Compassionate use programmes

Are saving lives

Patients' Advocates Capacity-building Workshops

EURORDIS
Rare Diseases Europe

23 May 2012

Patients seeking information

There is an abundance of health information, and in particular news about new products.

The main source of information is the industry itself, in the “Investors” section of their website.

This is often the main web pages to visit when you need accurate and timely information on the development status of any new medicine.

Term	Number of hits on www	Number of articles in PubMed
« promising new drug »	512 000	165
« promising new treatment »	402 000	325
« promising new cure »	23 500	557
Search done 15/05/2012		

A frequent situation

New drug being developed

New drug authorised

Marketing authorisation

Some patients have no more treatment options, their condition deteriorates. Some die.
They know some trials are in progress

When the drug is authorised, all patients can have access.

There is always one patient who will die the day before a drug is authorised and who knows the drug will be authorised next day

For all, this is a nightmare

Compassionate use is a response

New drug being developed

New drug authorised

Compassionate use

But whenever a compassionate use programme starts, there will always be patients for whom it will be too late.

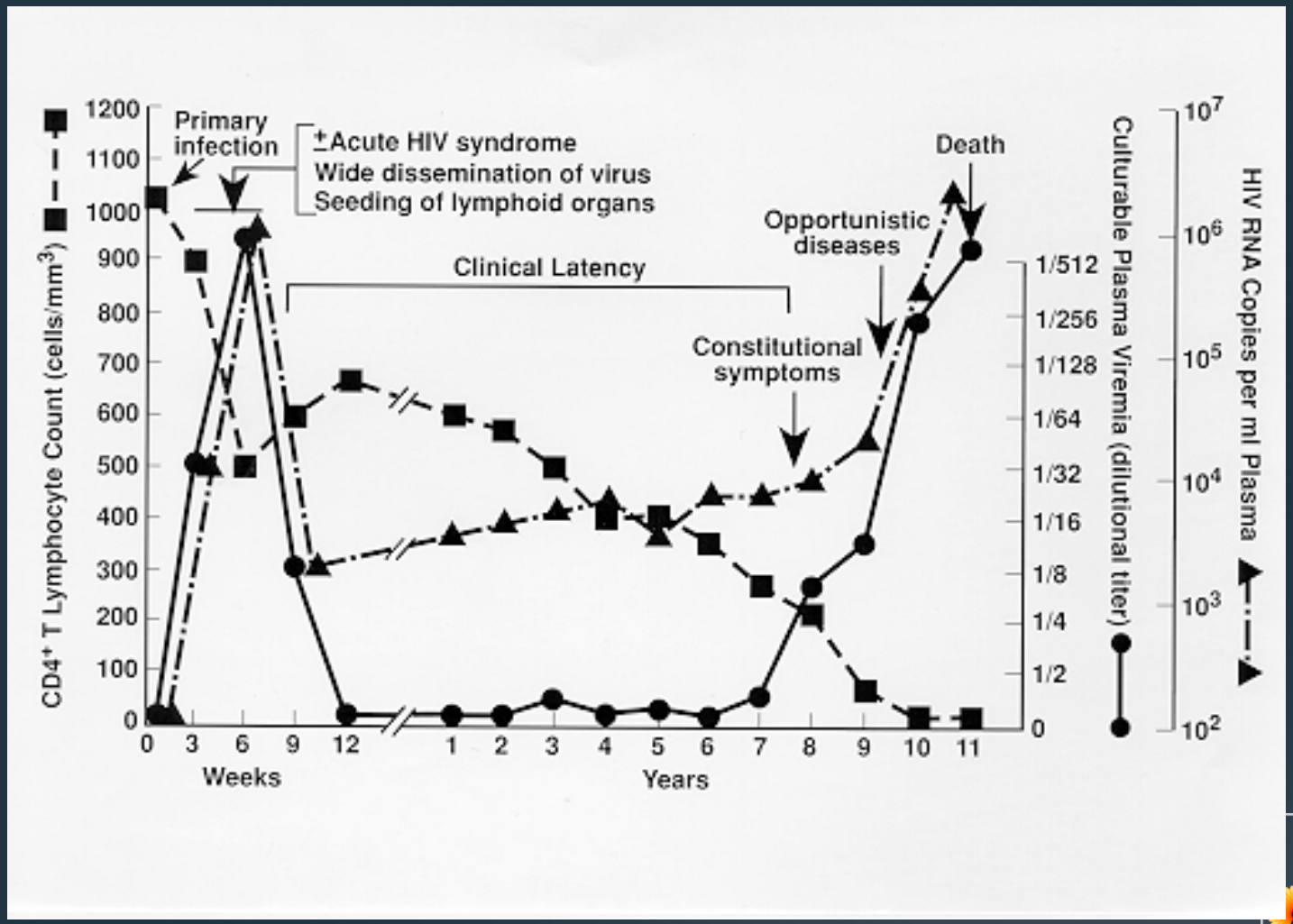
Capacity building

Example of

A SUCCESSFUL COMPASSIONATE USE PROGRAMME

Capacity building

The classical pathophysiology of HIV infection



A rapid CD4 recovery on HAART

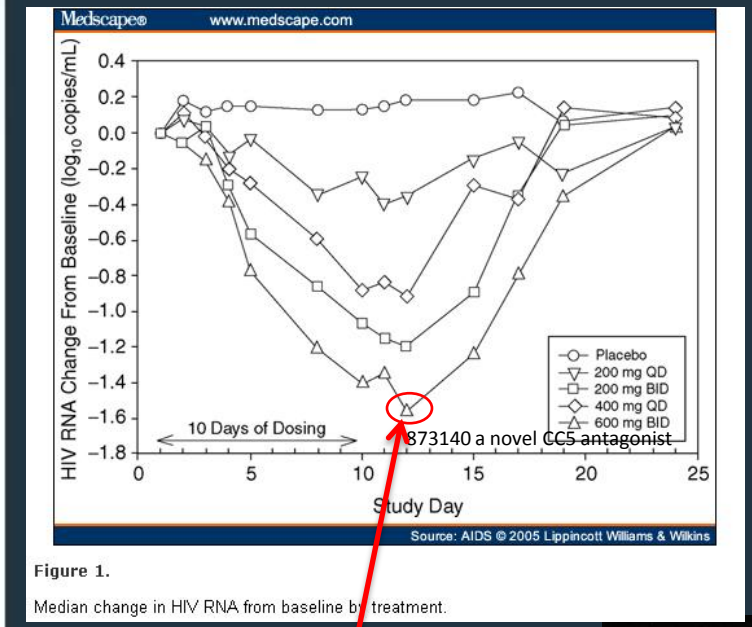
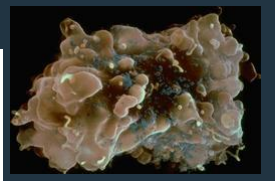


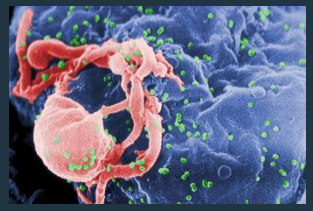
Figure 1.

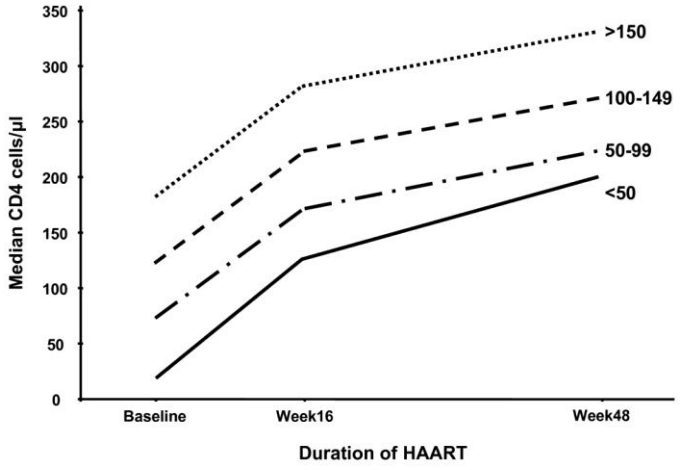
Median change in HIV RNA from baseline by treatment.

873140 a novel CC5 antagonist



-1,6 log = -97.5% HIV RNA





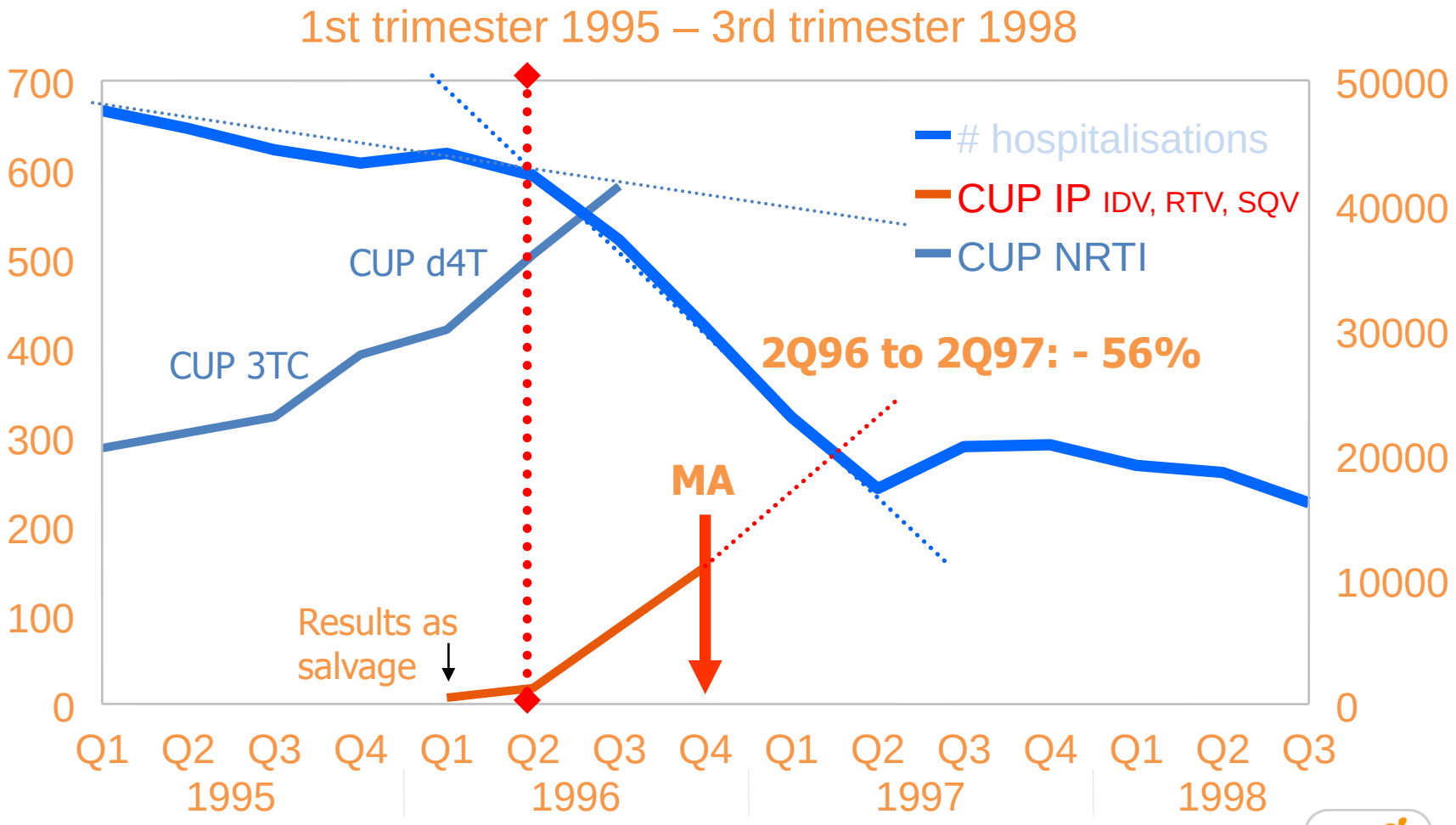
Baseline CD4 cell count (cells/µl)	Phase 1 (0-16 weeks)	Phase 2 (16-48 weeks)
≥150	21.9 (9.3, 42.9)	5.1 (-3.0, 15.5)
100-149	24.5 (13.4, 44.2)	5.3 (-2.1, 13.5)
50-99	26.0 (11.4, 42.9)	6.8 (-0.2, 14.6)
<50	26.0 (17.8, 40.8)	9.9 (2.3, 21.3)

Graph showing the median CD4 cell counts at baseline and during ART stratified by baseline CD4 cell count.
Below the graph, the median (IQR) rates of CD4 cell increase (cells/µl/month) are given for phase 1 (0 – 16 weeks) and phase 2 (16–48 weeks) of immune recovery. Lawn *et al. BMC Infectious Diseases* 2006 **6**:59

Capacity building

A success story

hospitalisation rates for 1000 AIDS patients, France 1995-1998



CUP: Compassionate Use Programme. Data from industry and BEH.

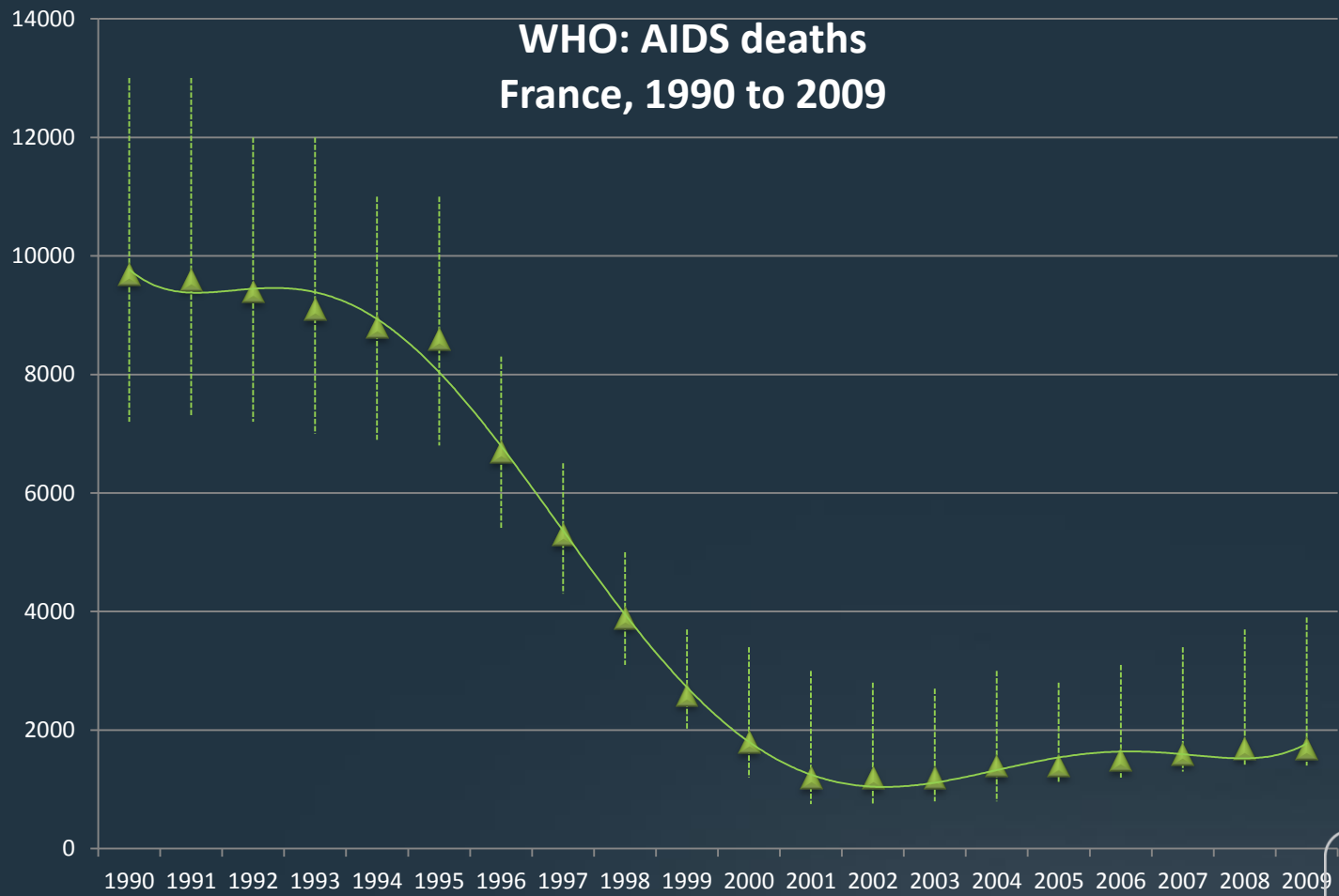
Capacity building

But to obtain this:

- A lottery had to be organised to distribute the first 250 treatments
- French Drug Agency requested Ethics Council opinion
- A group of 60 patients closed down an Abbott factory in Normandy 29/02/1996
- Simultaneously with FDA public hearing 29/02/1996
- As some 10 000 patients were expecting the new regimen

Capacity building

Hospitalisations first, then mortality declined



Capacity building

EU legislation on compassionate use

A TRIBUTE TO HIV/AIDS ADVOCATES

Capacity building

History

- US: Aids activists urged FDA to accelerate regulatory process
  - March on Wall Street, on 24 March 24 1987
  - FDA adopted the compassionate use scheme
- France 1988
  - French activists negotiated early access with health authorities
  - 1991: ATU in Code de la Santé Publique
- Denmark: 1995
- Germany: 2005
- Italy: 2006
- Spain: 2009

Actions in Europe

- December 1999
  - European Aids Treatment Group (EATG) presented its analysis of time delays in access to new products between US and EU, and within EU
- January 2000
  - EATG press release “Aids activists fight for European wide early access to drugs”
- March 2000
  - Daniel Vittecoq sent his draft proposal to EATG on an new conditional approval procedure
- 2001 EATG responded to EC audit on the regulatory framework
  - and asked EC both for a compassionate use legislation and for conditional approval

Capacity building

EATG met CPMP on several occasions since April 1996

ANNEX III to CPMP December 1999
Press Release

REPORT ON MEETING WITH THE EUROPEAN AIDS TREATMENT GROUP HELD ON 14 DECEMBER 1999

The CPMP met representatives of the European AIDS Treatment Group (EATG) on 14 December 1999 to exchange views and discuss information in relation to HIV/AIDS treatments. This meeting was the 3rd meeting of the CPMP and EATG held since 1995. Prof. Jean-Michel Alexandre chaired the meeting.

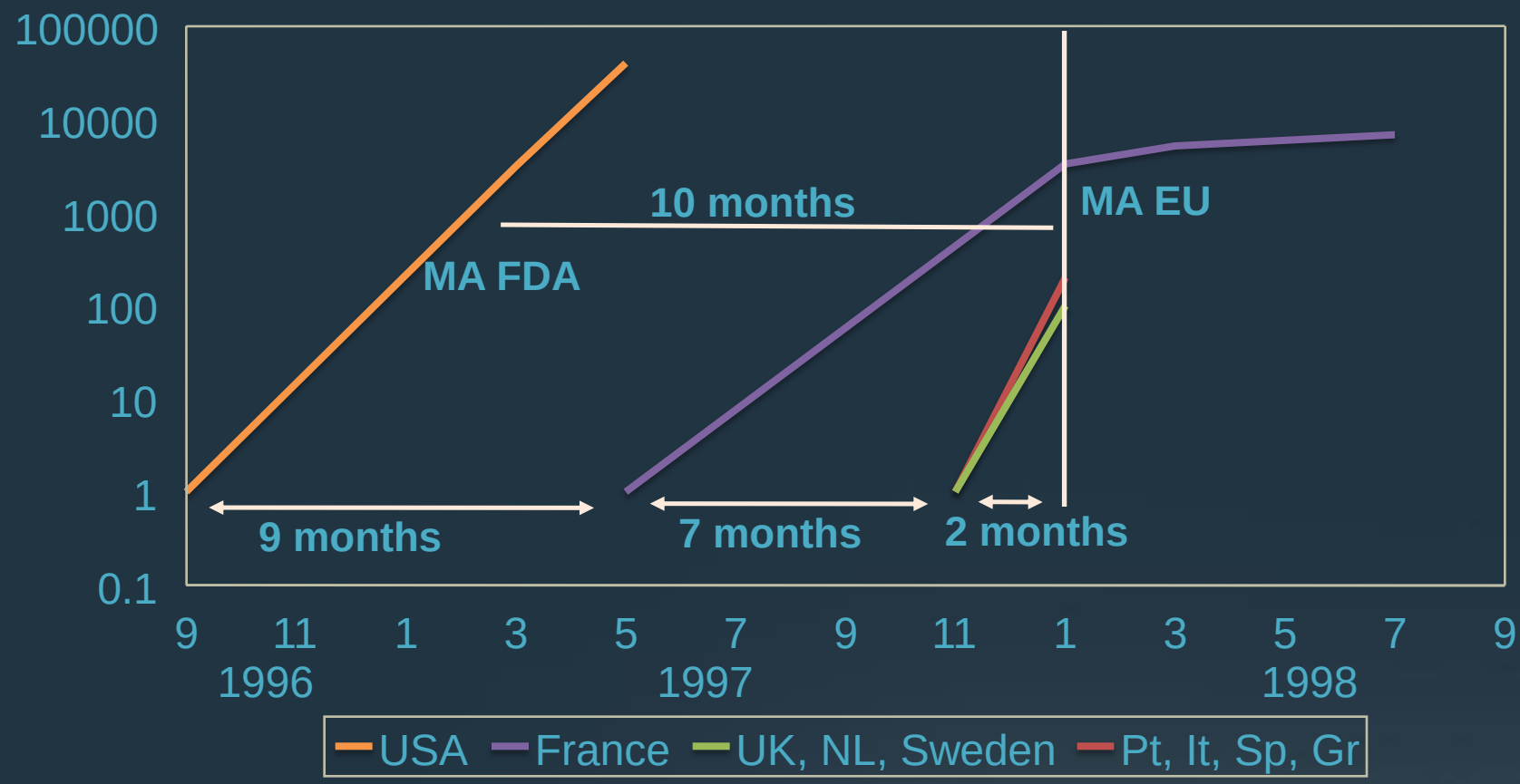
- EATG expressed their concern with respect to early access to promising medicinal products for HIV infected patients who have exhausted all available therapeutic options. EATG presented a comparison, which revealed a gap in access to new promising compounds through compassionate use programmes. Between the USA and the Member States of the European Union, the gap in access was up to 15 months. Within the European Union, additional differences exist between more sophisticated compassionate use systems in place in some Member States and less developed in others. Such differences in access may be due to strategies of the companies, lack of manufacturing production capacity and different national legislation or regulatory bodies being responsible within the Member States. It has been proposed to EATG that, during the Audit phase of the 2001 revision of the European system, they provide the Commission and the EMEA with a detailed report on the situation within the European Union explaining the practical difficulties and make proposals for improvement.

Data presented to CPMP

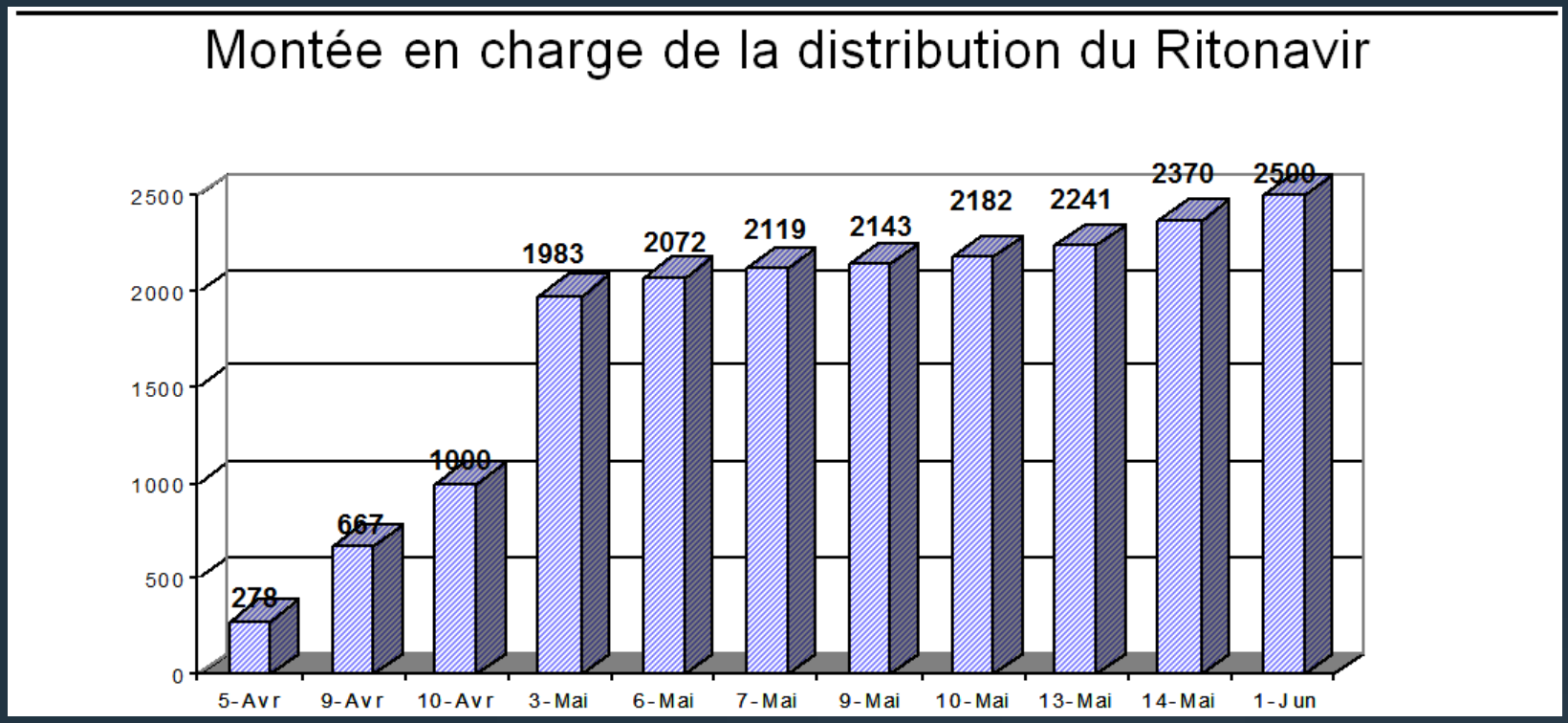
For HIV people in desperate need for new options: a persisting gap between US and EU

1995 : saquinavir (Invirase)	90 to 120 days delay between US and EU EAP
Nelfinavir (Viracept)	210 days between US and France, 420 days rest of EU
Abacavir (Ziagen)	150 to 900 days
Amprenavir (Agenerase)	60 to 390 days
Adefovir (Preveon)	450 days (only 1 EU state)
Norvir new capsule	30 days to > 180
Lopinavir ABT378/r	30 days to > 150
2000 : tenofovir PMPA	> 180 days

ATU provides access earlier than in any other EU MS, e.g. nelfinavir



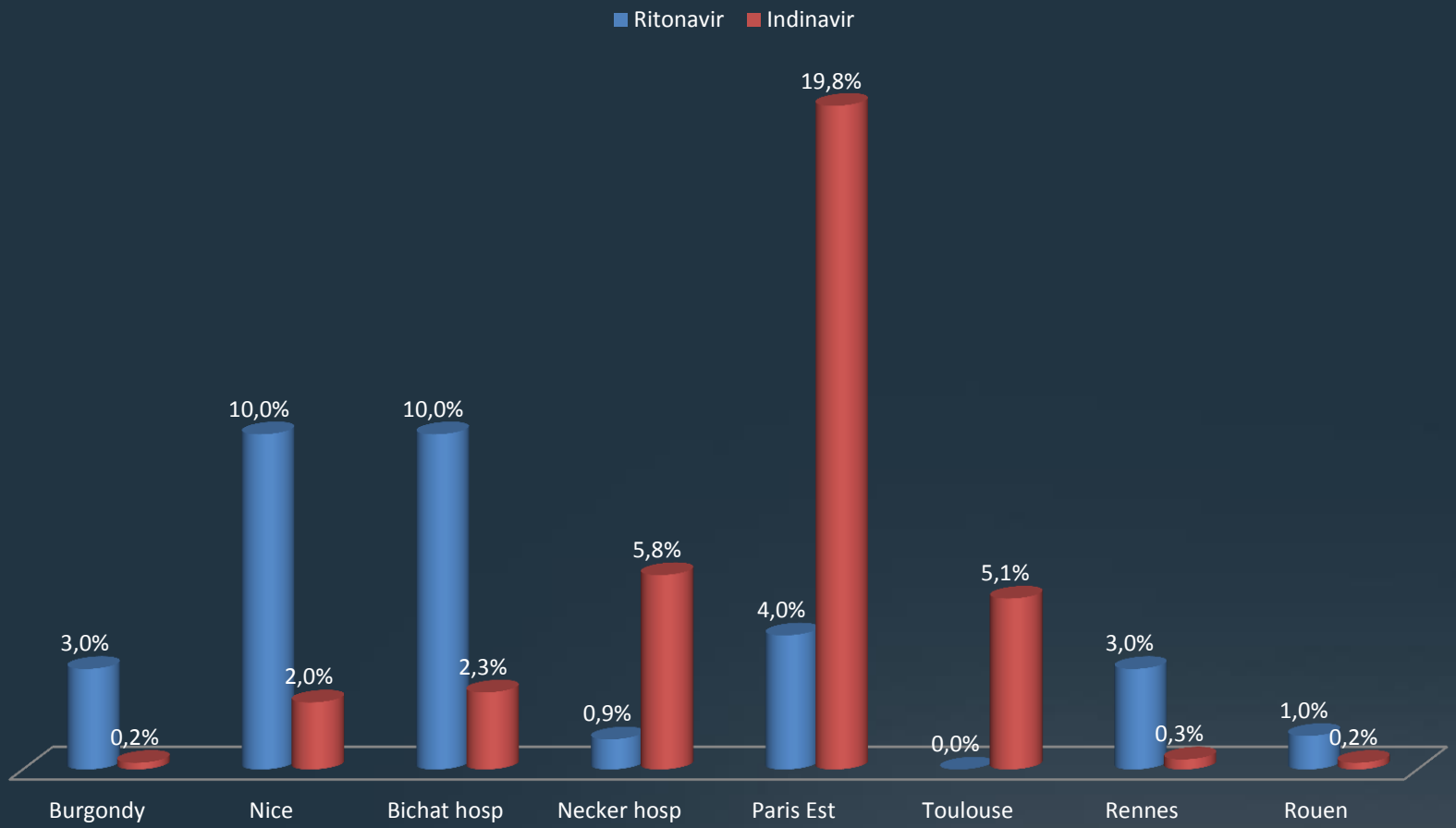
Patients' organisations could monitor the programme efficiency



Capacity building

Patients' organisations could monitor the programme efficiency

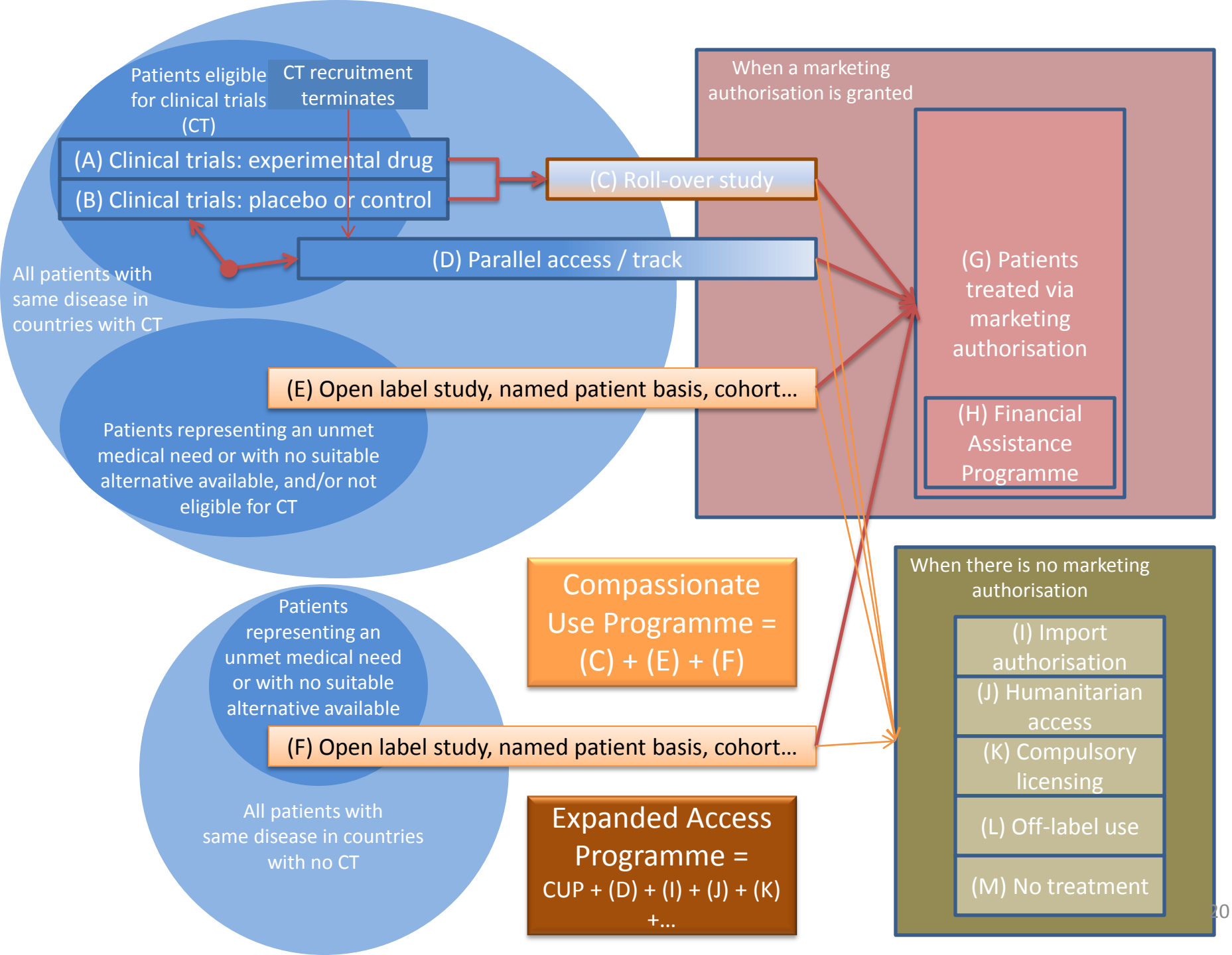
Sites with major differences in compassionate use prescriptions (% of patients compared to all patients treated with ritonavir or indinavir at national level)



REGULATION (EC) Nº 726/2004 Title V, article 83.2

Running a Compassionate Use Programme (CUP) consists in making a medicinal product available for compassionate reasons to a group of patients:

- *with a chronically or seriously debilitating disease*
- *<u>or</u> whose disease is considered to be life-threatening*
- *<u>and</u> who cannot be treated satisfactorily by an authorised medicinal product*


Patients eligible for clinical trials (CT)
CT recruitment terminates
(A) Clinical trials: experimental drug
(B) Clinical trials: placebo or control
(C) Roll-over study
(D) Parallel access / track
All patients with same disease in countries with CT
Patients representing an unmet medical need or with no suitable alternative available, and/or not eligible for CT
(E) Open label study, named patient basis, cohort…
When a marketing authorisation is granted
(G) Patients treated via marketing authorisation
(H) Financial Assistance Programme
Compassionate Use Programme = (C) + (E) + (F)
Patients representing an unmet medical need or with no suitable alternative available
(F) Open label study, named patient basis, cohort…
All patients with same disease in countries with no CT
Expanded Access Programme = CUP + (D) + (I) + (J) + (K) +…
When there is no marketing authorisation
(I) Import authorisation
(J) Humanitarian access
(K) Compulsory licensing
(L) Off-label use
(M) No treatment

Compassionate use is not

- A clinical trial nor an experiment
  - intention is to treat
- A substitute to product development
  - It parallels clinical trials
- A financial help programme nor a humanitarian programme
- A way to place a product on the market prior to the marketing authorisation
- A “gift” to clinicians who achieve their objectives in recruiting for clinical trials

Capacity building

Eurordis Study

RECENT ORPHAN DRUG COMPANIES EXPERIENCE WITH CUP, IN EUROPE

Capacity building

See session and poster 200

Theme 6, Friday, 25 May 2012 11:00-12:30

Session 4: Compassionate Use Programmes

Co-Chairs: Etelka Czondi, and Arielle North

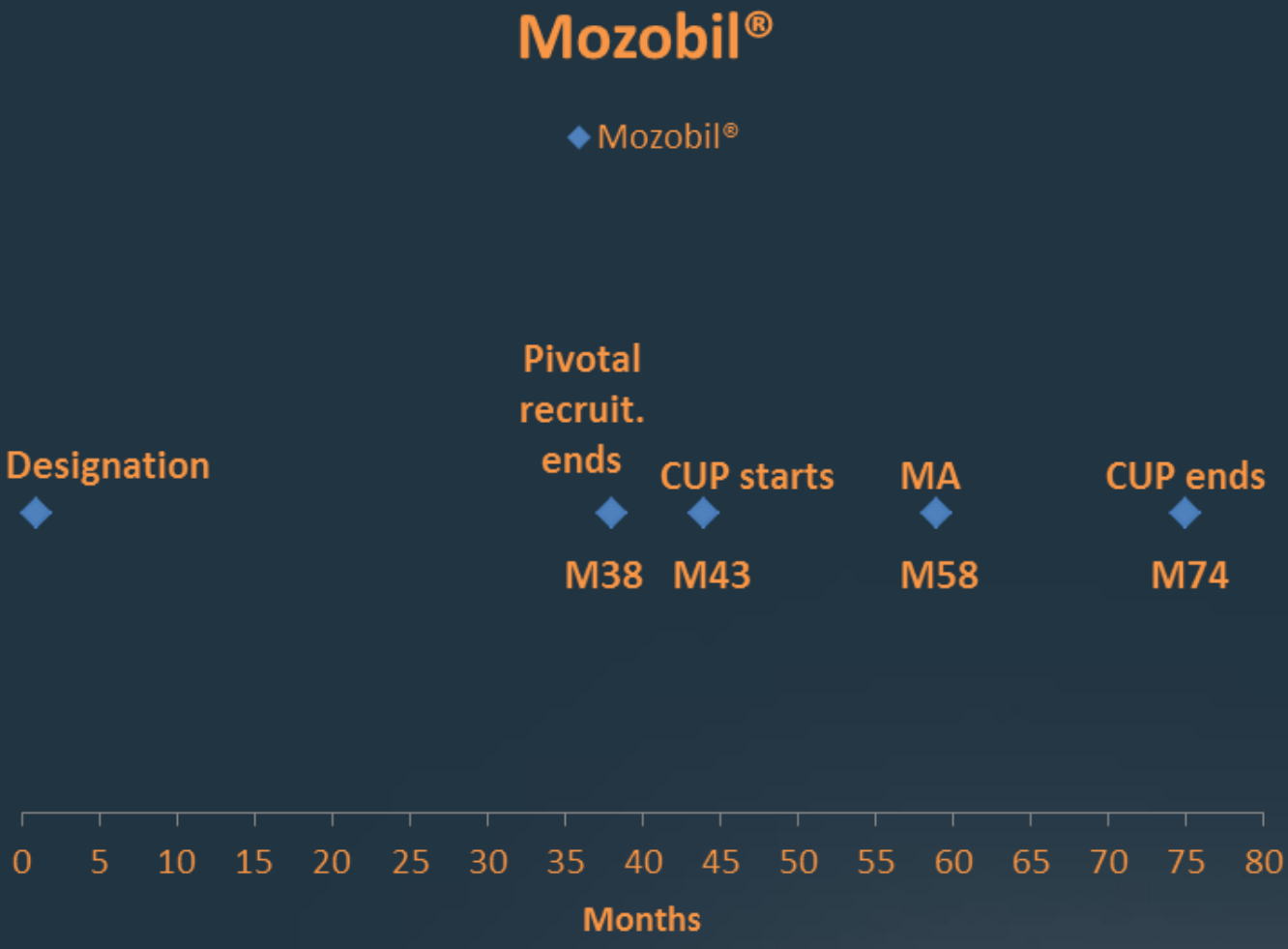
- Presentation 1: Presentation of main outcomes from EURORDIS ERTC workshop on 21/11/11
  - Speaker: Arielle North, Ancre consultant
- Presentation 2: Survey results: Overview of Recent Compassionate Use Programmes for OMPs and Issues Raised
  - Speaker: François Houÿez, EURORDIS, France
- Panel Discussion

Capacity building

Responses

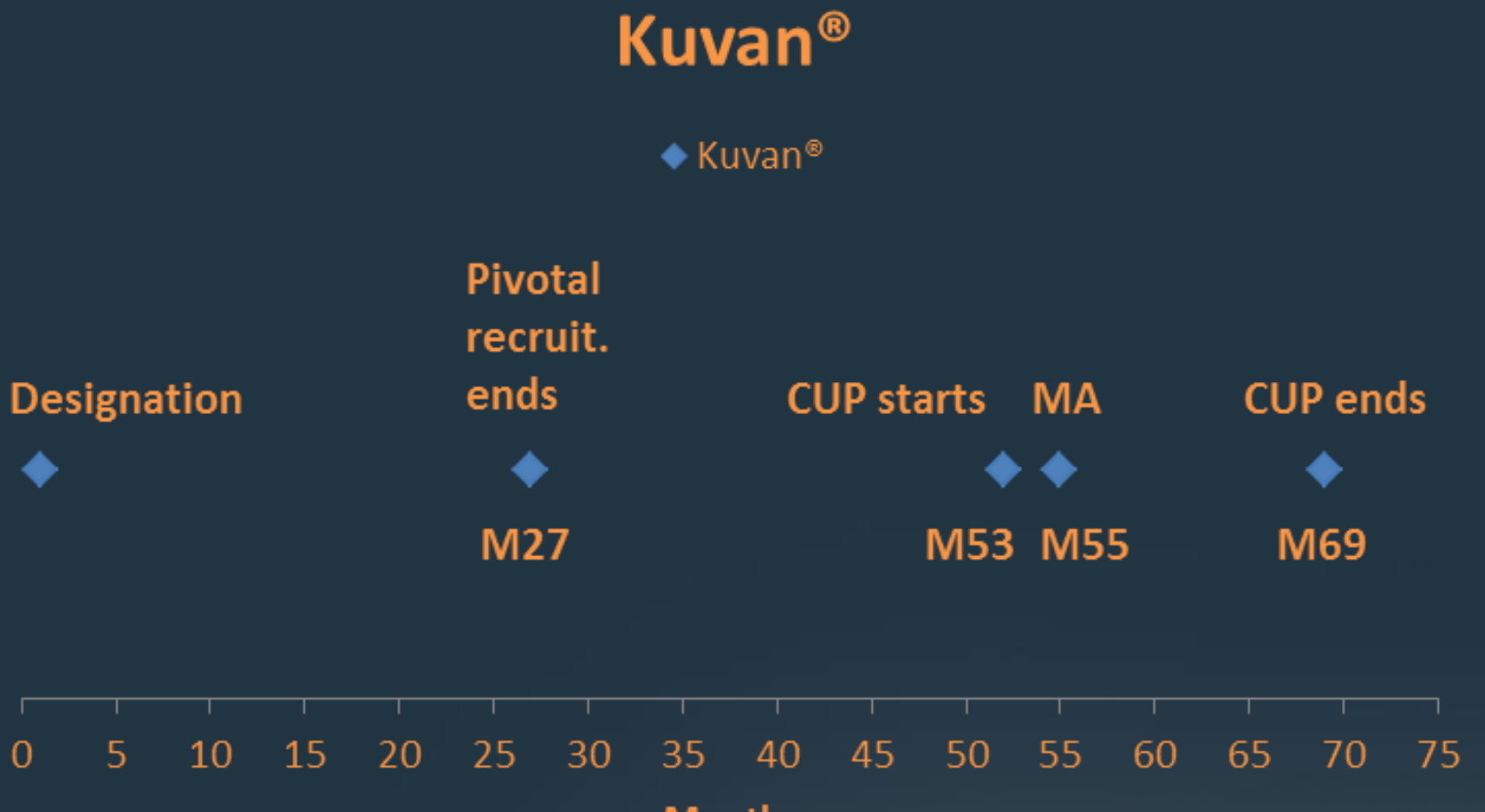
Company	Product	Indication	CUP in Europe?
Eusa Pharma	Inolimomab	Graft versus host disease	yes
Genzyme	Mozobil®	Treatment to mobilise progenitor cells prior to stem cell transplantation	yes
AstraZeneca	Vandetanib	Medullary thyroid carcinoma	Yes
Merck Serono	Kuvan®	Hyperphenylalaninaemia (HPA) in adult and paediatric patients of 4 years + with (PKU)	yes
Orphan Europe	Carglumic acid	NAGS deficiency, isovaleric acidaemia, methylmalonic acidaemia, propionic acidaemia	yes
Pharma Mar	Yondelis®	Soft Tissue Sarcoma	yes
Shire Pharmaceuticals	velaglucerase alpha (Vpriv)	Gaucher type 1	Yes
Johnson&Johnson	Decitabine	MDS	Yes
UCB	Xyrem®	Treatment of narcolepsy	No
Swedish Orphan BioVitrum	Kiobrina	Prevention of growth restriction in preterm infants	No
Chiesi Pharmaceutici	Ex vivo exp. auto. human corneal epithelium containing stem cells	Corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns	No
	Nymusa®	Primary apnoea of premature newborns	No
Novimmune	NI-0801	haemophagocytic lymphohistiocytosis	No
	NI-0501	haemophagocytic lymphohistiocytosis	No
Talecris Biother. Gmbh	Alpha-1-proteinase inhibitor	Congenital alpha-1 antitrypsin deficiency	No
Rare Partners sarl			No
Baxter			No
Dompé			No
FoldRx			No

Completed programmes (1)



Completed programmes (2)

Completed programmes (3)



Capacity building

A campaign to access

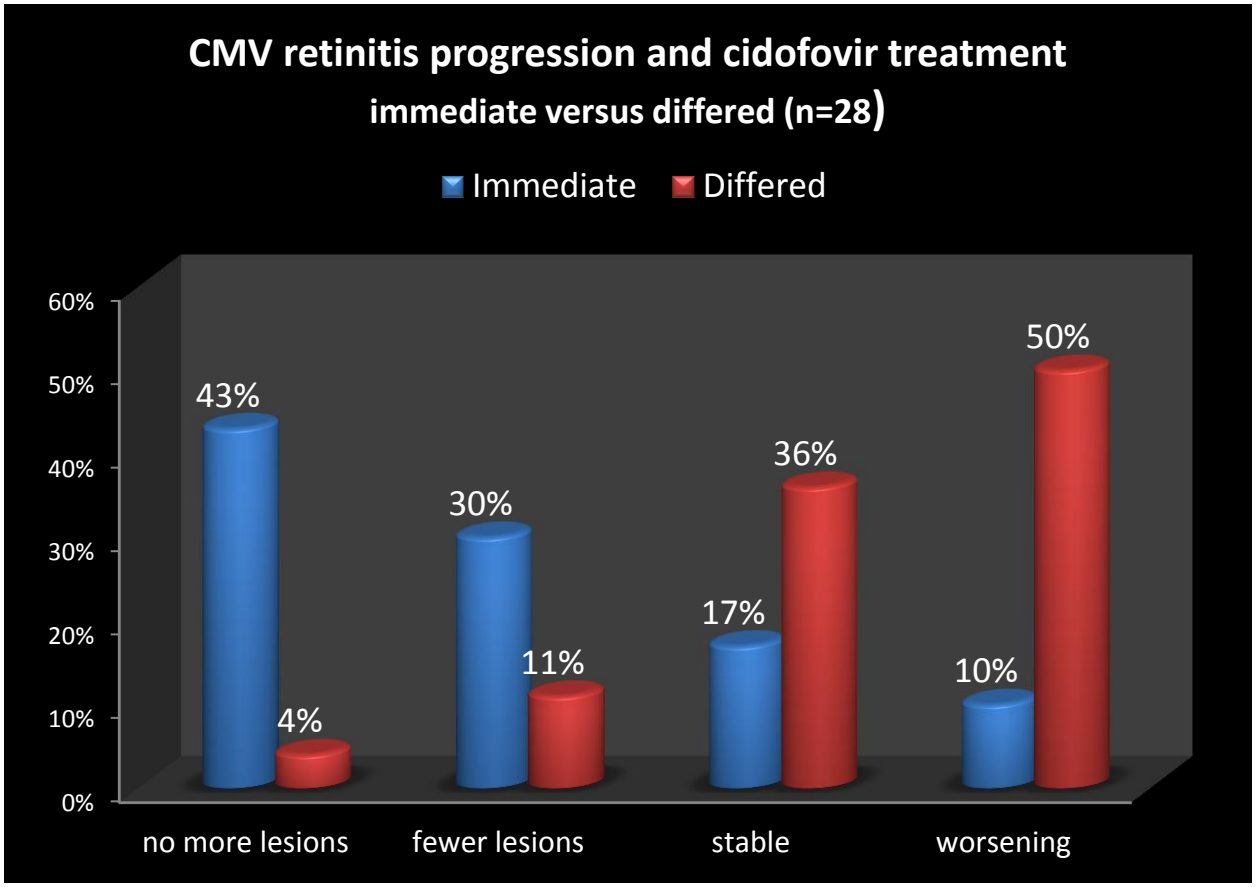
CIDOFOVIR, COMPASSIONATE USE FOR CYTOMEGOLOVIRUS INFECTION

Capacity building

Case : cidofovir

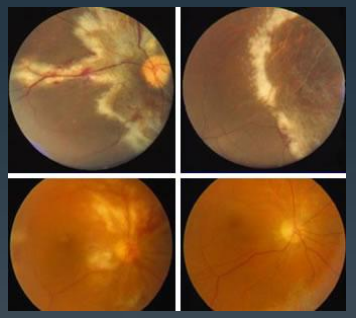
- Cytomegalovirus infection
  - In particular retinitis, transplant or HIV related
  - Treatment before 1993: daily ganciclovir IV, foscarnet IV. Rapid resistance, blindness.
  - Before dying of Aids, patients became blind
- Berlin 1993, World Aids Conference
  - *results of a dose ranging trial I/II HPMPC to treat CMV viruria in HIV infection, by Polis & Jaffe*

Preliminary efficacy results in 1995 CROI, Washington D.C.



The story of Philippe C.

- 11 April 1995: presentation of HPMPC at a public meeting
- Philippe C. was affected by Cytomegalovirus, losing sight rapidly
- Philippe asked me for information on this new treatment and how to access it immediately
- Promised he would kill himself rather than becoming blind before dying of the Cytomegalovirus infection



1/ Search for someone who knew about it

- Day 0, Paris, 11 April 95
- Paris, April 95: French specialists had no idea where HPMPC development stood: “Development stopped”.
- Paris, April 95: contact with Andy Velez† in Act Up New York. Gilead Sciences identified.
- Day 83, 3 July 95: 1st contact with CEO John Martin.
- Day 86, Foster City, 6 July: encouraging response from Howard Jaffe, vice-pdt @ Gilead

2/ Contacts with national authorities

- Contact with ANRS, ADM, clinicians: there is a need, a demand. How do we organise this? Clinical controlled trial? Compassionate use programme? Open label trial?
- Looking for an industrial partner to help Gilead to deal with Europe. Contact with the ministry of health.
- Foster City, Sept 95: Pr J. Dormont (ANRS) met with Gilead. US Compassionate use programme started.
- Oct 95, FDA: New Drug Application file
- ADM asked Gilead to send copy of the file

3/ Early obstacles

- Day 183, 11/10/1995: French POs met with the ADM. Gilead did not send the data the agency was asking for.
- Day 184, 12/10/1995: Elisabeth Hubert, state secretary for health “invited” to finance the ATU programme
- Day 211, 8/11: due date for the secretary of health response
- But on 7 November: the French government resigned. 5 priorities passed to her successor, including cidofovir.
- Day 227, 24/11: Hervé Gaymard’s cabinet still not constituted.
- Day 232, 29/11: patients met with Hervé Gaymard who agreed to finance the compassionate use programme

4/ More pressure from patients

- Day 234-240, 1-7 Dec 1995: “ATU nominative” obtained. TRT5 informed French clinicians on the new possibility to prescribe cidofovir on a named patient basis. The ADM to answer each request between Christmas and New Year.
- But still, product needed to be shipped to France
- Day 240, 7 Dec 1995: Jean-François Lacronique, in charge of medical affairs at the French Embassy in Washington DC flow to Foster City to reinsure the company and to insist for data to be transmitted to ADM.
- Day 248, 15 Dec 1995: Pr Christine Katlama contacted the minister to confirm clinicians’ interest.
- Day 255, 22 Dec 1995: all data are at the ADM and EMEA.

5/ Endless financial issues

- Day 279, 15/01/1996: TRT5 met with Gilead in Paris.
- Day 294, 30/01/96, Retrovirus conference, Washington DC: cidofovir confirmed as a major improvement
- Day 296, 1/02/96: ADM sent a request for export authorisation to Michele Li Moli, FDA.
- Day 303, 8/02/96: patients' ultimatum over Gilead as progresses were too slow. Endless financial negotiations with Isotec (importer)
- Day 313, 18/02/96: patients urged the FDA and the French embassy in DC to accelerate the process.

6/ Finally

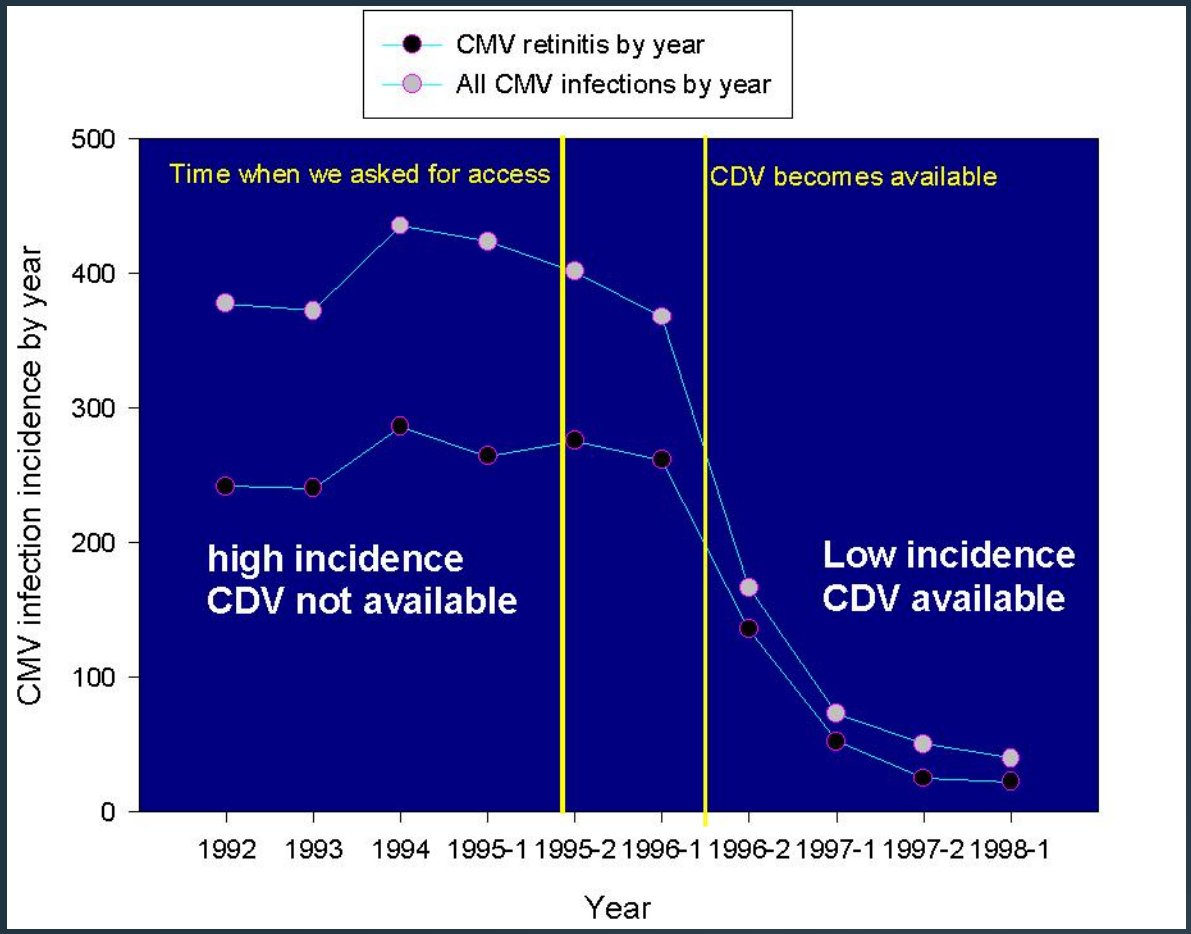
- Day 325, 1 March 96: Gilead staff visited the French CRO contracted for the ATU.
- Slow process since safety data must be cautiously monitored (renal toxicity and probenecid).
- March 96: TRT5 asked the Pharmacie Centrale des Hôpitaux to produce probenicid again (withdrawn)
- Day 336, 12 March 96: 1st French patient treated.

Epilogue

- This was 336 days after Philippe's request.
- Best possible case scenario: company willing to help
- Philippe lost vision on 20 February 1996 and committed suicide the same day, as he promised he would do.
- This was 315 days after his request and 11 days before 1st patient treated.
- He used 2 bullets, his agony must have lasted for 6 hours according to forensic doctor.
- We had received 314 phone calls.

End of the story for the company: for being too focused on profits, no profits at all.

France



IN PRACTICE

Capacity building

Messages to industry

- Be prepared to work with POs as early as possible
  - e.g. Tibotec SOP on development programme, CT and DSMBs, pricing policy, and early access
  - Patients are member of COMP and create CABs – soon to come CHMP agendas
    - Early informed on what's going on and dialogue with regulatory authorities (39 org. @ EMA)

Messages to industry

- Explain your production capacity planning
  - Stocks for CTs, stockpiling for filing, EAPs
- Consult when critical situations
  - E.g. 3TC expanded access 11/1994 +300% demand and 02/1005 +500% → pacing programme
  - Agree contingency plan with POs

Capacity building

Some Dos

- Define inclusion criteria for the compassionate use with patients and doctors
- Explain the plans country by country
- Accept no information on compassionate use programmes can be considered as confidential
- Collect information from the compassionate use programme, in particular toxicity data and special populations

Capacity building

And also

- Verify the terms of the programmes
  - E.g. “patients who are considered potentially unreliable” as exclusion criteria
- To identify compassionate use programmes, look for:
  - “expanded” or “compassionate” on https://www.clinicaltrialsregister.eu
  - Verify it is “open label”
  - You can also visit:
- E.g. compassionate Use of Mepolizumab in Subjects With Hypereosinophilic Syndrome (HES) (open)
  - https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000838-39/BE
- E.g. compassionate use for thalidomide (closed)
  - http://clinicaltrials.gov/ct2/show/NCT00081757

Capacity building

Some “Don’t does”

1. Not enough supply to satisfy the demand
   - A lottery the less unethical method
   - But nobody will take the responsibility
   - Successful cases of “waiting list with shipment where drug most needed approach”
     - E.g. 3TC pacing programme 1994-1995
2. Programme ends
   - Continue providing drug to patients until price & reimbursement decision
   - Continue enrolling patients, or not: but be clear about it from the beginning

Some other “Don’t does”

3. Recruit in EAP as a gift to good regulatory trials recruiting sites
   - “for each patient in phase III, you’ll get one patient in a compassionate use programme”
4. Don’t mix compassionate use programmes with humanitarian or financial support programmes
5. Critical situations
   - POs can be consulted, but do not replace the responsible person

Capacity building

BACK UP SLIDES

Capacity building

Hétérogénéité géographique

Bichat	10 %	Paris Est	4 %	Clermont Ferrand	3 %
Paris Centre	3 %	Saint Louis	6 %	Tourcoing	1 %
Laennec	3 %	Paris Sud	3 %	Martinique	1 %
Pitié	11 %	CISIH 92	7 %	Réunion	1 %
CISIH 93	3 %	Bordeaux	6 %	Tours	1 %
Lyon	1 %	Caen	2 %	Guadeloupe	1 %
Grenoble	1 %	Marseille	10 %	Rennes	3 %
Nancy	3 %	Bourgogne	3 %	Toulouse	0 %
Nantes	3 %	Strasbourg	2 %	Montpellier	1 %
Nice	10 %	Rouen	1 %		

Norvir® sur Paris

Broussais	3 %	Cochin	4 %
H. Mondor	2 %	Pitié	23 %
Louis Mourier	4 %	Poincaré	3 %
Rotschild	2 %	Saint Louis	13 %
Saint Antoine	6 %	Necker	2 %
A. Paré	2 %	Avicenne	3 %
Bicêtre	3 %	Bichat	22 %
Beclère	4 malades	Garches	31 malades

Indinavir® en France: 1 720

CISIH	En cours	CISIH	En cours	CISIH	En cours
Bourgogne	3	Bichat	39	Toulouse	87
Bordeaux	60	Cochin	150	Tourcoing	32
Caen	24	Necker	100	Tours	9
Grenoble	58	Paris Sud	82	Auvergne	34
Lyon	49	Salpétrière	159	Montpellier	26
Marseille	137	Saint Louis	39	Rennes	5
Nancy	25	Paris Est	341	Rouen	3
Nantes	27	CISIH 92	76	Strasbourg	26
Nice	35	CISIH 93	66	Guadeloupe	5
Guyane	1	La Réunion	7	Martinique	15