

# ***Cytomégalo­virus et trans­plan­ta­tion ré­nale.***

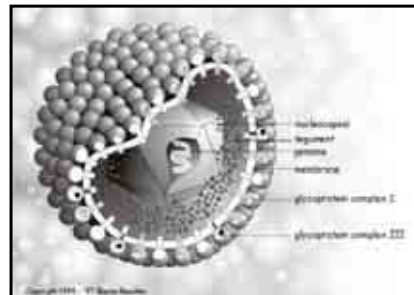
**Chris­to­phe LEGENDRE**  
**Hôpital Necker**  
**Paris**

Sé­mi­naire d'En­se­igne­ment du DESC d'In­fec­ti­o­logie

Saint Mandé, 13 jan­vier 2004

**β-HHV**

- HHV-1
- HHV-2
- HHV-3
- HHV-4
- HHV-5 \* CMV
- HHV-6
- HHV-7
- HHV-8
- HHV-n...



## ***History: the beginning***

- ***1964: Infectious pulmonary disease in patients receiving immunosuppressive therapy for organ transplantation.***  
– Hill RB Jr et al, N Engl J Med
- ***1978: « Should renal-transplant patients be screened for cytomegalovirus? »***  
– Editorial, Lancet

## ***History: the clinical era***

- ***1977: Infectious disease syndromes attributable to CMV and their significance among renal transplant recipients.***  
– Rubin RH et al, Transplantation
- ***1980: CMV disease in renal allograft recipients: a prospective study of the clinical features, risk factors and impact on renal transplantation.***  
– Peterson PK et al, Medicine

## ***History: the therapeutic era***

- **1985: Foscarnet for CMV infections.**  
– Ringdén O et al, *Lancet*
- **1986: Treatment of serious CMV infections with 9-(1,3-dihydroxy-2-propoxymethyl) guanine in patients with AIDS and other immunodeficiencies.**  
– Collaborative DHPG Treatment Study Group, *N Engl J Med*

## ***History: the prevention era***

- **1983: CMV disease. Can it be prevented?**  
– Balfour HH, *Annals of Internal Medicine*



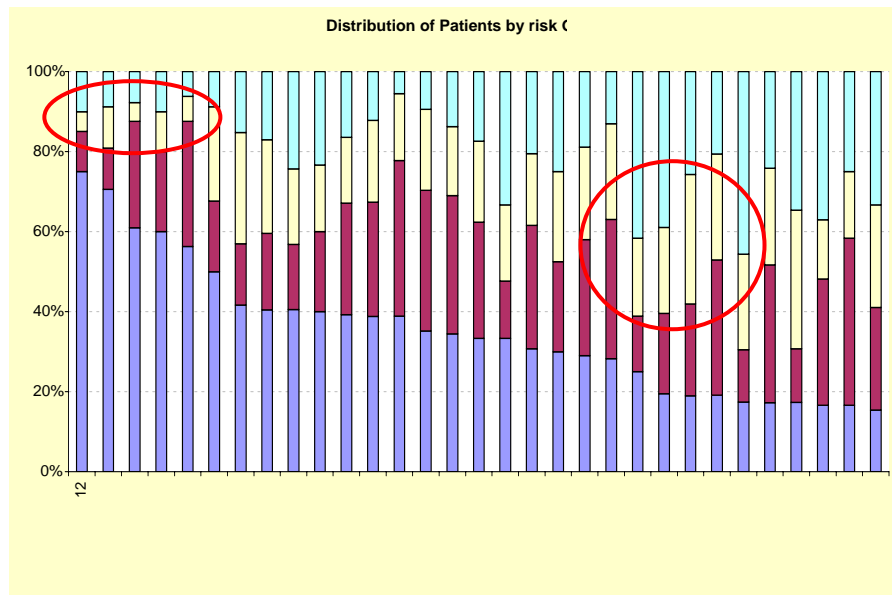
- **1991: Options for prevention of CMV disease.**  
– Balfour HH, *Annals of Internal Medicine*

***CMV-positive recipients***



***CMV-negative recipients***

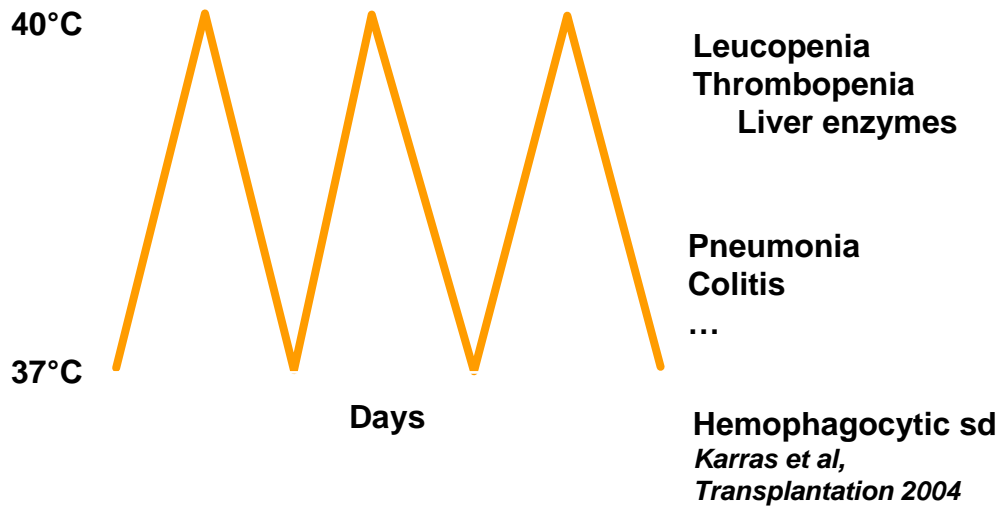




## ***Definitions***

- ***Primary infection =  $D + / R -$***
- ***Secondary infection =  $R +$*** 
  - ***Reactivation =  $R + / D +$  or  $D -$***
  - ***Superinfection =  $R + / D +$***
- ***CMV infection = asymptomatic***
- ***CMV disease = symptomatic***

## ***CMV disease***

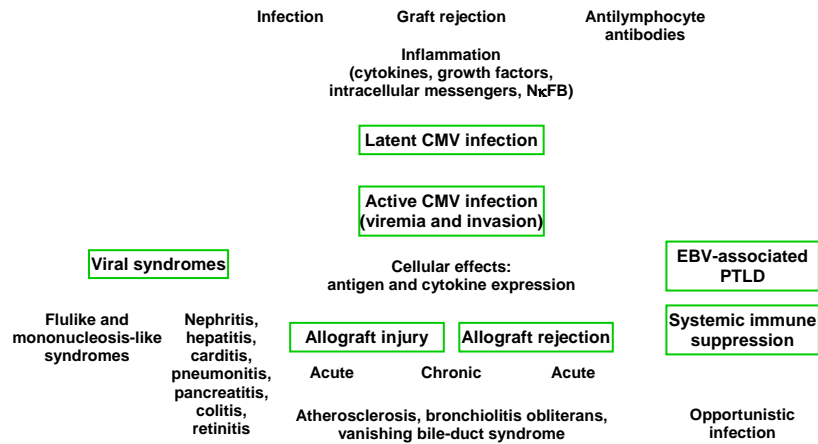


## ***Risk factors***

- **CMV-negative recipient**
- **Organ from a CMV-positive donor**
- **Poly or monoclonal anti-lymphocyte antibodies**
- **Acute rejection**
- **HLA mismatches**
- **CMV shedding**
- **Multiples gB genotypes** (*Coaquette, Clin Infect Dis 2004*)

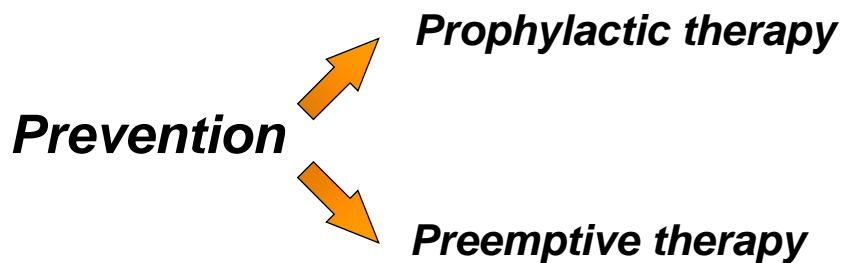
**D+/R- > D+/R+ > D+/R- > D-/R-**

# Effects of CMV: Overview



*Fishman JA et al., N Engl J Med 1998*

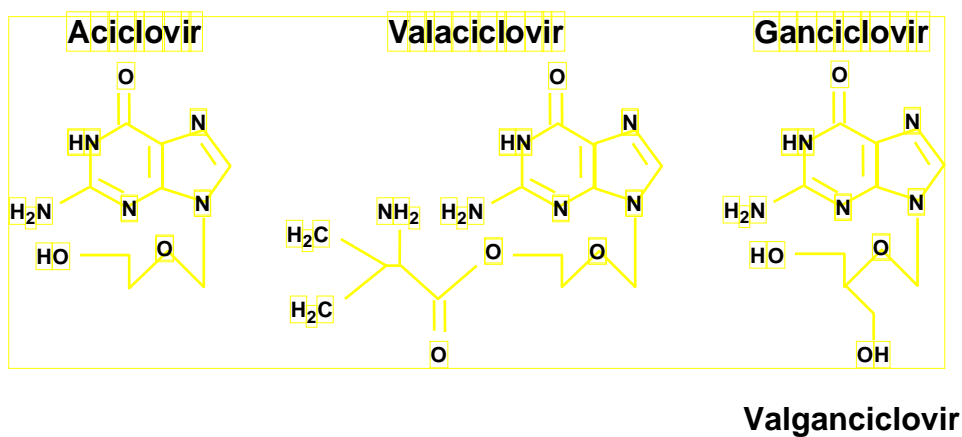
# Strategy of CMV infection prevention



## ***Prophylactic therapy***

- ***Prevention of CMV transmission***
- ***Modulation of immunosuppression***
- ***Alpha-interferon***
- ***Anti-CMV vaccination***
- ***Gamma-globulin***
- ***Chemoprophylaxis***

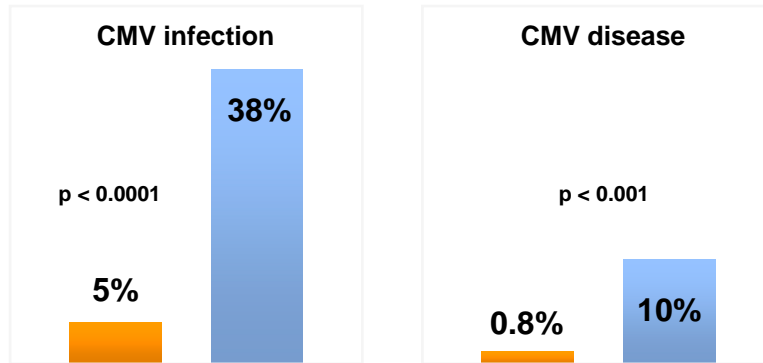
## ***Prophylactic therapy*** ***Chemoprophylaxis***



## ***Prophylactic therapy***

***I.V. ganciclovir***

***Liver transplantation***

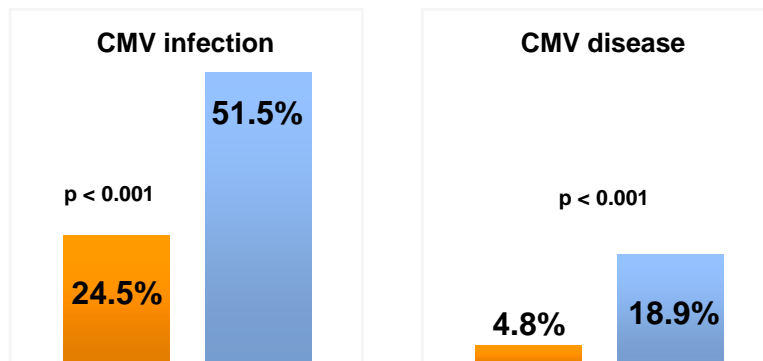


*Winston D et al, Lancet 1995*

## ***Prophylactic therapy***

***Oral ganciclovir***

***Liver transplantation***

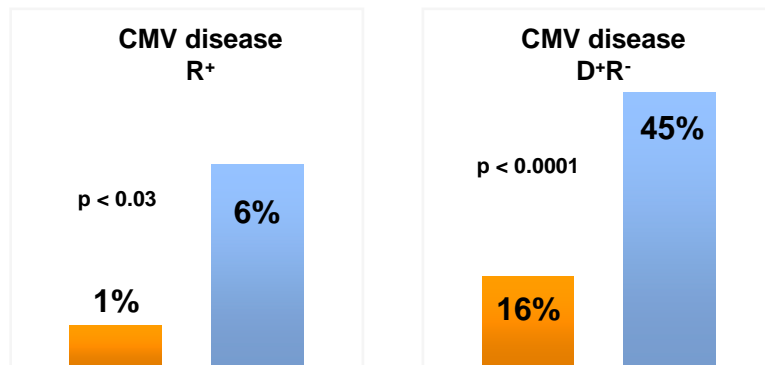


*Gane E et al, Lancet 1997*

# Prophylactic therapy

## Valaciclovir

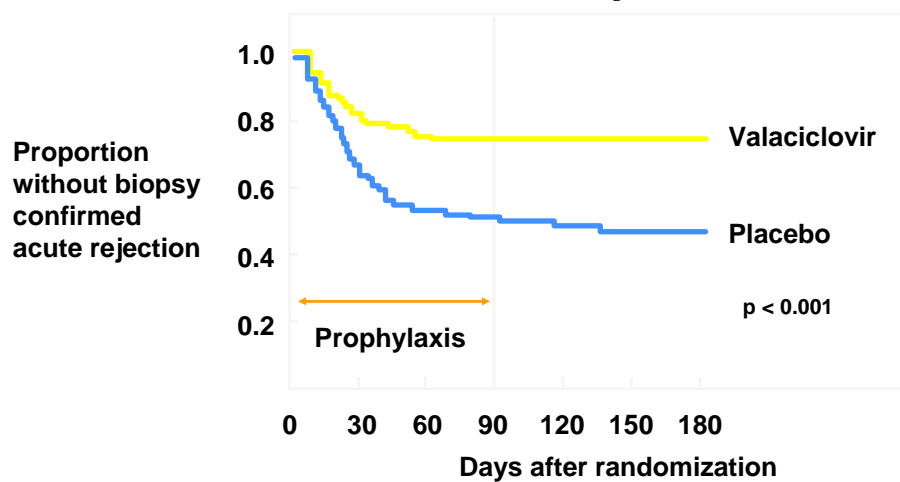
### Renal transplantation



Lowance D et al, N Engl J Med 1999

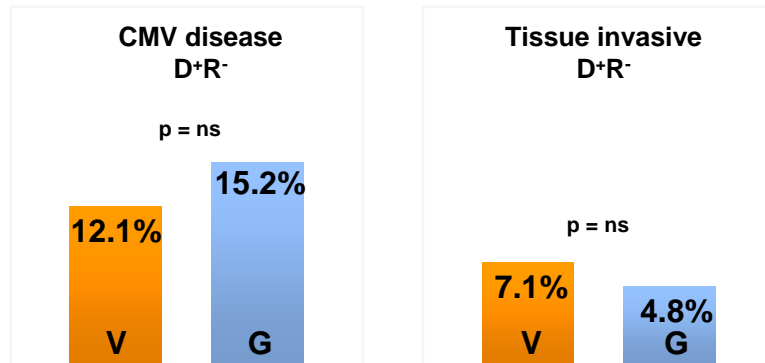
# CMV and acute rejection

## Renal Transplantation



Lowance D et al, N Engl J Med 1999

# ***Prophylactic therapy Valganciclovir vs oral ganciclovir Organ transplantation***

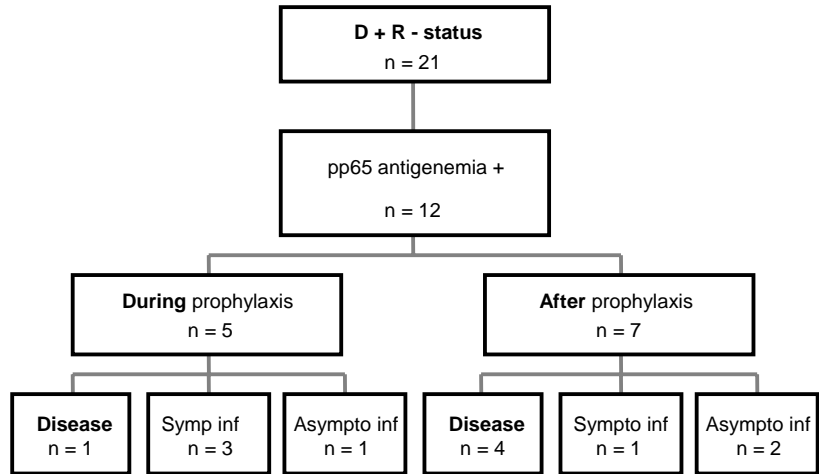


*Paya C et al, Am J Transplant 2004*

*Paya C et al,  
Am J Transplant 2004*

## ***Prophylaxis = valaciclovir***

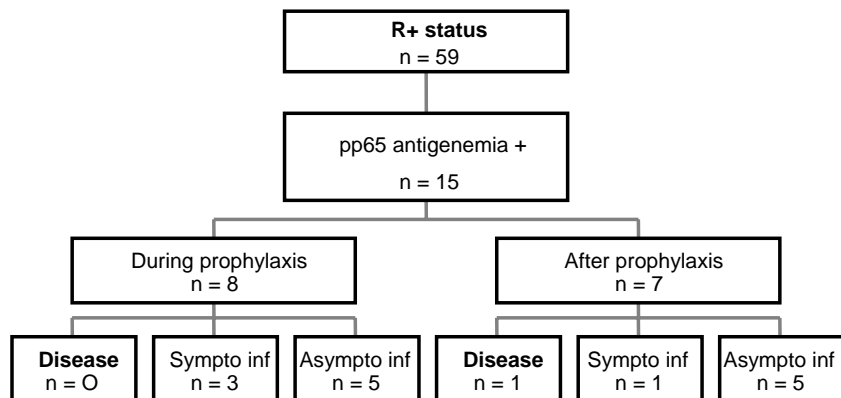
### ***Experience from Saint-Louis hospital***



***Thèse D. Anglicheau 2001***

## ***Prophylaxis = valaciclovir***

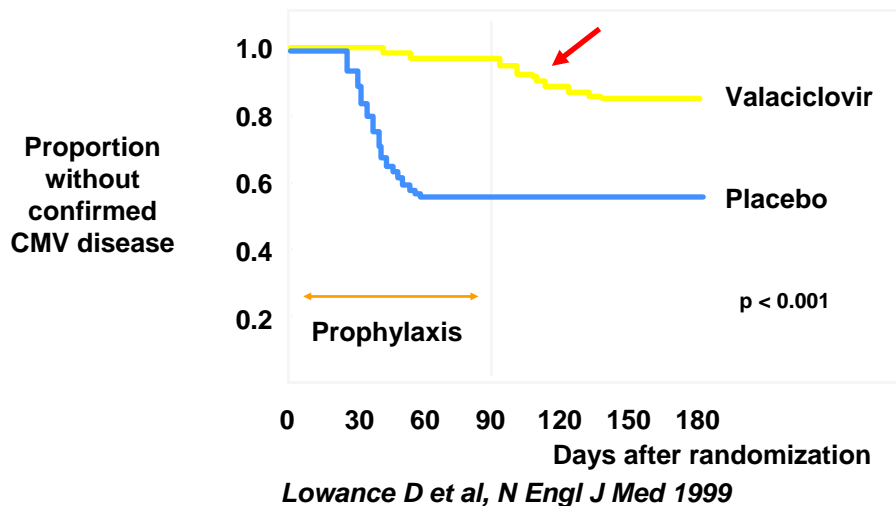
### ***Experience from Saint-Louis hospital***



***Thèse D. Anglicheau 2001***

## Late CMV disease

### Valaciclovir



## Les maladies récidivantes

### Expérience de Boston

Turgeon N et al, Transplant Infect Dis 2000

Etude chez 37 patients avec maladie à CMV

Tt = ganciclovir IV 14j puis oral 2-3mois

10 (27%) ont présenté une récurrence

Les facteurs de risque:

Statut D+R-

Pic antigénémie pp65

2 cas de résistance au ganciclovir

## ***Preemptive therapy « traitement anticipé »***

- ***Patients at risk = viral replication***
- ***Situations at risk:***
  - ***Treatment of rejection***
  - ***Recurrences***

## ***Preemptive therapy***

***Patients at risk = viral replication***

### ***Viral monitoring***

- ***CMV-Ag***
- ***CMV-DNA***



----- +

- 1) ***Evaluation of risk***
- 2) ***Anti-viral therapy***
- 3) ***Modulation of immunosuppression***

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***TR***

## ***Preemptive therapy***

***Patients at risk = viral replication***

### ***Viral monitoring***

- *CMV-Ag*
- *CMV-DNA*



***+***

- 1) *Evaluation of risk*
- 2) *Anti-viral therapy*
- 3) *Modulation of immunosuppression*

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***TR***

## ***Preemptive therapy***

***Patients at risk = viral replication***

### ***Viral monitoring***

- *CMV-Ag*
- *CMV-DNA*



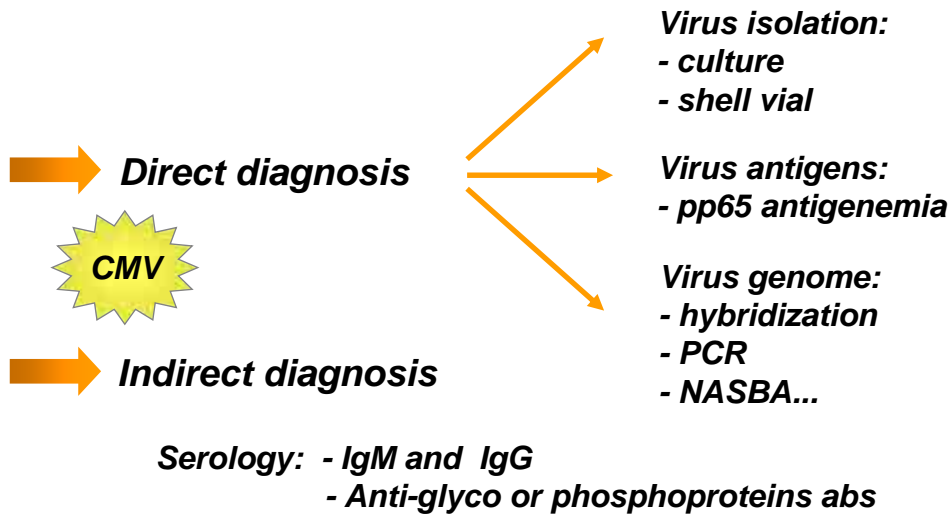
***+***

- 1) *Evaluation of risk*
- 2) *Anti-viral therapy*
- 3) *Modulation of immunosuppression*

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***TR***

## **CMV: diagnostic tools**



**Comparaison de  
3 méthodes:  
Ag pp65  
qualitative PCR  
quantitative Taqman PCR**

QuickTime™ et un  
décompresseur TIFF (non compressé)  
sont requis pour visionner cette image.

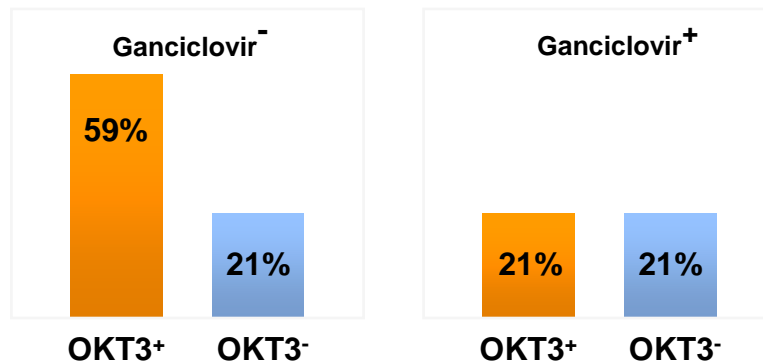
*Meier-Koenig U et al, Transplantation 2004*

*Meier-Koenig U et al, Transplantation 2004*

## ***Preemptive therapy***

***Situations at risk = Rejection***

***CMV disease***



*Hibberd P et al, Ann Intern Med 1995*

## ***Preemptive therapy***

***Situations at risk = Recurrences***

- ***After a 14-21 day ganciclovir treatment, the incidence of recurrence is:***
  - ***60% in R- patients***
  - ***20% in R+ patients (Rubin RH)***
  - ***30% (Matas A et al, Transplantation 1999)***
- ***Oral ganciclovir may prevent recurrence***
  - ***(Nankivell BJ et al, Clinical Transplantation 1998)***

## **Preemptive therapy**

**Patients at risk = viral replication**

### **Viral monitoring**

- CMV-Ag
- CMV-DNA



+

- 1) **Evaluation of risk**
- 2) **Anti-viral therapy**
- 3) **Modulation of immunosuppression**

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**TR**

*Anglicheau D et al, NDT 2003*

## **Prophylactic + Preemptive therapy**

### **Viral monitoring**

- CMV-Ag
- CMV-DNA



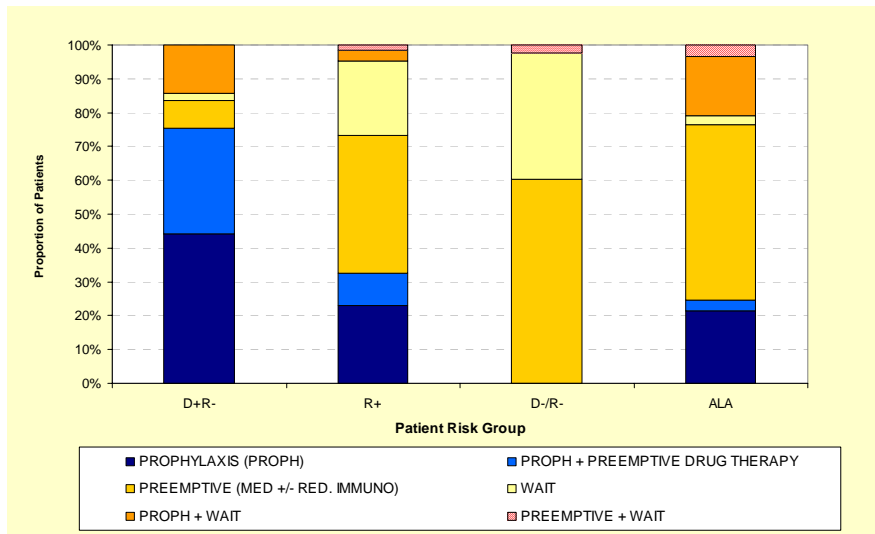
+

- 1) **Evaluation of risk**
- 2) **Anti-viral therapy**
- 3) **Modulation of immunosuppression**

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**TR**

**Prophylaxis**



# Valaciclovir

**Das J et al, ATC 2003**  
**Incidence de 15%**  
**(167 patients étudiés)**  
**Facteur de risque = RRF**

TABLE 3. MOST FREQUENT ADVERSE EVENTS.\*

EVENT	SERONEGATIVE GROUP (N=102) (N=100)		SEROPOSITIVE GROUP (N=204) (N=204)	
	number of patients (percent)			
Hypertension	16 (16)	16 (15)	18 (9)	9 (4)
Anemia	14 (14)	16 (15)	22 (11)	21 (10)
Leukopenia	14 (14)	11 (10)	12 (6)	14 (7)
Fever	13 (13)	14 (13)	12 (6)	19 (9)
Abdominal pain	13 (13)	13 (12)	13 (6)	21 (10)
Diarrhea	12 (12)	16 (15)	15 (7)	20 (10)
Headache	8 (8)	14 (13)	21 (10)	19 (9)
Nausea	9 (9)	6 (6)	16 (8)	16 (8)
Peripheral edema	10 (10)	12 (11)	13 (6)	17 (8)
Vomiting	7 (7)	9 (8)	18 (9)	14 (7)
Itching	9 (9)	7 (7)	13 (6)	7 (3)
Hallucinations	5 (5)	0†	21 (10)	3 (1)‡
Confusion	6 (6)	2 (2)	16 (8)	5 (2)§
Constipation	6 (6)	4 (4)	15 (7)	12 (6)
Pain	4 (4)	11 (10)	18 (9)	10 (5)
Insomnia	7 (7)	4 (4)	10 (5)	6 (3)
Edema	10 (10)	6 (6)	3 (1)	8 (4)
Hypophosphatemia	7 (7)	5 (5)	3 (1)	5 (2)

\*The 12 commonest events in the seronegative group, the seropositive group, and each valacyclovir group are included. †P values were calculated by Fisher's exact test.

†P=0.03 for the comparison with the seronegative valacyclovir group.

‡P<0.001 for the comparison with the seropositive valacyclovir group.

§P=0.02 for the comparison with the seropositive valacyclovir group.

Lowance D et al, N Engl J Med 1999

**Valaciclovir**

**Ganciclovir**

**Zélitrex®**  
12 comprimés/j  
Fonction rénale



**Cymévan®**  
6 à 12 gélules/j  
Fonction rénale

**Valganciclovir**

**Rovalcyte®**  
2 gélules/j  
Fonction rénale

## **Les questions actuelles**

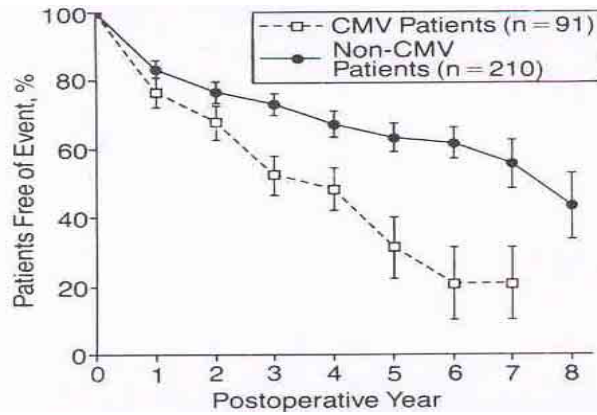
- **Quelle stratégie chez les receveurs CMV+ ?**
- **Le monitoring virologique reste-t'il utile ?**
- **Le rôle de certains immunosuppresseurs:**
  - **Évérolimus = prévention**
  - **Leflunomide = traitement**

## **Consequences**

- ***Is CMV infection deleterious?***
- ***Is CMV the only culprit?***
- ***Is CMV prevention cost-effective?***
- ***Is CMV prevention safe?***

## ***Is CMV infection deleterious?***


- ***Heart transplantation:***
  - *Grattan MT et al, J.A.M.A. 1989*
  - *Valentine H, A.S.T.P. 1998*
- ***Liver transplantation:***
  - *Falagas ME et al, Transplantation 1999*
- ***Kidney transplantation:***
  - *Pouteil-Noble C et al, Transplantation 1993*
  - *Akposso K et al, Transplantation 1997*
  - *UNOS data, 1998*
  - *Lowance D et al, N Engl J Med 1999*



**Grattan MT et al. JAMA 1989**

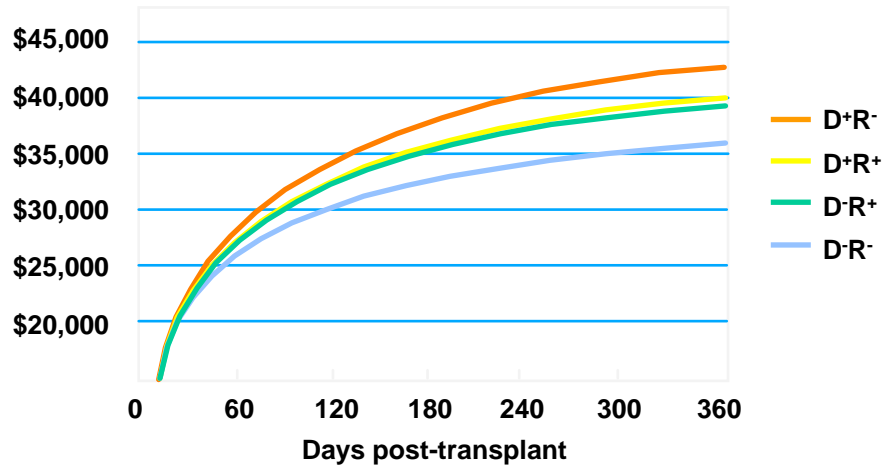
***A likely guilt hidden by weak proofs (Potena L)***

## ***Is CMV the only culprit?***

- β-HHV**
- HHV-1
  - HHV-2
  - HHV-3
  - HHV-4
  - HHV-5
  - **HHV-6**
  - **HHV-7**
  - HHV-8
  - HHV-n...
- 
**CMV**  
*Razonable RR, Clin Transplant 2003*

## ***Is CMV prevention cost-effective?***

***Accumulated Medicare payments to hospital***



*Woodward RS et al, A.S.T., 1999*

## ***Is prophylaxis with valaciclovir cost-effective?***

- ***Economical data coming from the study by Lowance et al, N Engl J Med 1999.***
  - *Legendre Ch et al, Transplantation 2000*
- ***Prophylaxis is efficient and cost-effective in the D+R- subgroup of patients.***
- ***About 1500 euros saved per patient.***

## ***Is prophylaxis with valaciclovir cost-effective?***

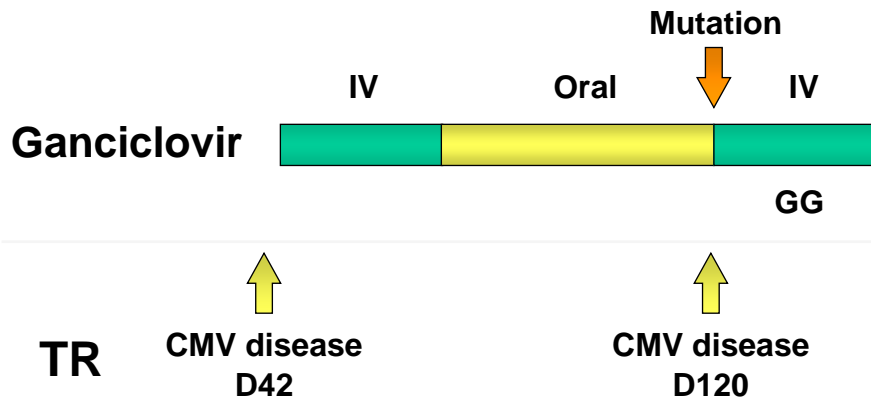
- **Total health care cost was \$3619 lower (Australia).**
  - *Tilden DP et al, Clinical Transplant 2004*

## ***Is prophylaxis with valaciclovir cost-effective?***

<b>Stratégie de prise en charge de la maladie à CMV</b>	<b>Type de traitement</b>	<b>Coûts liés au traitement</b>	<b>Proportion de patients indemnes de maladie à CMV</b>
STRATEGIE 1	Prophylaxie par GCV oral	7725 €	84 %
STRATEGIE 2	Prophylaxie par VCV oral	5171 €	<b>90 %</b>
STRATEGIE 3	GCV IV préemptif	10 241 €	58 %
STRATEGIE 4	« Attendre et traiter »	6017 €	55 %

***Soumis pour publication***

## ***Is CMV prevention safe?***

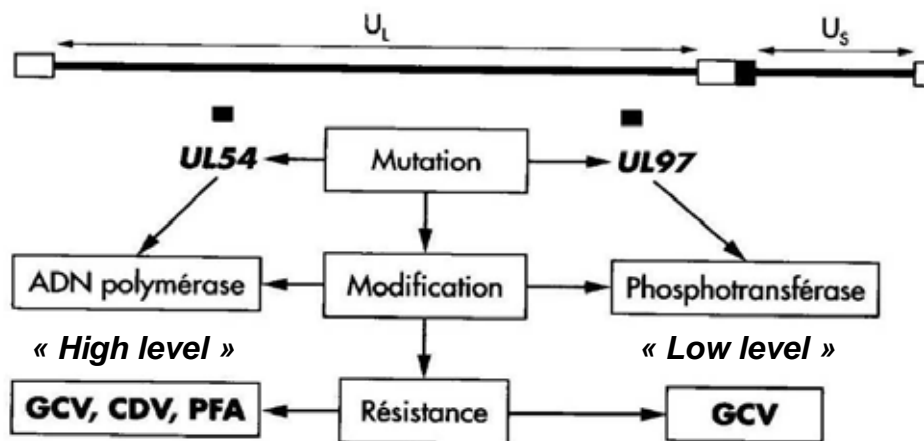


*Bienvenu B et al, Transplantation 2000*

## ***Lessons from AIDS***

- ***Drew WL et al, J Infectious Dis 1991***
  - ***8% after a 3-month treatment***
- ***Jabs DA et al, J Infectious Dis 1998***
  - ***11% after a 6-month treatment***
  - ***27,5% after a 9-month treatment.***

## ***CMV resistance to antiviral drugs***



## ***Definitions***

- **Clinical:**
  - ***In case of CMV disease:***
    - ***no efficacy of IV ganciclovir on symptoms,***
    - ***persistence of viral replication during IV ganciclovir,***
  - ***During preemptive therapy:***
    - ***persistence of viral replication,***
    - ***overt CMV disease,***
  - ***During prophylaxis:***
    - ***presence of viral replication.***

## **Definitions**

- **Virological:**
  - **Phenotypic:**
    - *Viral culture with a known dose of virus in the presence of increasing doses of antiviral drug,*
    - *IC50 = dose of antiviral drug to inhibit 50% of viral growth.*
    - *Resistance if IC50 greater than 8 or 12µmol/l*
  - **Genotypic:**
    - *Analysis of mutations within UL97 and UL54 genes.*

## **Prevalence of resistant strains**

- ***Emergence of ganciclovir-resistant CMV disease among recipients of solid-organ transplants.***
  - *A.P. Limaye et al, Lancet 2000*
- **Methods:**
- ***240 patients RT (kidney, pancreas and liver)***
- ***Prophylaxis with oral GCV during 100 days.***
- ***CMV strains tested in case of clinical resistance to GCV.***
- ***One year of follow-up.***

## **Prevalence of resistant strains**

- *A.P. Limaye et al, Lancet 2000*
- **Results:**
- **7% in D+R- patients (n=67) versus 0% in R+ patients (p=0.002).**
- **20% in the group of 25 patients who developed CMV disease during the first year.**
- **Risk factors: immunosuppression (kidney+pancreas > kidney, liver), time of exposure to oral GCV.**

## **Prevalence of resistant strains**

- **High incidence of ganciclovir-resistant CMV infection among lung transplant recipients receiving preemptive therapy.**  
– *A.P. Limaye et al, J Infectious Dis 2002*
- **Methods:**
- **45 patients with a mean follow-up of 6,7 months.**
- **Preemptive therapy in R+ and D+R- patients (until septembre 99).**
- **CMV strains tested in case of clinical resistance to GCV.**

## ***Prevalence of resistant strains***

- ***A.P. Limaye et al, J Infectious Dis 2002***
- ***Results:***
- ***9% out of 45 patients developed a CMV infection with a strain resistant to GCV.***
- ***More frequent in D+R- patients (p=0.04).***
- ***Equally frequent in case of preemptive therapy and in case of prophylaxis.***

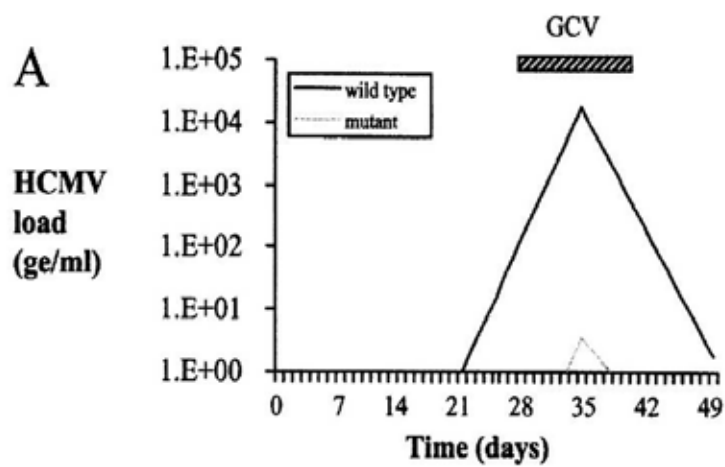
## ***Prevalence of resistant strains***

- ***Absence of CMV-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients.***
  - ***Boivin G et al, J Infect Dis 2004***
- ***301 organ-transplant recipients treated with oral G or ValG for 100 days.***
- ***OralG = 1.9% UL97 mutations and 6.1% if CMV suspected***
- ***ValG = 0% UL97 mutations.***

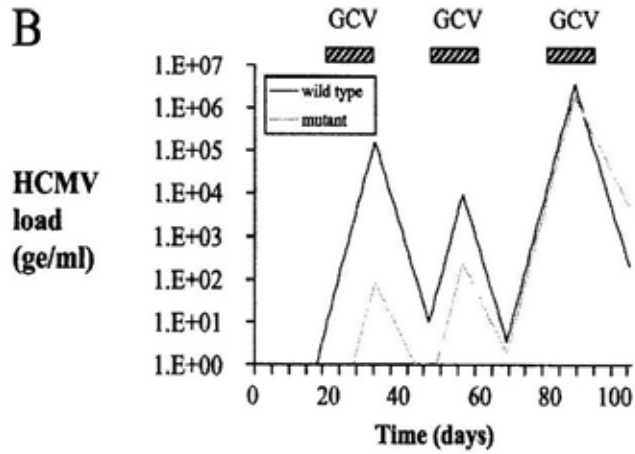
## ***The 3 factors of resistance***

- ***Immunosuppression load***
- ***Intensity of viral replication***
- ***Duration of prophylaxis***

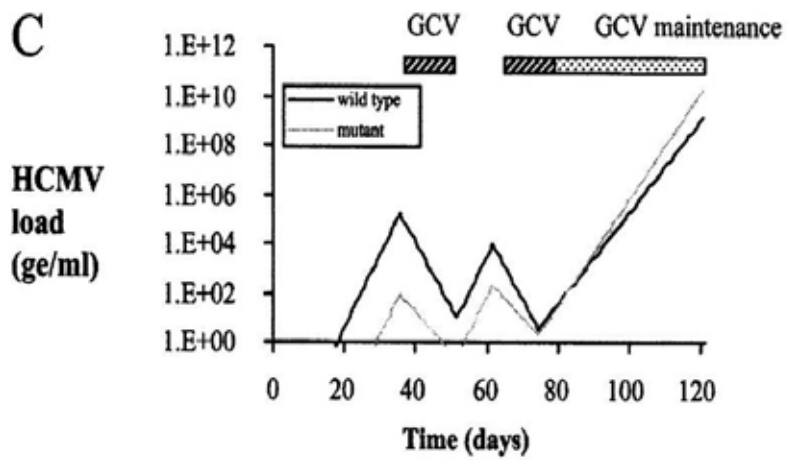
## ***Use of dynamic models***



## Use of dynamic models



## Use of dynamic models



## **Conclusions**

**« The therapeutic prescription for the transplant recipients has two components: immunosuppressive therapy that prevents or treats allograft rejection and an antimicrobial strategy to make immunosuppression safe. »**



**Merci de votre  
attention!**

## *Mutations in UL97 gène.*

<b>Types de souches</b>	<b>Changement d'AA</b>	<b>Position du codon</b>	<b>Sous-domaine catalytique</b>
Mutant	Met → Ile	460	VI
Mutant	Délétion Ala-Ala-Cys-Arg	590-593	IX
Isolat	Met → Ile/Val	460	VI ←
Isolat	Asn → Ser	510	VII
Isolat	His → Glu	520	VIII
Isolat	Ala → Thr	590	IX
Isolat	Ala → Asp/Val	591	IX
Isolat	Cys → Gly	592	IX
Isolat	Ala → Val/Thr	594	IX ←
Isolat	Délétion Ala-Ala-Cys-Arg	591-594	IX
Isolat	Leu → Ser/Phe/Thr/Trp	595	IX
Isolat	Délétion Leu	595	IX ←
Isolat	Glu → Gly/Asn	596	IX
Isolat	Asn → Ile	597	IX
Isolat	Gly → Val	598	IX
Isolat	Lys → Met	599	IX
Isolat	Délétion Leu	600	X
Isolat	Cys → Trp/Tyr	603	X
Isolat	Cys → Tyr	607	X
Isolat	Ala → Asn	606	X
Isolat	Val → Ile	651	X