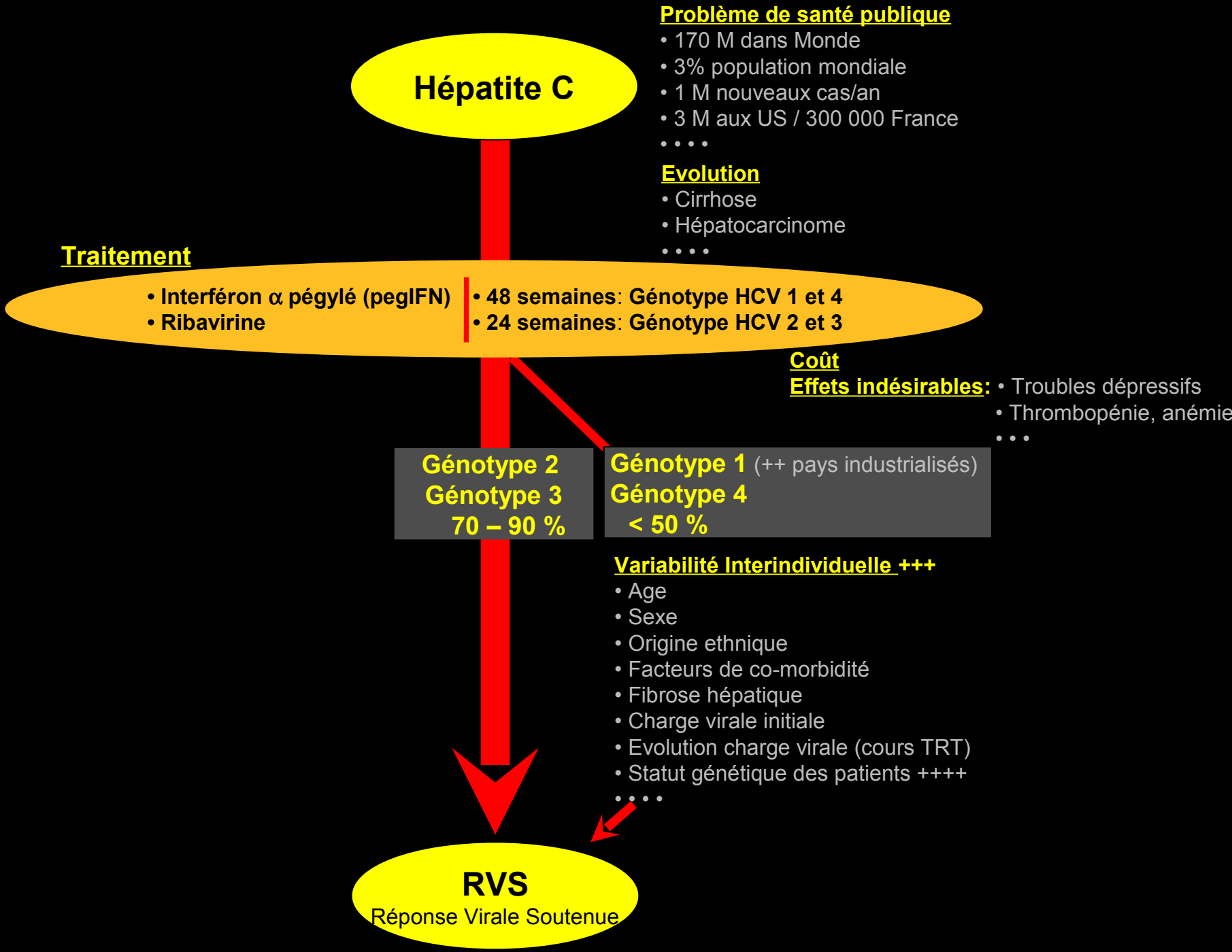

Hépatite C
Problème de santé publique
• 170 M dans Monde
• 3% population mondiale
• 1 M nouveaux cas/an
• 3 M aux US / 300 000 France
• • • •
Evolution
• Cirrhose
• Hépatocarcinome
• • • •
Traitement
• Interféron α pégylé (pegIFN)
• Ribavirine
• 48 semaines: Génotype HCV 1 et 4
• 24 semaines: Génotype HCV 2 et 3
Coût
Effets indésirables: • Troubles dépressifs
• Thrombopénie, anémie
• • •
Génotype 2
Génotype 3
70 – 90 %
Génotype 1 (++ pays industrialisés)
Génotype 4
< 50 %
Variabilité Interindividuelle +++
• Age
• Sexe
• Origine ethnique
• Facteurs de co-morbidité
• Fibrose hépatique
• Charge virale initiale
• Evolution charge virale (cours TRT)
• Statut génétique des patients ++++
• • • •
RVS
Réponse Virale Soutenue

Genome Wide Association Studies (GWAS)

1 - **Ge D** et al., Nature 2009; 461 : 391–401.
2 - **Tanaka Y** et al., Nat Genet 2009; 41 : 1105–9.
3 - **Suppiah V** et al., Nat Genet 2009; 41 : 1100–4.
4 - **Rauch A** et al., Gastroenterology. 2010; 138 : 1338-45.

Caucasian, African-American, Hispanic, Japanese

HCV genotype 1

Rs8103142
Lys70Arg

Rs12972991
Rs8099917
Rs12979860
Rs810996
Rs1298075

Gène Interleukine 28B ***IL28B***
Gène Interleukine 28A ***IL28A***
Gène Interleukine 29 ***IL29***

I II III IV V

3182 pb
7560 pb

5' 3'

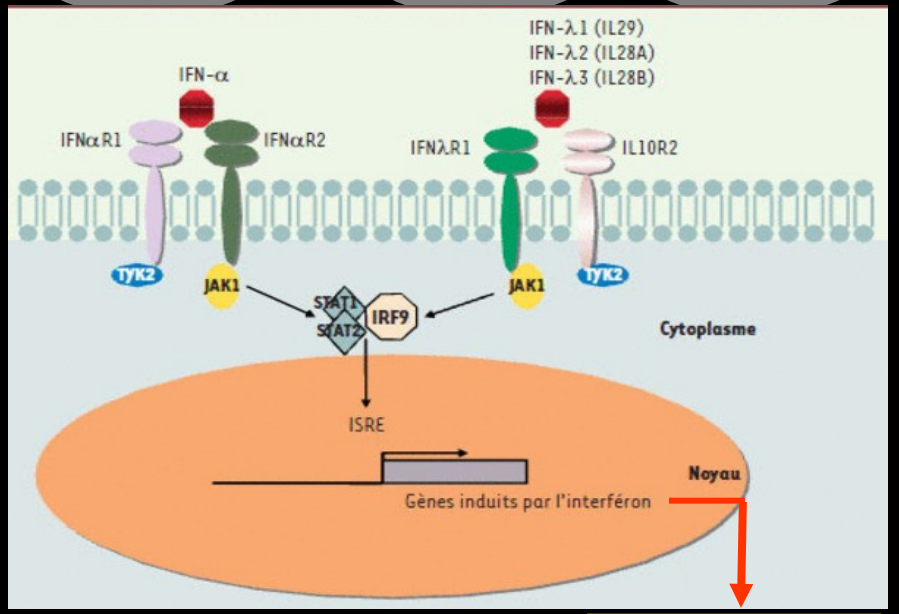
g – 7560 T > G **g – 3182C > T**

Chromosome 19 (19q13.13)

Genotype Caucasiens
T/T: 12%
T/C: 51%
C/C: 37% Asie ↑ Afrique ↓

$p = 2.82 \times 10^{-27}$
$p = 1.88 \times 10^{-21}$
$p = 4.37 \times 10^{-26}$
$p = 1.32 \times 10^{-16}$
$p = 1.21 \times 10^{-28}$

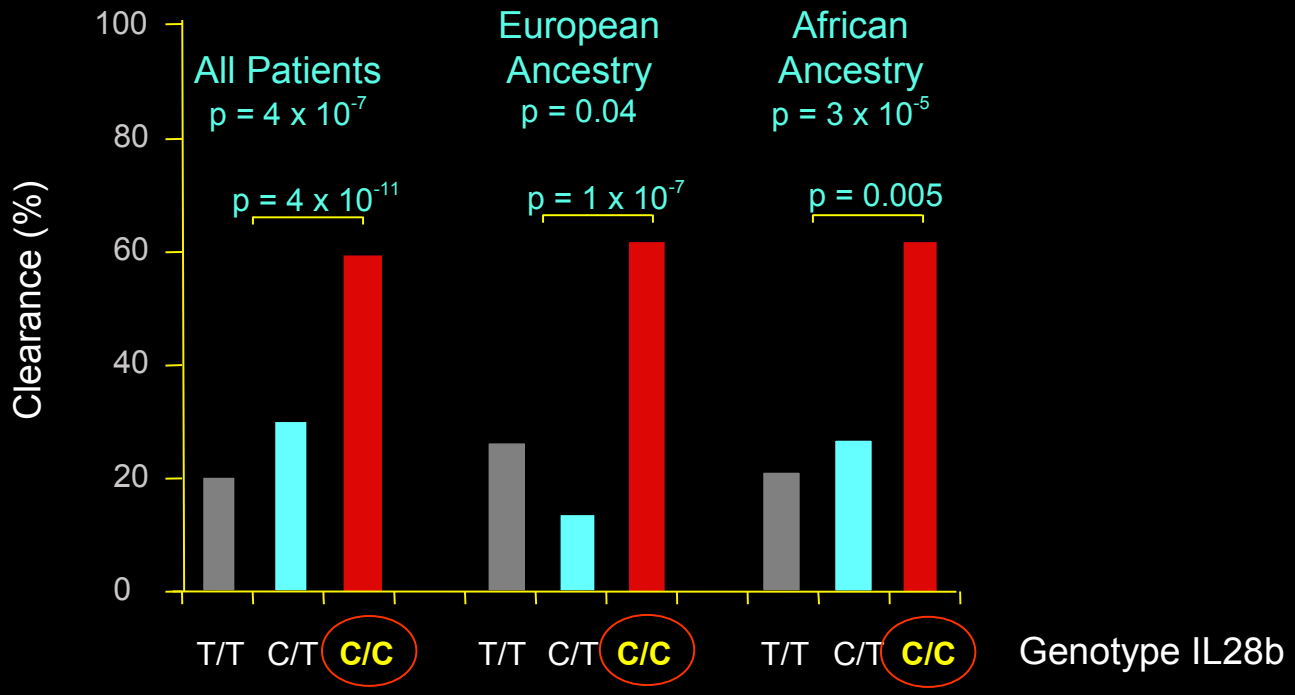
Interféron λ 3 **Interféron λ 2** **Interféron λ 1**

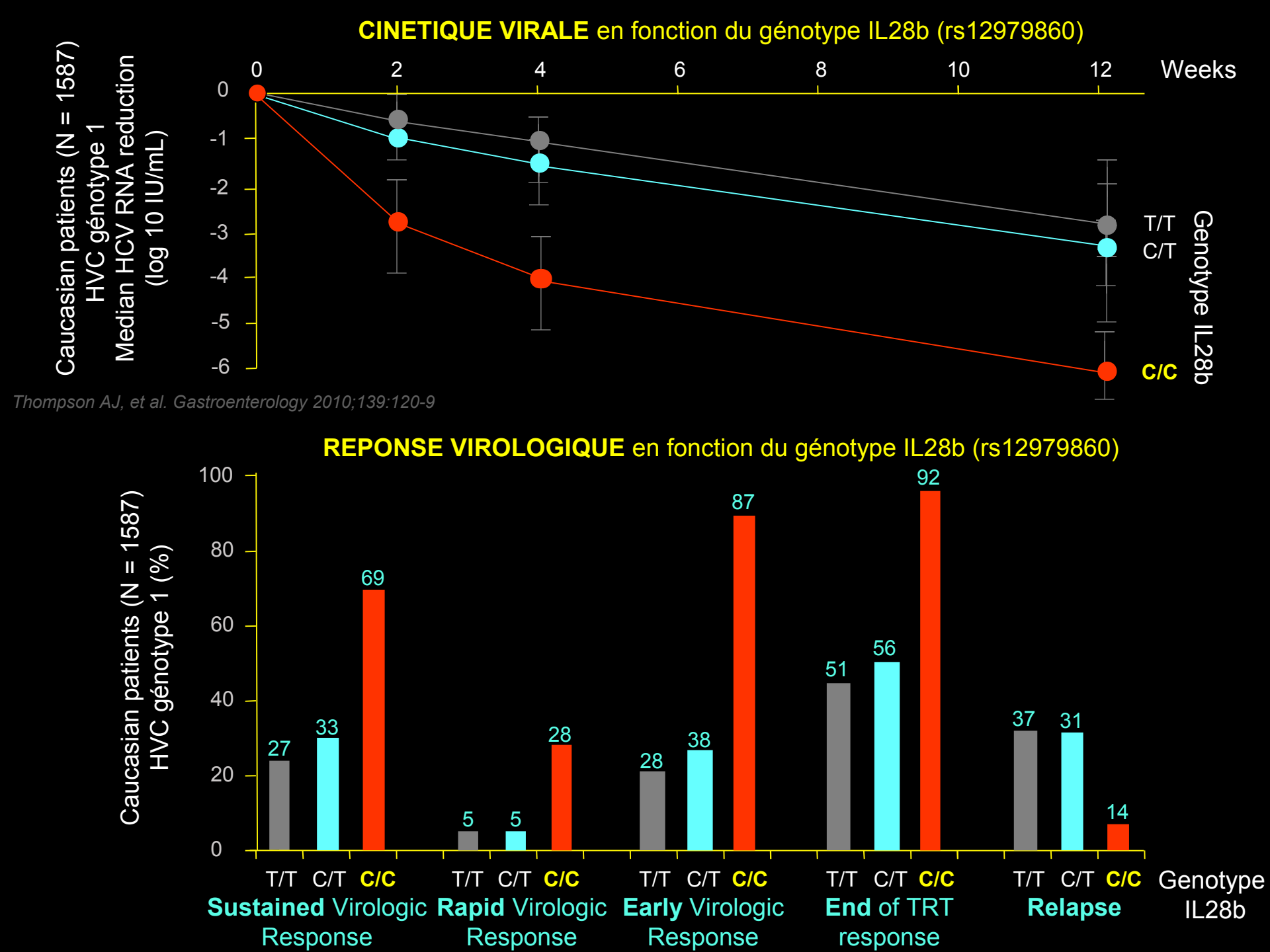


Clairance virale
Spontanée ou induite par le Traitement

Réponse anti virale

Influence du génotype IL28b (rs12979860) sur la **CLAIRANCE SPONTANEE du VHC**




CINETIQUE VIRALE en fonction du génotype IL28b (rs12979860)
Caucasian patients (N = 1587)
HVC génotype 1
Median HCV RNA reduction
(log 10 IU/mL)
0
-1
-2
-3
-4
-5
-6
0
2
4
6
8
10
12
Weeks
T/T
C/T
C/C
Genotype IL28b
Thompson AJ, et al. Gastroenterology 2010;139:120-9
REPONSE VIROLOGIQUE en fonction du génotype IL28b (rs12979860)
Caucasian patients (N = 1587)
HVC génotype 1 (%)
100
80
60
40
20
0
27
33
69
5
5
28
28
38
87
51
56
92
37
31
14
T/T C/T C/C
Sustained Virologic Response
Rapid Virologic Response
Early Virologic Response
End of TRT response
Relapse
Genotype IL28b

Le génotype IL28b est le meilleur facteur prédictif préthérapeutique de RVS chez les patients ayant une hépatite C de génotype 1

FACTEURS PRETHERAPEUTIQUES associés à la RVS (analyse multivariée)

	Odds Ratio	IC 95%	P
Genotype C/C vs non-C/C (rs12979860)	**5.2**	**4.1 – 6.7**	**< 0.0001**
Charge viral < vs > 600 000 UI/ml	3.1	2.3 - 4.1	< 0.0001
Caucasiens vs afro-américains	2.8	2.0 – 4.0	< 0.0001
Hispaniques vs afro-américains	2.1	1.3 – 3.6	0.004
METAVIR F012 vs F3F4	2.7	1.8 – 4.0	< 0.0001
Glycémie à jeun < vs > 5.6 mmol/l	1.7	1.3 – 2.2	< 0.0001

Des études prospectives sont encore nécessaires pour qu'il soit inclus définitivement aux recommandations thérapeutiques

Influence du génotype IL28B dans les nouvelles stratégies thérapeutiques DAA (Directly acting antiviral agent)

Arrivée des DAA

A ajouter à la bithérapie standard pour limiter l'apparition de résistance

Inhibiteurs des protéases NS3-4A du HCV (telaprevir et boceprevir)
Inhibiteurs de la polymerase NS5B du HCV
Inhibiteurs NS5A du HCV
Inhibiteur de la cyclophilin A Debio-025 (alisporivir)
……

Ajout d'un inhibiteur de protéase n'est pas sans problèmes additionnels

Coût supplémentaire
Effets indésirables Fatigue, fièvre, maux de tête, nausée, anémie, mauvais dysgeusie, rash cutané…
Virus résistance

Sustained Viral Responses by *IL28B* genotype (rs12979860) SPRINT-2 and RESPOND-2 phase 3 trials of BOCEPREVIR

Trial cohort SPRINT – 2	Treatment - naïve patients			
HCV Genotype 1 infection N = 1097	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control **pegIFN/ribavirin** (48 weeks)	38%	78%	28%	27%
pegIFN/ribavirin + Boceprevir Response Guided Therapy (stop 28 weeks)	63%	82%	65%	55%
pegIFN/ribavirin (4 weeks) followed by **pegIFN/ribavirin/Boceprevir** (44 weeks)	66%	80%	71%	59%

Trial cohort RESPOND - 2	Prior therapy failed with pegIFN/ribavirin			
HCV Genotype 1 infection N = 403	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control **pegIFN/ribavirin** (48 weeks)	21%	46%	17%	50%
pegIFN/ribavirin + Boceprevir Response Guided Therapy (stop 36 weeks)	59%	79%	61%	55%
pegIFN/ribavirin (4 weeks) followed by **pegIFN/ribavirin/Boceprevir** (44 weeks)	66%	77%	73%	72%

Sustained Viral Responses by *IL28B* genotype (rs12979860) ADVANCE and REALIZE phase 3 trials of TELAPREVIR

Trial cohort ADVANCE	Treatment - naïve patients			
HCV Genotype 1 infection N = 454	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control pegIFN/ribavirin (48 weeks)	38%	64%	25%	23%
Telaprevir + pegIFN/ribavirin Response Guided Treatment (stop 24 weeks)	78%	90%	71%	73%
Telaprevir + pegIFN/ribavirin (8 weeks) Followed by pegIFN/ribavirin (40 weeks)	67%	87%	58%	59%

Trial cohort REALIZE	Prior therapy failed with pegIFN/ribavirin			
HCV Genotype 1 infection N = 527	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control pegIFN/ribavirin (48 weeks)	-	29%	16%	13%
Telaprevir + pegIFN/ribavirin (12 weeks) Followed by pegIFN/ribavirin (36 weeks)	-	79%	60%	61%

Influence du génotype IL28b sur d'autres DAA

Inhibiteur de protéase TMC 435 + pegIFN/ribavirin → Influence ± 0
Inhibiteur de polymerase PSI-7977 + pegIFN/ribavirin → Influence ± 0
Inhibiteur de polymerase ANA598 + pegIFN/ribavirin → Influence +++

Influence variable selon le DAA

TREATMENT ALGORYTHM

HCV Genotype 1 (and 4) infection

IL28b variations are strongly associated with SVR

Naïve Patients

IL28b Rs12979860 C/C

- pegIFN/ribavirin
  24 - 48 weeks (individualized duration)

Benefit and Response-guided approach during triple-therapy is unclear

IL28b Rs12979860 C/T or T/T

- Postponement of therapy
- pegIFN/ribavirin + telaprevir / boceprevir
  24 weeks if extended RVR (eRVR)
  48 weeks if no eRVR
- pegIFN/ribavirin (48-72 weeks)
  If contraindication to triple therapy

Prior null responders to standard therapy

Quadruple therapy or DAA agents with a higher genetic barrier to resistance (pegIFN/ribavirin + NS5B/cyclophilin inhibitor)

HCV Genotype 2 & 3 infection

IL28b variations are only weakly associated with SVR

IL28b Rs12979860 C/C

- Whether a good response genotype may be an argument of shortened TRT duration (eg 12 weeks) is unclear

IL28b Rs12979860 C/T or T/T

- A poor response IL28b genotype might indicate a need for prolonged therapy of 48 wks in patients who do not attein an RVR

Lange CM & Zeuzen S. J Hepatol 2011;55:692-701 Clark JC & Thompson AJ. J Gastroenterol Hepatol sept 2011

Ajout d'un inhibiteur d'un DAA n'est pas sans:

Coût supplémentaire
Effets indésirables Fatigue, fièvre, maux de tête, nausée, anémie, mauvais dysgeusie, rash cutané…
Virus résistance risquant de compromettre les options thérapeutiques futures

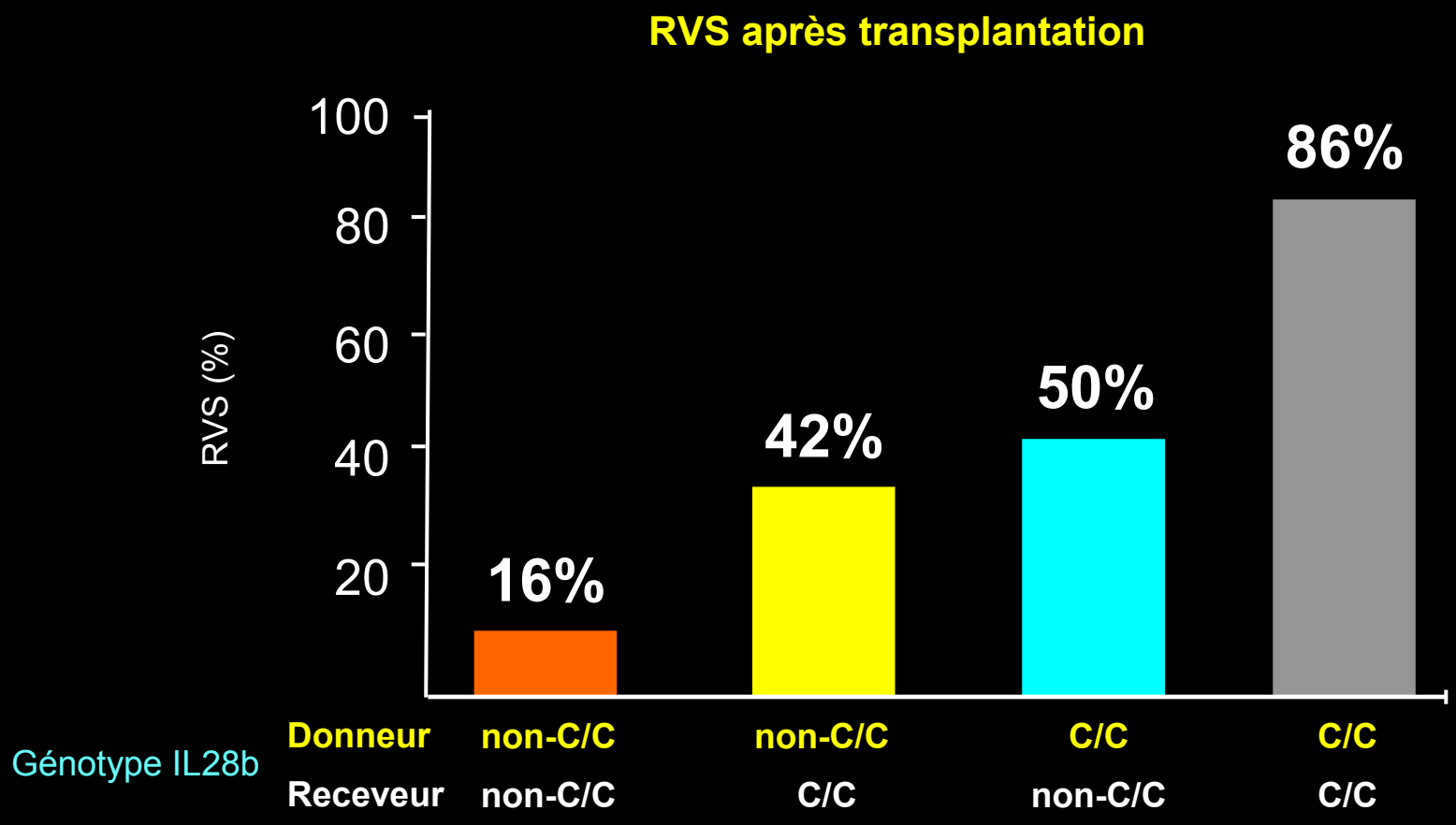
Autres facteurs:

Facteurs individuels (âge, ethnie…)
Facteurs de co-morbidité
Degré de fibrose hépatique
Facteurs viraux (charge virale initiale, évolution de la charge virale au cours du Trt…)
Nouveaux facteurs prédictif : Déficit en vitamine D,
Taux sérique d'Interferon gamma-inducible protein-10 (IP-10),
Resistance à la stétaose/insuline….
Autres facteurs génétiques: Natural killer (NK) cell receptor KIR2DL3 et de son ligand
Human leukocyte antigen C group 1 (HLA-C1)
ITPA, UGT1A1, CYP27B1…

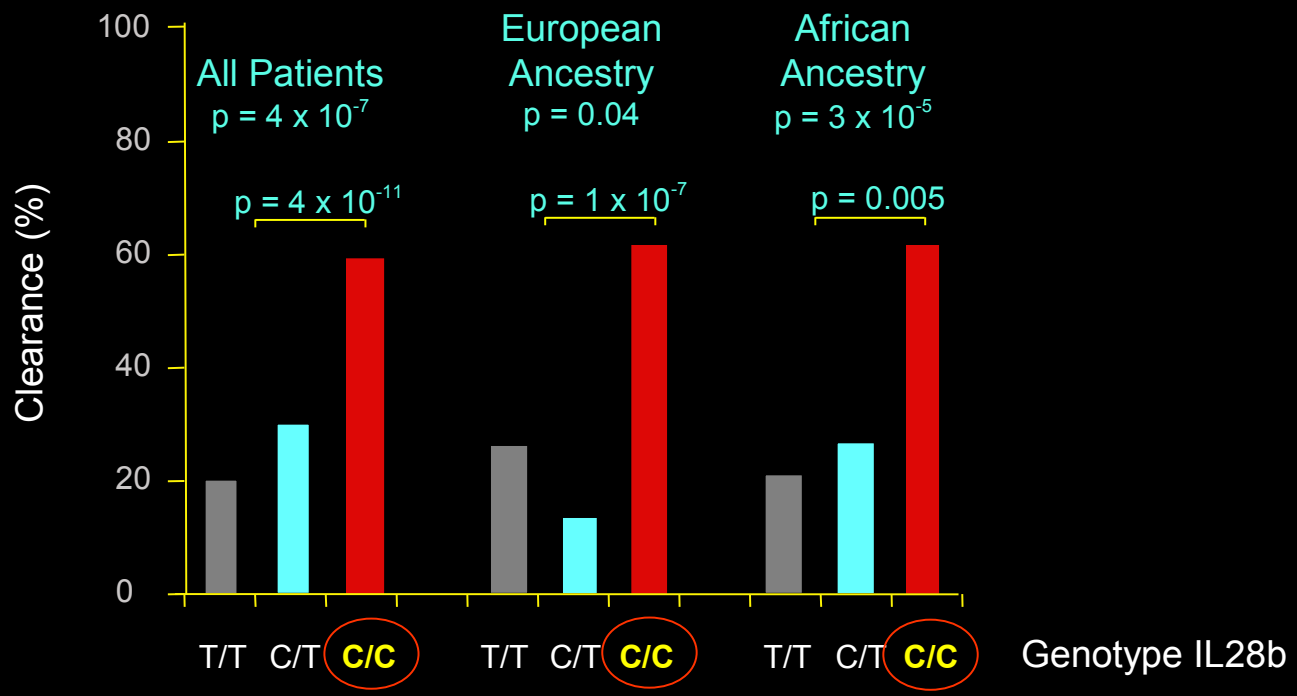
Programme de prédiction prenant en considération de nombreux facteurs de variabilité: http://ideasydesarrollo.com/fundacion/prometheusindex.php?lang=ing

Autres: Patient demand for shorter duration, less toxic regimen
Public health equity

Impact du polymorphisme de L'IL28B sur réponse au traitement après transplantation chez les patients infectés par le VHC



Influence du génotype IL28b (rs12979860) sur la **CLAIRANCE SPONTANEE du VHC**



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IL28b Rs12979860 C/C

- <u>pegIFN/ribavirin</u>
  24 - 48 weeks (individualized duration)

Benefit and Response-guided approach during triple therapy is unclear

- pegIFN/ribavirin + telaprevir / boceprevir
  12 - 24 weeks if extended RVR (eRVR)
  48 weeks if no eRVR

IL28b Rs12979860 C/T or T/T

- pegIFN/ribavirin + telaprevir / boceprevir
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  If contraindication to triple therapy

<u>Prior null responders to standard therapy</u>

- Quadruple therapy or DAA agents with a higher genetic barrier to resistance (pegIFN/ribavirin + NS5B/cyclophilin inhibitor)

HCV Genotype 2 & 3 infection

IL28b variations are only weakly associated with SVR

IL28b Rs12979860 C/C

- Whether <u>a good response genotype</u> may be an argument of shortened TRT duration (eg 12 weeks) is unclear

IL28b Rs12979860 C/T or T/T

- A <u>poor response IL28b</u> genotype might indicate a need for prolonged therapy of 48 wks in patients who do not attein an RVR

Lange CM & Zeuzen S. J Hepatol 2011;55:692-701 Clark JC & Thompson AJ. J Gastroenterol Hepatol sept 2011

TREATMENT ALGORYTHM

HCV Genotype 1 (and 4) infection

IL28b variations are strongly associated with SVR

Naïve Patients

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  24 - 48 weeks (individualized duration)

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  48 weeks if no eRVR

IL28b Rs12979860 C/T or T/T

- Postponement of therapy
- pegIFN/ribavirin + telaprevir / boceprevir
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  48 weeks if no eRVR
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Characteristics of four pivotal GWAS on treatment-induced HCV clearance

	Ge D et al. *Nature 2009; 461 : 391–401*	***Tanaka Y et al.*** *Nat Genet 2009; 41 : 1105–9.*	***Suppiah V et al.*** *Nat Genet 2009; 41 : 1100–4.*	***Rauch A et al.*** *Gastroenterology 2010;138 : 1338-45.*
Primary endpoint /	SVR vs non response	NVR vs VR (Non Virological Response, defined as less than 2 log10 IU/ml decrease in HCV RNA at week 12)	SVR vs non response	SVR vs non response
Genotype	HCV 1	HCV 1	HCV 1	HCV 1, 2, 3, 4
Adherence control	Non-SVR patient excluded if <80% adherent	All patients excluded if < 80% adherent during the first 12 weeks	No specific adherence criteria	>80% adherent
Top SNP	rs12979860 OR (CC genotype, SVR): 2.0 (1.8-2.3) p =1.06 x 10^{-25}	rs8099917 OR (G allele, NVR) 27.1 (CI 14.6-50.3) P = 2.68 x 10^{-32} (rs12979860 not genotyped)	rs8099917 OR (T allele, SVR) 1.98 (CI 1.6-2.5) p = 9.25 x 10^{-9} (rs12979860 not genotyped)	rs8099917 OR (G allele, no SVR): 5.19; 95% (CI, 2.90 – 9.30) p = 3.11 x 10^{-8} (Data for rs12979860 not presented)
Alleles	C /T CC = Good response CT, TT = Poor response	T /G TT = Good response GT, GG = Poor response	T /G TT = Good response GT, GG = Poor response	T /G TT = Good response GT, GG = Poor response
SVR According To IL28B genotype	SVR rates (Caucasians) CC = 82%, CT = 42%, TT = 33% (Afro Amer) CC = 53%, CT, TT = 18%	SVR rates TT = 64% (125/194) GT = 13% (15/113), GG = 0% (0/5)	SVR rates 56 % vs 36% (T/T vs T/G, G/G)	SVR rates 74 % vs 50% (T/T vs T/G, G/G)
Cohort	n = 1137 North America (Caucasian, african-American, Hispanic)	Discovery phase n = 154 Validation phase n = 172 Japanese	Discovery phase n = 293 Validation phase n = 555 Australia / Northern Europe (Caucasian)	N = 465 Northern Europe (Caucasian)