

# IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART), CD4 CELL COUNTS, AND VIRAL LOAD ON AIDS-DEFINING EVENTS (ADE) INCIDENCE

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**Background:** HAART significantly reduces ADE incidence, mainly by the way of improved immune status when effective viral suppression has been obtained. In patients with virologic failure and deep immunosuppression, impact of maintenance of HAART on ADE incidence in comparison with the pre-HAART era is poorly documented.  
**Key words:** AIDS-defining events or Death (ADE-D), highly active antiretroviral therapy (HAART), CD4 count.

## DATA

### ❖ DATABASE

- HIV-1 infected patients from the French Hospital Database on HIV (FHDH), aged at least 13 years.
- Two study periods: the pre-HAART era [1992-1994] and the HAART era [2000-2002].
- Follow-up between January 1, 1992 and December 31, 1994 for the 1st period and between January 1, 2000 and December 31, 2002 for the 2nd period.
- Patients with a low level of CD4 count (<200 cells/mm<sup>3</sup>) and two informed consecutive measures of CD4 count in the study period were selected.
- During the HAART era, patients with at least 6 months of prescribed HAART treatment were selected.

### ❖ STUDY POPULATION

Several groups of patients were defined during these 2 periods:

#### 2 cohorts of pre-HAART era patients [1992-1994]:

- Without treatment group (Gp1):** patients without treatment, with a follow-up censored at the initiation of a monotherapy treatment.
- Monotherapy group (Gp2):** patients on monotherapy treatment, with a follow-up censored at the initiation of a treatment containing at least two antiretroviral drugs.

#### 3 cohorts of HAART-treated patients [2000-2002]:

- HAART interruption Group (Gp3):** patients having a HAART treatment interruption of at least 3 months, with at least 2 follow-up visits without treatment.
- Detectable plasma viral load (VL) Group (Gp4):** patients with at least 2 VL values  $\geq$  500 cp/ml while on HAART treatment without interruption.
- Undetectable VL Group (Gp5):** patients with 2 VL values < 500 cp/ml while on HAART treatment without interruption.

### ❖ PATIENTS' CHARACTERISTICS

- During the pre-HAART era:** 3 050 patients for Gp1 (78.7% men) and 10 560 for Gp2 (79.7% men) were selected.
- During the post-HAART era:** 6 624 patients (73.6% men) were selected, including:
- 4 563 patients with at least two detectable VL values (Gp4), including 51.8% patients with a VL level at baseline above 30 000 cp/ml.
  - 3 008 patients with undetectable VL values (Gp5)
  - 1 047 patients who had at least once a HAART interruption (Gp3), including 56.0% patients with a VL level at baseline above 30 000 cp/ml.
  - The median HAART interruption was 4.6 months (IQR: [2.7- 8.9]).
  - For the study period, the median values of VL were 81 600 cp/ml (IQR: [9 600- 275 846]) and 24 000 cp/ml (IQR: [2 520-122 000]) for Gp3 and Gp4 *resp.*

#### Patients' characteristics at baseline

	pre-HAART era		post-HAART era
	Without treatment (Gp1)	Monotherapy (Gp2)	Overall population
<b>Transmission Group (%)</b>			
Homosexual	1 235 (40.5%)	4 188 (39.7%)	1754 (26.5%)
Intravenous drug user	863 (28.3%)	3 133 (29.7%)	1533 (23.1%)
<b>Heterosexual</b>			
Other	707 (23.2%)	2 231 (21.1%)	2589 (39.1%)
Other	245 (8.0%)	1 008 (9.5%)	748 (11.3%)
<b>Median values [IQR]</b>			
Age	34.5 [30.1 - 41.3]	34.5 [30.2 - 41.3]	39.8 [35.2 - 46.2]
CD4 cells count	62 [20 - 140]	84 [29 - 149]	130 [78 - 169]
Follow up (in months)	3.8 [1.5 - 8.4]	9.8 [4.9 - 17.3]	10.7 [4.5 - 22]

IQR: Interquartile range

## METHODS

### ❖ VARIABLES

We compared the incidences of new ADE among each group. The incidence of new events was then calculated for AIDS events of different aetiologies:

- Viral events:** Cytomegalovirus disease, Herpes-simplex disease, Kaposi's sarcoma, progressive multifocal leukoencephalopathy (PML).
- Fungal events:** pulmonary or esophageal candidiasis, extra-pulmonary cryptococcosis, pneumocystis carinii pneumonia.
- Protozoal events:** brain or disseminated toxoplasmosis, isosporiasis, cryptosporidiosis.
- Bacterial events:** pulmonary and extra-pulmonary tuberculosis, recurrent bacterial pneumonia, recurrent Salmonella sepsis, atypical mycobacteriosis.
- Other events:** HIV-related encephalopathy, invasive cervical cancer, non-Hodgkin lymphoma, primary brain lymphoma, and unspecified events with unknown aetiology.

### ❖ STATISTICAL ANALYSIS

- The incidence rates (IR) [events/100 person-years] (E/100 PY) and 95% confidence interval (95%CI), were determined among each group for two CD4 count strata:  $\leq$ 50 and 50-200 cells/mm<sup>3</sup>.
- IRs were compared using a z-test between two independent proportions.
- Multivariate analyses were performed using Cox's proportional-hazards models with counting process. The model took into account:
  - time-dependant continuous variables: CD4 count stratum and the study group
  - fixed variables: baseline characteristics (gender, AIDS status and HIV transmission group).

## RESULTS (1)

- Overall, estimated ADE IRs were significantly higher during pre-HAART era *versus* HAART era and IRs significantly decreased from Gp3 to Gp5.
- ADE IRs were significantly higher among patients without treatment or on monotherapy compared to patients on HAART interruption.
- ADE IRs were significantly lower among patients with detectable or undetectable VL than among patients on HAART interruption, even when CD4 count was <50cells/mm<sup>3</sup>.
- In Gp3 and Gp4, ADE IR (overall stratum) was significantly higher for patients with a VL level at baseline above 30 000cp/ml compared to patients with a lower level of VL:
  - 30.8 ( $\pm$ 5.9 (95%CI)) and 15.6 ( $\pm$ 4.3) *resp.* for Gp 3 ( $p < .0001$ ).
  - 20.0 ( $\pm$ 1.9 (95%CI)) and 8.2 ( $\pm$ 1.2) *resp.* for Gp4 ( $p < .0001$ ).

#### ADE IRs [E/100 PY] 95%CI (*p-value*)\*, for each CD4 stratum and each aetiology

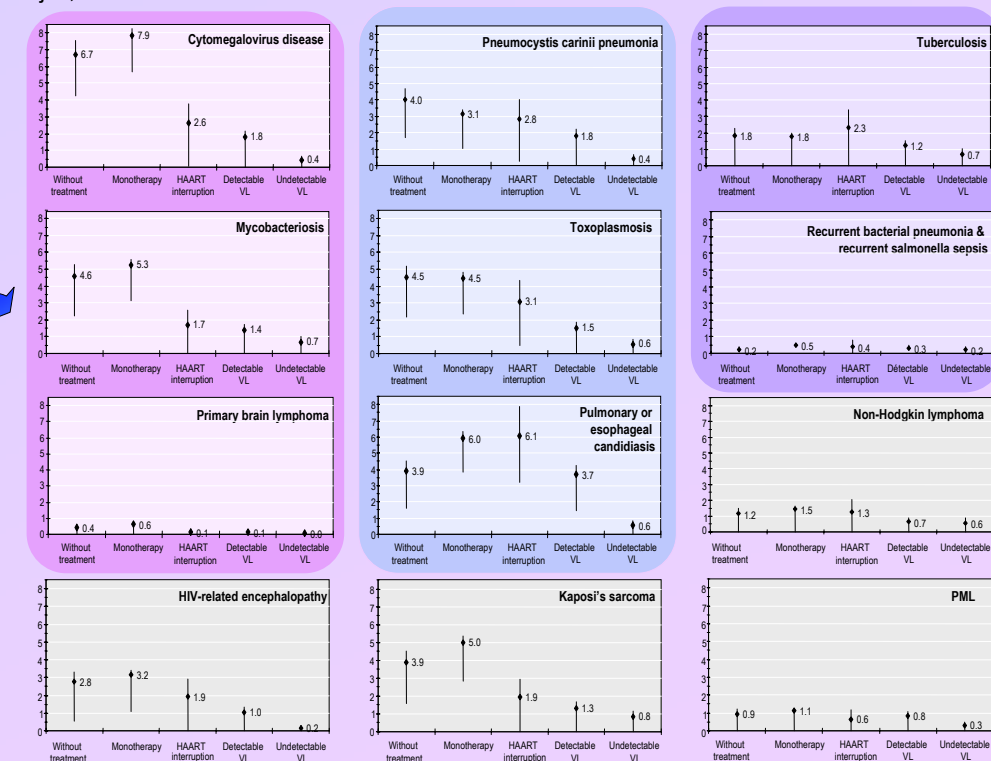
CD4 counts (cells/mm <sup>3</sup> )	Aetiology	Pre-HAART era [1992-1994]			HAART era [2000-2002]	
		Without treatment (Gp1)	Monotherapy (Gp2)	Interruption (Gp3)	Detectable (Gp4)	Undetectable (Gp5)
$\leq$ 50	<b>New ADE</b>	63.5 $\pm$ 4.6 ( $p = .150$ )	68.4 $\pm$ 2.3 ( $p = .0028$ )	58.0 $\pm$ 11.0	44.4 $\pm$ 4.6 ( $p = .0009$ )	27.3 $\pm$ 9.6 ( $p < .0001$ )
	<b>Viral</b>	12.8 $\pm$ 1.7 ( $p = .2043$ )	13.4 $\pm$ 0.8 ( $p = .083$ )	10.6 $\pm$ 2.9	7.0 $\pm$ 0.9 ( $p = .0039$ )	4.6 $\pm$ 0.9 ( $p < .0001$ )
50-200	<b>New ADE</b>	32.6 $\pm$ 2.1 ( $p < .0001$ )	33.6 $\pm$ 1.0 ( $p < .0001$ )	23.5 $\pm$ 3.7	14.3 $\pm$ 1.2 ( $p < .0001$ )	5.7 $\pm$ 1.0 ( $p < .0001$ )
	<b>Viral</b>	9.7 $\pm$ 1.0 ( $p = .0110$ )	11.9 $\pm$ 0.5 ( $p < .0001$ )	5.9 $\pm$ 1.7	4.3 $\pm$ 0.6 ( $p = .0478$ )	1.8 $\pm$ 0.5 ( $p < .0001$ )
<b>Total</b>	<b>Fungal</b>	8.7 $\pm$ 1.0 ( $p = .6078$ )	9.5 $\pm$ 0.5 ( $p = .8969$ )	9.3 $\pm$ 2.2	6.0 $\pm$ 0.7 ( $p = .0006$ )	1.2 $\pm$ 0.4 ( $p < .0001$ )
	<b>Protozoal</b>	6.3 $\pm$ 0.8 ( $p = .0251$ )	6.9 $\pm$ 0.4 ( $p = .0034$ )	4.2 $\pm$ 1.4	1.8 $\pm$ 0.4 ( $p < .0001$ )	0.8 $\pm$ 0.3 ( $p < .0001$ )
<b>Bacterial</b>	<b>Bacterial</b>	6.2 $\pm$ 0.8 ( $p = .0308$ )	7.2 $\pm$ 0.4 ( $p = .0012$ )	4.2 $\pm$ 1.5	3.0 $\pm$ 0.5 ( $p = .0718$ )	1.6 $\pm$ 0.5 ( $p < .0001$ )
	<b>Other</b>	4.2 $\pm$ 0.7 ( $p = .3446$ )	5.1 $\pm$ 0.3 ( $p = .0415$ )	3.5 $\pm$ 1.3	1.9 $\pm$ 0.4 ( $p = .0044$ )	0.8 $\pm$ 0.4 ( $p < .0001$ )

\*: *p-value* corresponding to the comparison of each group vs Gp3.

#### Hazard Ratios (HRs), [95%CI] and *p-value*, versus Gp3 adjusted on CD4 count stratum, gender, AIDS status and HIV transmission group

	Pre-HAART era [1992-1994]		Interruption (Gp3)	HAART era [2000-2002]	
	without treatment (Gp1)	Monotherapy (Gp2)		Detectable (Gp4)	Undetectable (Gp5)
<b>New ADE</b>	1.06 [0.90-1.25] ( $p = .4721$ )	1.22 [1.05-1.43] ( $p = .0102$ )	1	0.60 [0.51-0.72] ( $p < .0001$ )	0.34 [0.27-0.43] ( $p < .0001$ )
<b>Viral events</b>	1.02 [0.76-1.36] ( $p = .9124$ )	1.41 [1.07-1.85] ( $p = .0142$ )	1	0.63 [0.46-0.86] ( $p = .0033$ )	0.44 [0.29-0.65] ( $p < .0001$ )
<b>Fungal events</b>	0.66 [0.52-0.84] ( $p = .0009$ )	0.78 [0.62-0.97] ( $p = .0244$ )	1	0.55 [0.43-0.71] ( $p < .0001$ )	0.17 [0.11-0.26] ( $p < .0001$ )
<b>Protozoal events</b>	1.32 [0.91-1.93] ( $p = .1461$ )	1.60 [1.12-2.29] ( $p = .0100$ )	1	0.54 [0.36-0.81] ( $p = .0030$ )	0.27 [0.15-0.50] ( $p < .0001$ )
<b>Bacterial events</b>	1.35 [0.92-1.96] ( $p = .1245$ )	1.73 [1.20-2.47] ( $p = .0028$ )	1	0.86 [0.58-1.28] ( $p = .4625$ )	0.57 [0.35-0.93] ( $p = .0257$ )
<b>Other events</b>	0.94 [0.63-1.40] ( $p = .7539$ )	1.14 [0.78-1.65] ( $p = .5025$ )	1	0.58 [0.38-0.89] ( $p = .128$ )	0.47 [0.27-0.81] ( $p = .0070$ )

#### ADE IRs, 95% CI for different ADE [E/100 PY]



## RESULTS (2)

- For viral, protozoal, bacterial and other events, IRs and HRs were lower during the HAART era than during the pre-HAART era.
- For fungal events, IRs and HRs were higher in the HAART interruption group than in all other groups.
- For cytomegalovirus disease, mycobacteriosis, primary brain lymphoma, pre-HAART IRs were higher than post-HAART IRs.
- For pneumocystis carinii pneumonia, toxoplasmosis, pulmonary or esophageal candidiasis, IRs in the HAART interruption group were not different than IRs in pre-HAART era groups.
- For tuberculosis, recurrent bacterial pneumonia and recurrent salmonella sepsis, IRs were not influenced by the study group.

## CONCLUSION

- Patients from HAART era groups had a lower incidence of ADE than patients from pre-HAART era groups with similar CD4 count level.
- Even among patients with deep immunologic and virologic failure, maintenance of HAART protects from ADE occurrence.
- HAART interruption was mostly deleterious for ADE (pneumocystis carinii pneumonia, toxoplasmosis, pulmonary or esophageal candidiasis) occurring within a low level of immunosuppression; whereas HAART interruption less influenced ADE (cytomegalovirus disease, mycobacteriosis, primary brain lymphoma) occurring within a deep level of immunosuppression.
- Occurrence of bacterial events (tuberculosis, recurrent bacterial pneumonia and recurrent salmonella sepsis) is less influenced by immunosuppression level and study groups had a low influence on their occurrence.
- For fungal events, IRs were lower among patients from the pre-HAART era groups compared to patients on HAART interruption, probably due to effective prophylaxis largely prescribed during pre-HAART era.