL
Range [<50-31559]
Therapeutic Rate : 1000-4000 ng/mL

- Undetectable: 2,9% (n=5)
- <1000 ng/mL: 2,9% (n=5)
- >4000 ng/mL: 27,8% (n=47)

NVP



Median : 5643 ng/mL
Range [<25-16971]
Therapeutic Rate : 3000-8000 ng/mL

- Undetectable: 1,2% (n=2)
- <3000 ng/mL: 3,6% (n=6)
- >8000 ng/mL: 12,7% (n=21)

Success / Failure
M24 Cohort

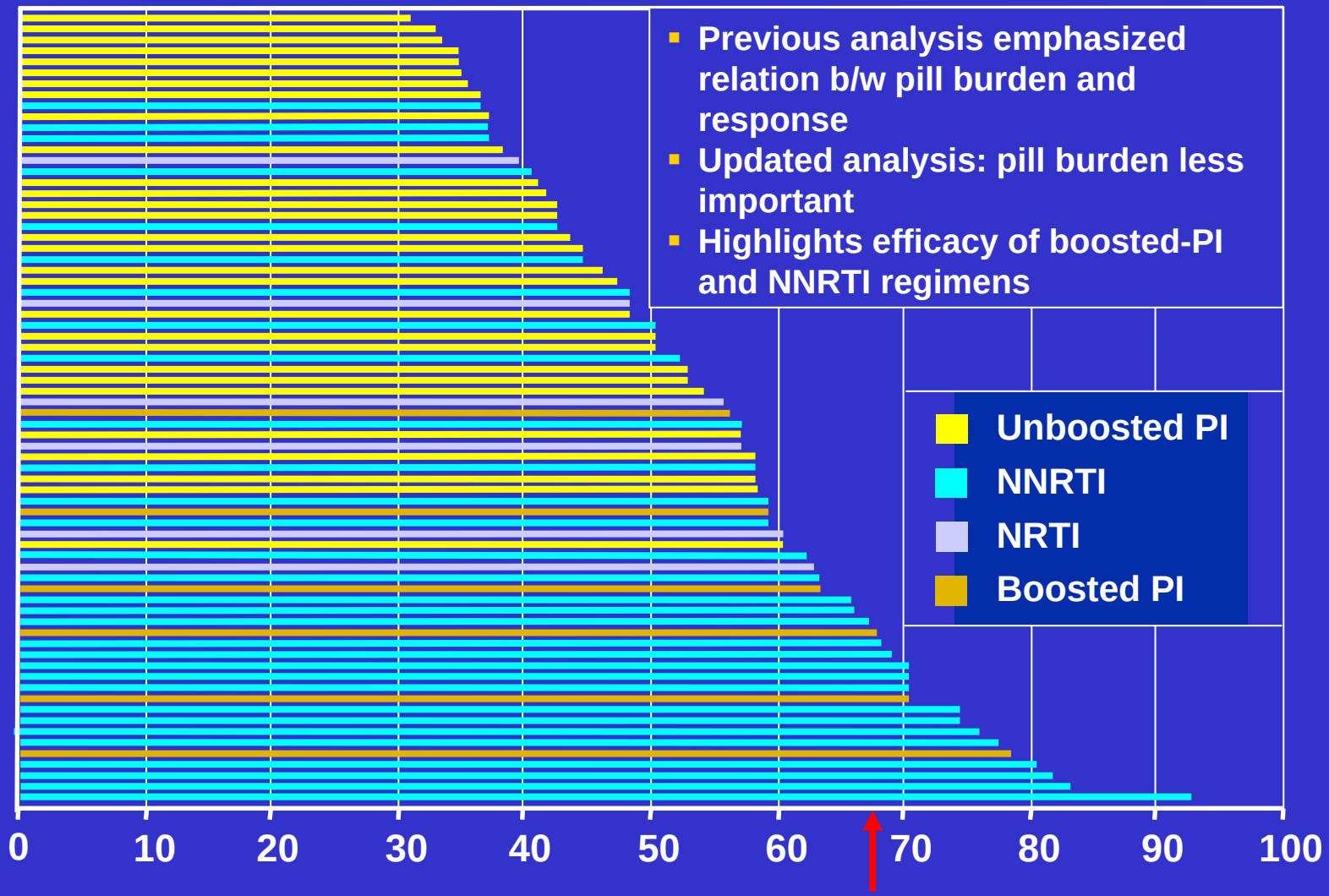
- 88 % of virological success on treatment
- 75 % of treatment success in an intention-to-treat analysis

  (104 failures : 53 deaths + 7 lost to follow-up + 40 virological failures > 400 copies/ml + 4 missing data)

  [67.8 % if virological failure = > 40 copies/ml]

Collated Results of HAART Studies

% With VL < 50 at Week 48



Bartlett JA et al. Abstract 586.

Conclusions

- Observational Cohort with simplified follow-up
- Severity of the patients included in this cohort in Cambodia (median CD4 = 13 cells/ml)
- At 24 months :
  - 84 % of patients still on treatment
  - 88% of virological success among patients still on treatment
  - 75 % of success in an ITT analysis of the whole cohort
- Perspectives:
  - M36, M42…studies (Long term outcomes ?)
  - Second line efficacy study

Main Collaborators

Infectious Disease Department, PBNS Hospital, Phnom Penh

- Ngeth ChanChhaya
- Prak Narom
- Chea You Sreng

Hôpital Kremlin-Bicêtre

- Jean-François Delfraissy
- Anne-Marie Taburet

Institut Pasteur du Cambodge

- Eric Nerrienet, Ly Nary
- Jean-Marc Reynes
- Didier Monchy, Chan Than Srey

MSF in Phnom Penh

- Didier Laureillard
- Marcelo Fernandez
- Catherine Quillet

Inserm U379

- Bruno Spire

Hôpital Necker-Enfants Malades

- Christine Rouzioux

Epicentre

- Gloria Puertas, Loretxu Pinoges
- Laurent Ferradini

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