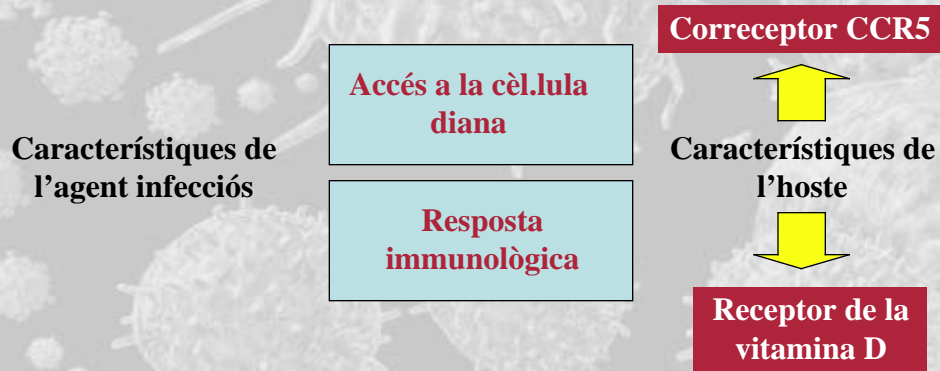


Àgents patògens Susceptibilitat a la infecció Variabilitat en la Progressió Clínica



Infecció per HIV-1

Variabilitat en la susceptibilitat a la infecció

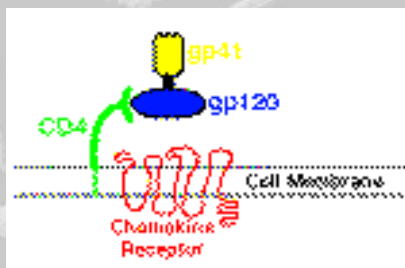
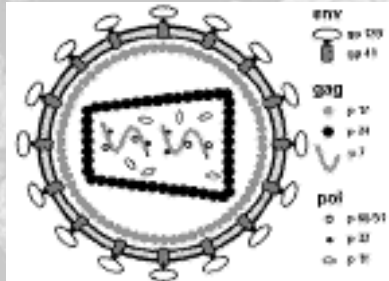
Individus exposats no infectats

Variabilitat en la progressió clínica

- **Progressors ràpids**
- **Progressors lents**
- **No progressors**

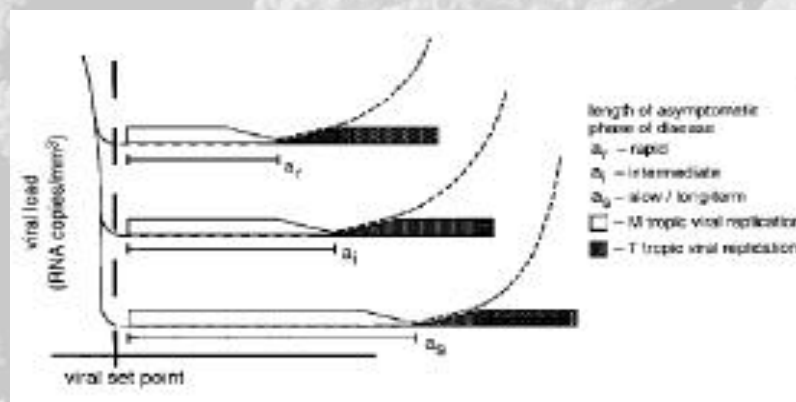
Sistema HLA
Mannose Binding Protein
Receptors de quimiocines
Quimiocines
Altres?

La porta d'entrada a la cèl·lula de l'hoste

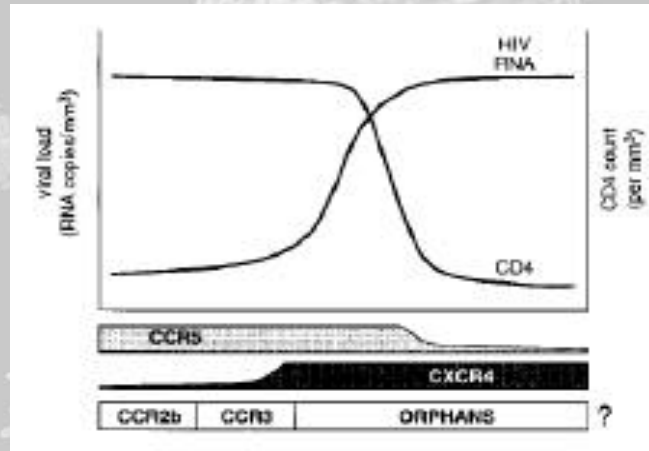


El virus aprofita com a receptor la mol·lècula CD4 i com a correceptor als receptors de quimiocines

Progressió clínica a SIDA

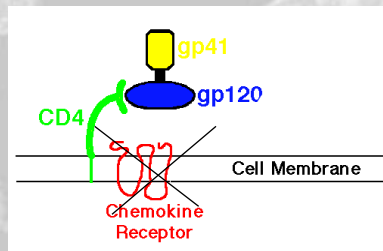


Us de correceptors durant la progressió clínica



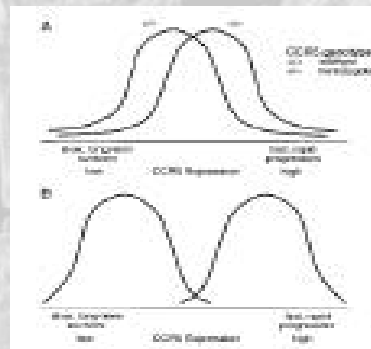
Individus exposats i no infectats

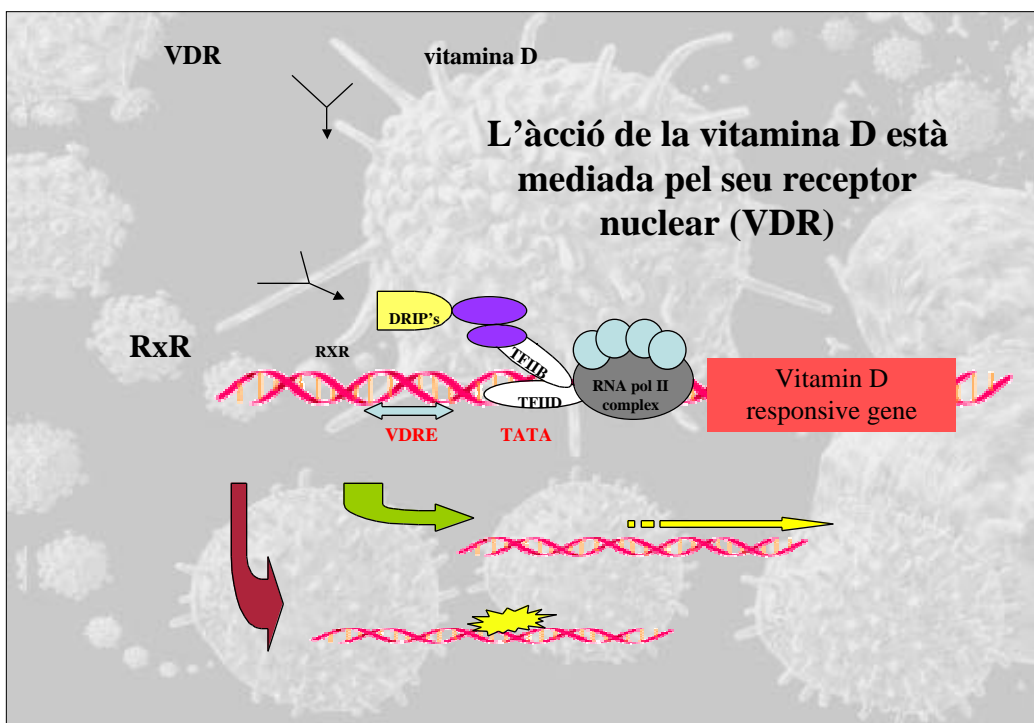
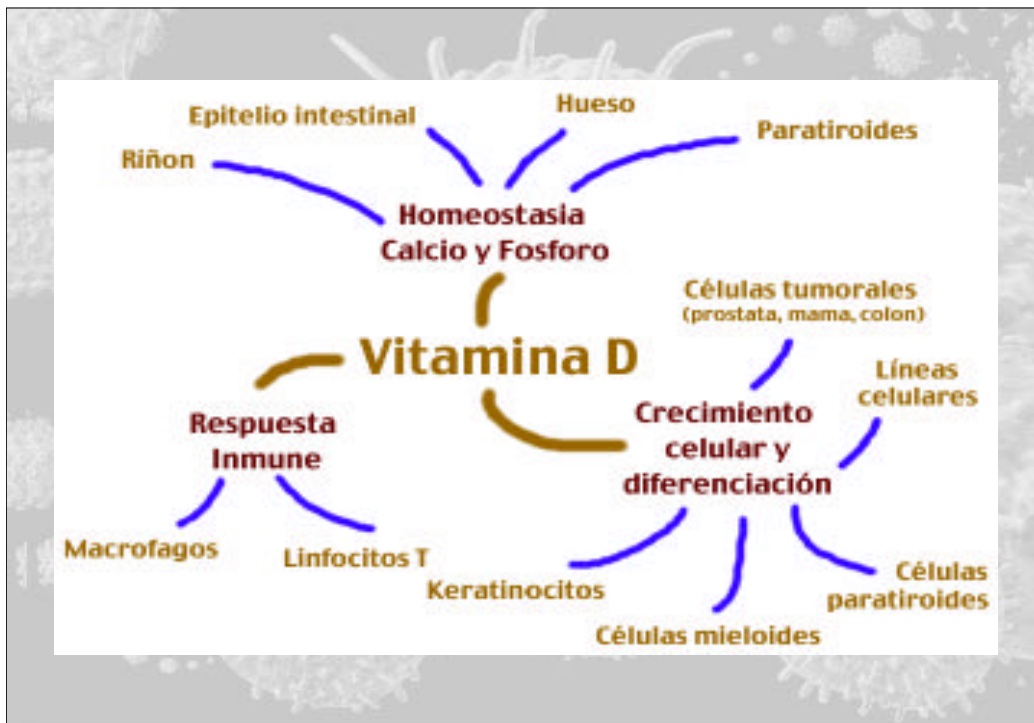
- **Deleció CCR5** 32
- Resistència a la infecció en homozigots
- Millor progressió clínica en heterozigots



- Població Caucasiana
 - Prevalència dels homozigots 2-3%
 - Aproximadament un 15-20% Heterozigots
- Baixa prevalència en altres poblacions

Expressió CCR5 Fenotip/Genotip





Genes que responden a la Vitamina D

Ruta Biosintética

24, hidroxilasa 
1, α hidroxilasa 

Homeostasia del Calcio/Fosforo

Osteocalcina 
Osteopontina 
Calbindina D_{9k} 
Calbindina D_{28k} 
Canal de Calcio epitelial 
Hormona paratiroidea 

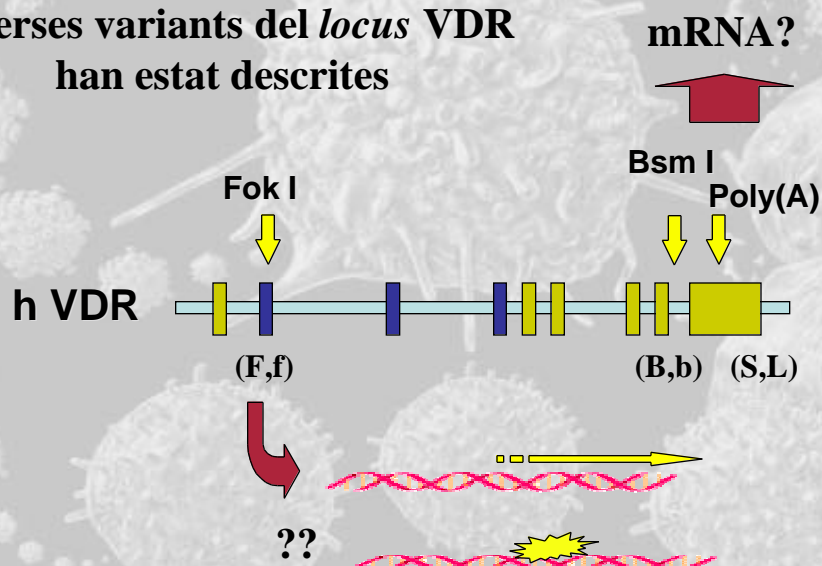
Respuesta Inmune

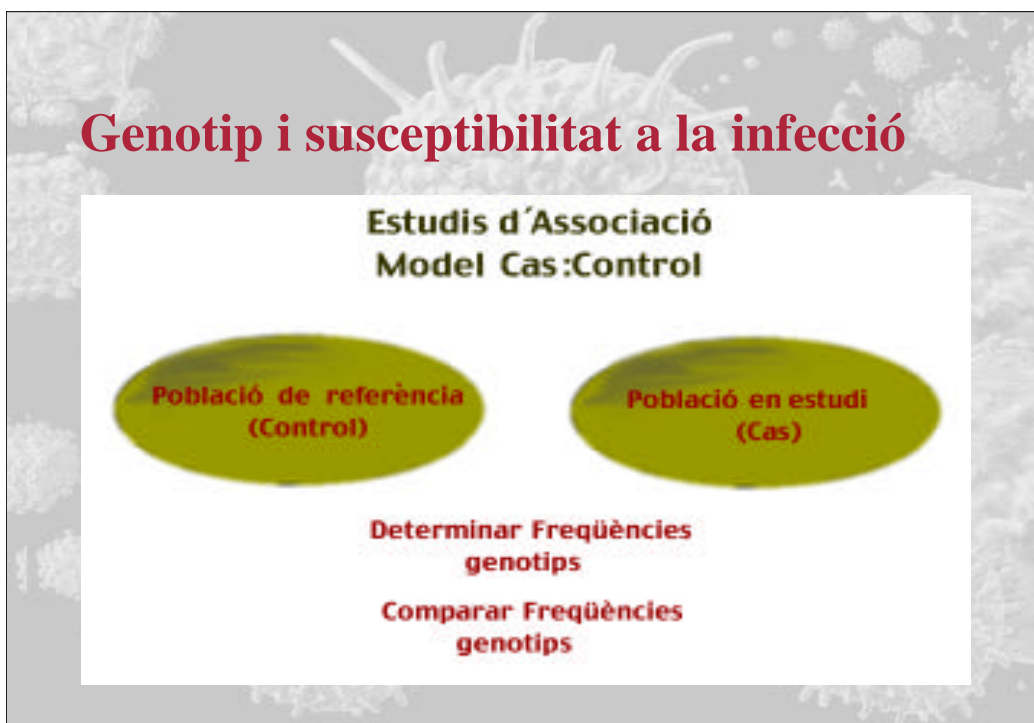
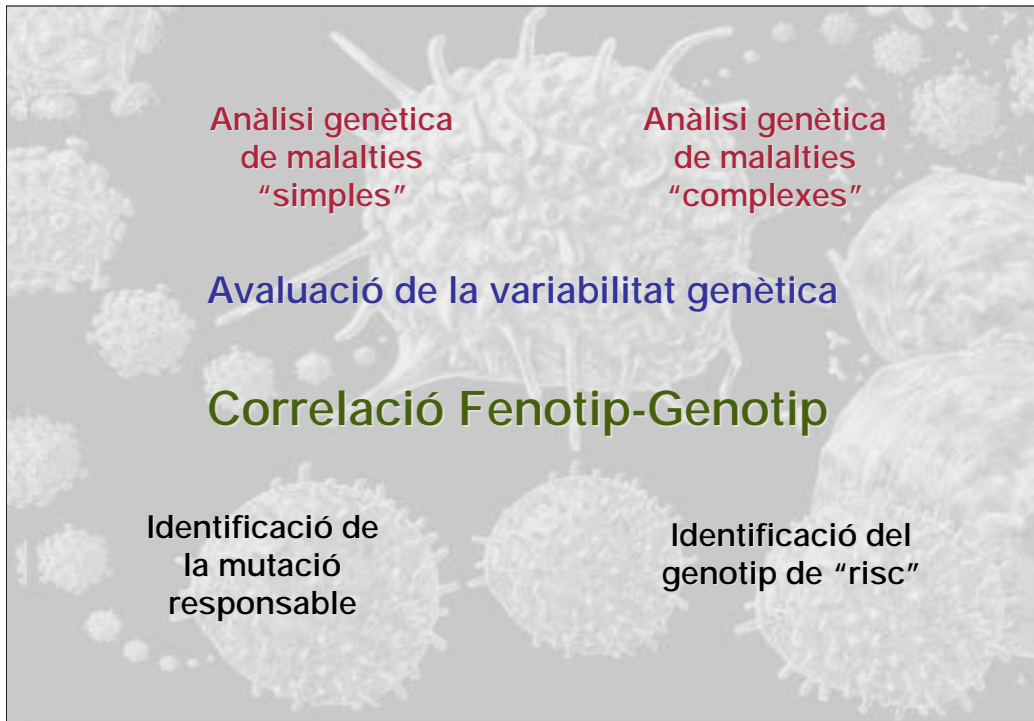
Interleucina 2 (IL-2) 
Interleucina 12 (IL-12) 
Interferón γ 
Tumor Necrosis Factor α 

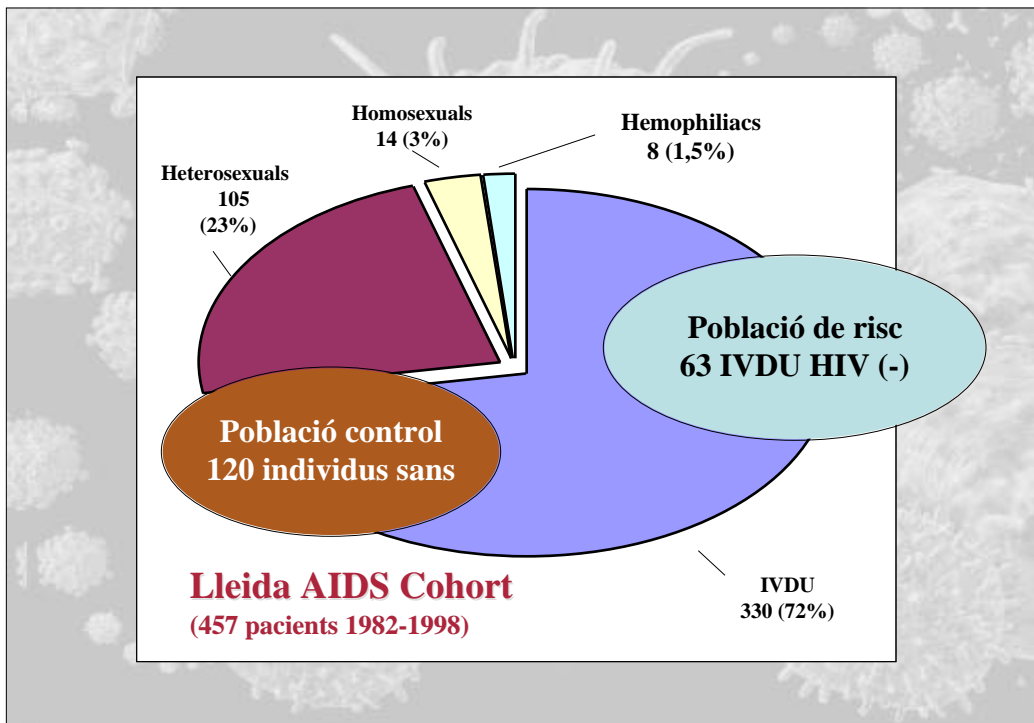
Proliferación y diferenciación

proteína p21 
proteína p27 

Diversas variants del *locus* VDR han estat descrites







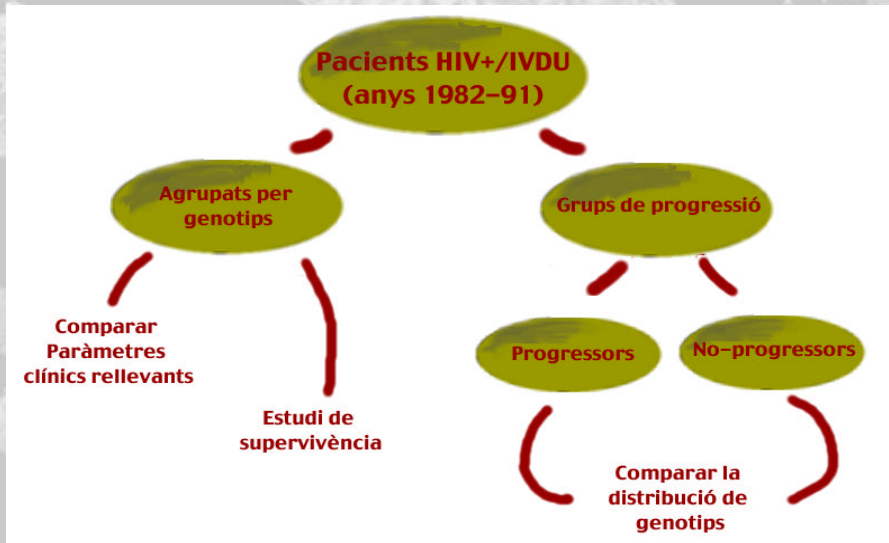
Genotype distribution in patients arranged according to risc group

| CCR5 | Controls | IVDU/HIV+ | Heterosexuals | Risc/HIV- |
|-------|----------|-----------|---------------|-----------|
| w/wt | 81,7 | 86 | 90,5 | 79 |
| w/32 | 15,8 | 14 | 9,5 | 19 |
| 32/32 | 2,6 | 0 | 0 | 1,6 |

0,023
 0,074
 0,874
 0,084
 0,063

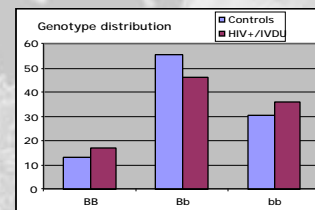
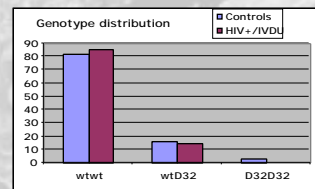
El locus Vdr no està implicat en la infecció
L'al.lel 32 en homozigosi confereix resistència a la infecció
Els heterozigots no estan protegits (IVDU)
(Heterosexuals ?)

Genotip i progressió clínica

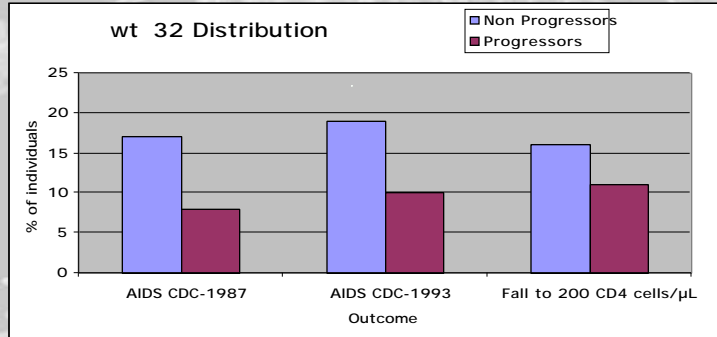


Genotype and allele distribution of CCR5 and VDR polymorphisms in healthy control population and HIV+/IVDU patients.

| | Controls n = 120 n (%) | HIV+/IVDU n = 185 n (%) | p value |
|-------------------|------------------------------|-------------------------------|---------|
| Locus CCR5 | | | |
| Genotypes | | | |
| wtwt | 98 (81.6) | 158 (85.4) | 0.09 |
| wt 32 | 19 (15.8) | 27 (14.6) | |
| 32 32 | 3 (2.6) | 0 | |
| Alleles wt | | | |
| 32 | 215 (89.6) | 343 (92.7) | 0.178 |
| | 25 (10.4) | 27 (7.3) | |
| Locus VDR | | | |
| Genotypes | | | |
| BB | 16 (13.4) | 32 (17.3) | 0.271 |
| Bb | 67 (55.8) | 86 (46.5) | |
| bb | 37 (30.8) | 67 (36.2) | |
| Alleles | | | |
| B | 99 (41.2) | 150 (40.5) | 0.862 |
| b | 141 (58.8) | 220 (59.5) | |

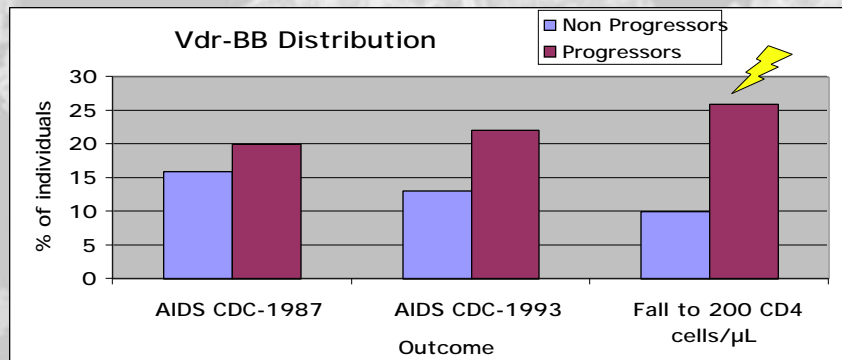


| End point | CCR5 genotypes in all patients (n,%) | | | | | |
|--------------------------------|--------------------------------------|---------|--|-------------|--------|---------|
| | Non Progressors | | | Progressors | | p value |
| | wtwt | wt 32 | | wtwt | wt 32 | |
| AIDS CDC-1987 | 113 (83) | 23 (17) | | 45 (92) | 4 (8) | 0,137 |
| AIDS CDC-1993 | 77 (81) | 18 (19) | | 81 (90) | 9 (10) | 0.085 |
| Fall to 200 CD4 cells/ μ L | 83 (84) | 16 (16) | | 66 (89) | 8 (11) | 0.314 |



AIDS CDC-1993 : CCR5-wt 32 vs. CCR5-wtwt, odds ratio (OR): 0.9; 95%(CI): 0.8-1

| End point | VDR genotypes in all patients (n,%) | | | | | | p value |
|--------------------------------|-------------------------------------|---------|---------|-------------|---------|---------|---------|
| | Non-Progressors | | | Progressors | | | |
| | Vdr-BB | Vdr-Bb | Vdr-bb | Vdr-BB | Vdr-Bb | Vdr-bb | |
| AIDS CDC-1987 | 22 (16) | 65 (48) | 49 (36) | 10 (20) | 21 (43) | 18 (37) | 0.753 |
| AIDS CDC-1993 | 12 (13) | 49 (51) | 34 (36) | 20 (22) | 37 (41) | 33 (37) | 0.169 c |
| Fall to 200 CD4 cells/ μ L | 10 (10) | 51 (52) | 38 (38) | 19 (26) | 29 (39) | 26 (35) | 0.022 e |



AIDS CDC-1993 : Vdr-BB vs. Non Vdr-BB (Vdr-Bb + Vdr-bb), p= 0.085, OR: 1.4; 95%CI: 0.9-3.4

Fall to 200 CD4 cells/ μ L: Vdr-BB vs. Non Vdr-BB (Vdr-Bb + Vdr-bb), p=0.007, OR: 2.5; 95%CI: 1.25-5.1

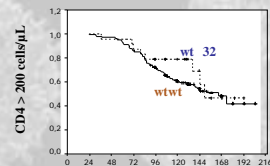
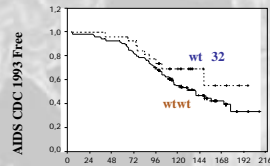
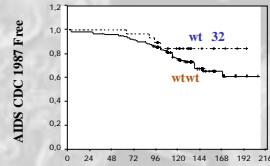
Survival Analysis for *CCR5* genotypes (all patients considered)

Kaplan-Meier Analysis for progression to outcome

| Outcome | Mean time to outcome (months) | | |
|--------------------------------|-------------------------------|-------|---------|
| | wtwt | wt 32 | p value |
| AIDS-CDC 1987 | 163 | 173 | 0.221 |
| AIDS-CDC 1993 | 133 | 148 | 0.17 |
| Fall to 200 CD4 cells/ μ L | 145 | 149 | 0.353 |

Cox Proportional Hazards Ratio (HR) for progression to outcome (wt 32 vs .wtwt)

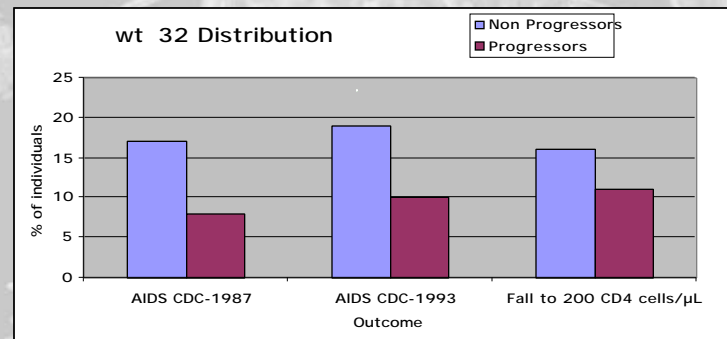
| Outcome | HR (95%CI) | p value |
|--------------------------------|----------------|---------|
| AIDS-CDC 1987 | 0.52 (0.2-1.5) | 0.218 |
| AIDS-CDC 1993 | 0.61 (0.3-1.2) | 0.158 |
| Fall to 200 CD4 cells/ μ L | 0.71 (0.3-1.5) | 0.363 |



Time from first HIV-1 positive test

End point CCR5 genotypes in all patients (n,%)

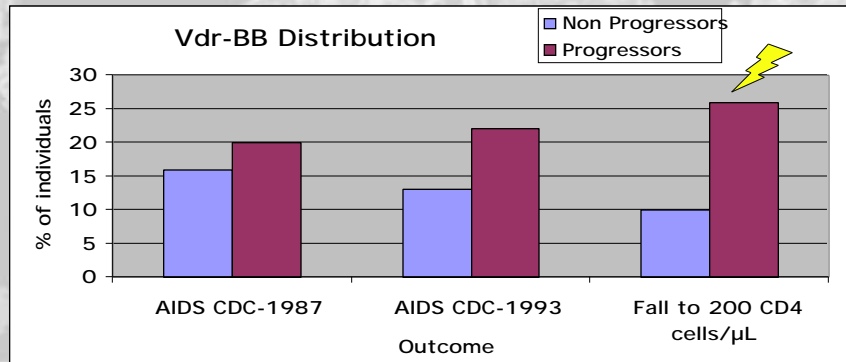
| End point | Non Progressors | | Progressors | | p value |
|--------------------------------|-----------------|---------|-------------|--------|---------|
| | wtwt | wt 32 | wtwt | wt 32 | |
| AIDS CDC-1987 | 113 (83) | 23 (17) | 45 (92) | 4 (8) | 0,137 |
| AIDS CDC-1993 | 77 (81) | 18 (19) | 81 (90) | 9 (10) | 0.085 |
| Fall to 200 CD4 cells/ μ L | 83 (84) | 16 (16) | 66 (89) | 8 (11) | 0.314 |



AIDS CDC-1993 : CCR5-wt 32 vs. CCR5-wtwt, odds ratio (OR): 0.9; 95%(CI): 0.8-1

End point VDR genotypes in all patients (n,%)

| End point | Non-Progressors | | | Progressors | | | p value |
|--------------------------------|-----------------|---------|---------|-------------|---------|---------|---------|
| | Vdr-BB | Vdr-Bb | Vdr-bb | Vdr-BB | Vdr-Bb | Vdr-bb | |
| AIDS CDC-1987 | 22 (16) | 65 (48) | 49 (36) | 10 (20) | 21 (43) | 18 (37) | 0.753 |
| AIDS CDC-1993 | 12 (13) | 49 (51) | 34 (36) | 20 (22) | 37 (41) | 33 (37) | 0.169 c |
| Fall to 200 CD4 cells/ μ L | 10 (10) | 51 (52) | 38 (38) | 19 (26) | 29 (39) | 26 (35) | 0.022 e |



AIDS CDC-1993 : Vdr-BB vs. Non Vdr-BB (Vdr-Bb + Vdr-bb), p= 0.085, OR: 1.4; 95%CI: 0.9-3.4

Fall to 200 CD4 cells/ μ L: Vdr-BB vs. Non Vdr-BB (Vdr-Bb + Vdr-bb), p=0.007, OR: 2.5; 95%CI: 1.25-5.1

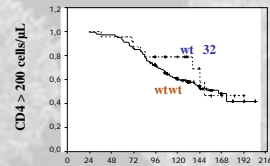
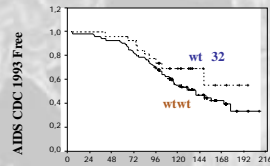
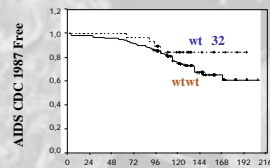
Survival Analysis for CCR5 genotypes (all patients considered)

Kaplan-Meier Analysis for progression to outcome

| Outcome | Mean time to outcome (months) | | |
|--------------------------------|-------------------------------|-------|---------|
| | wtwt | wt 32 | p value |
| AIDS-CDC 1987 | 163 | 173 | 0.221 |
| AIDS-CDC 1993 | 133 | 148 | 0.17 |
| Fall to 200 CD4 cells/ μ L | 145 | 149 | 0.353 |

Cox Proportional Hazards Ratio (HR) for progression to outcome (wt 32 vs. wtwt)

| Outcome | HR (95%CI) | p value |
|--------------------------------|----------------|---------|
| AIDS-CDC 1987 | 0.52 (0.2-1.5) | 0.218 |
| AIDS-CDC 1993 | 0.61 (0.3-1.2) | 0.158 |
| Fall to 200 CD4 cells/ μ L | 0.71 (0.3-1.5) | 0.363 |



Time from first HIV-1 positive test

Survival Analysis for *Vdr* genotypes (all patients considered)

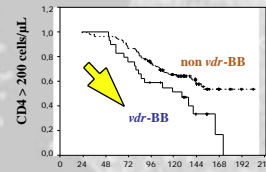
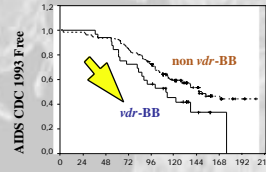
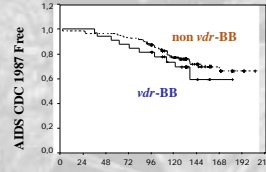
Kaplan-Meier Analysis for progression to outcome

Outcome Mean time to outcome (months)

| | <i>vdr</i> -BB | <i>vdr</i> -Bb | <i>vdr</i> -bb | p value |
|--------------------------------|----------------|----------------|----------------|---------|
| AIDS-CDC 1987 | 142 | 169 | 157 | 0.66 |
| AIDS-CDC 1993 | 112 | 146 | 131 | 0.039 |
| Fall to 200 CD4 cells/ μ L | 117 | 156 | 141 | 0.007 |

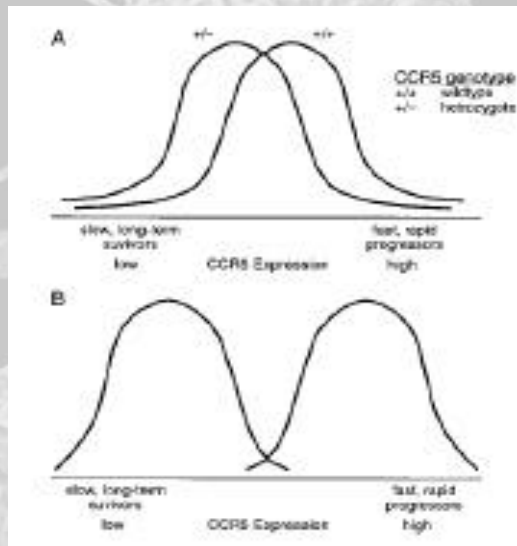
Cox Proportional Hazards Ratio (HR) for progression to outcome (BB vs . non BB)

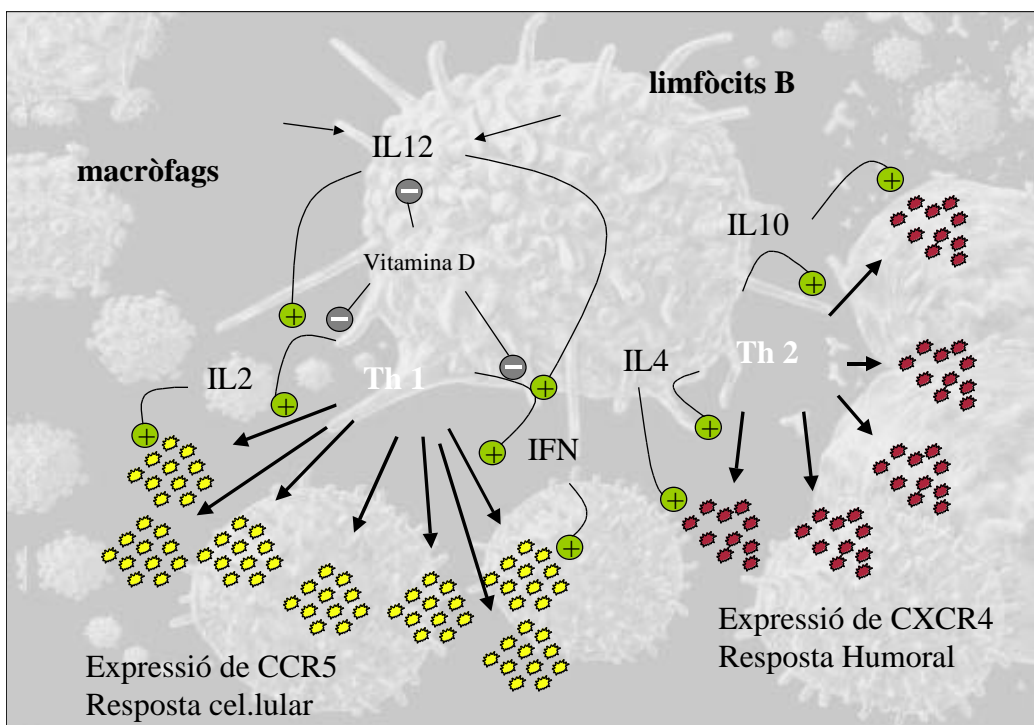
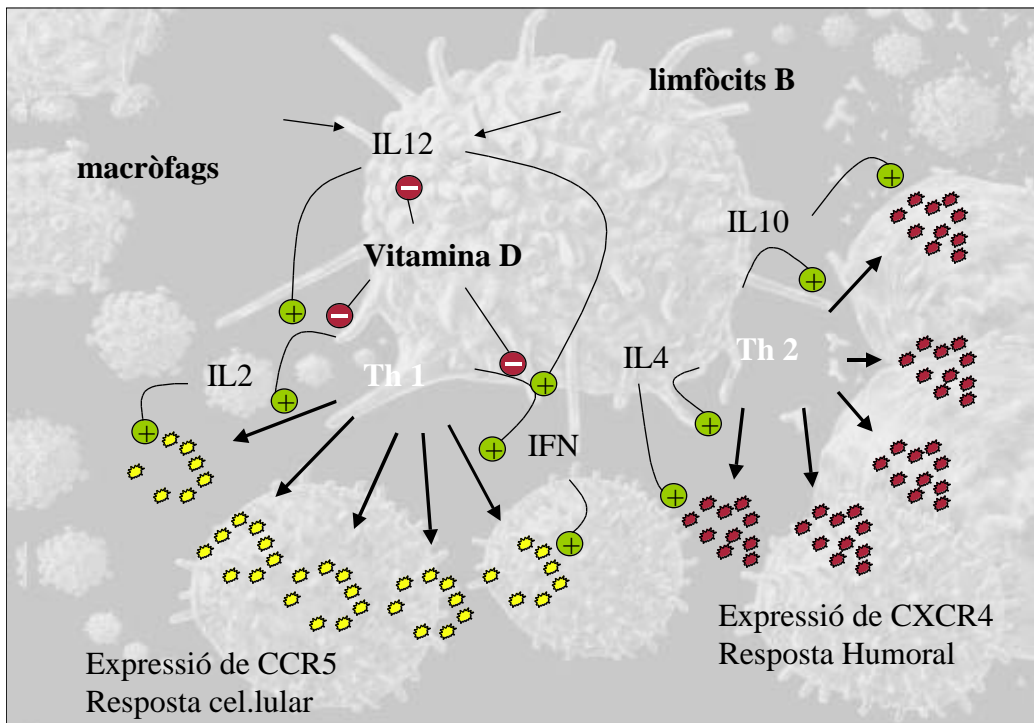
| Outcome | HR (95%CI) | p value |
|--------------------------------|---------------|---------|
| AIDS-CDC 1987 | 1.4 (0.7-2.8) | 0.351 |
| AIDS-CDC 1993 | 1.7 (1-2.8) | 0.041 |
| Fall to 200 CD4 cells/ μ L | 2.1 (1.2-3.5) | 0.006 |

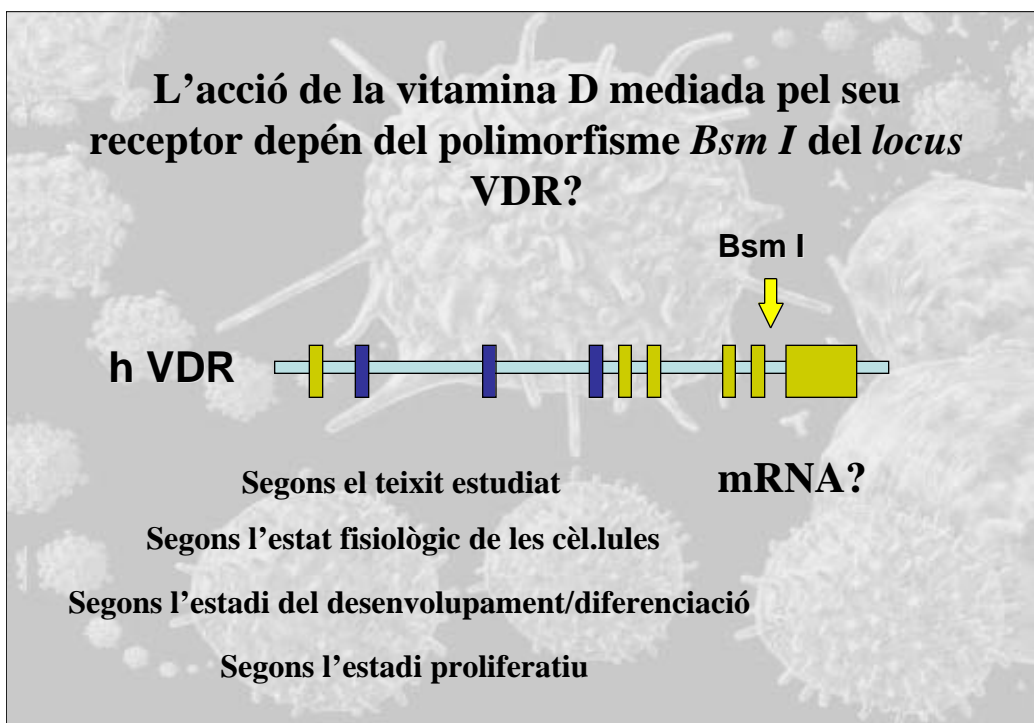
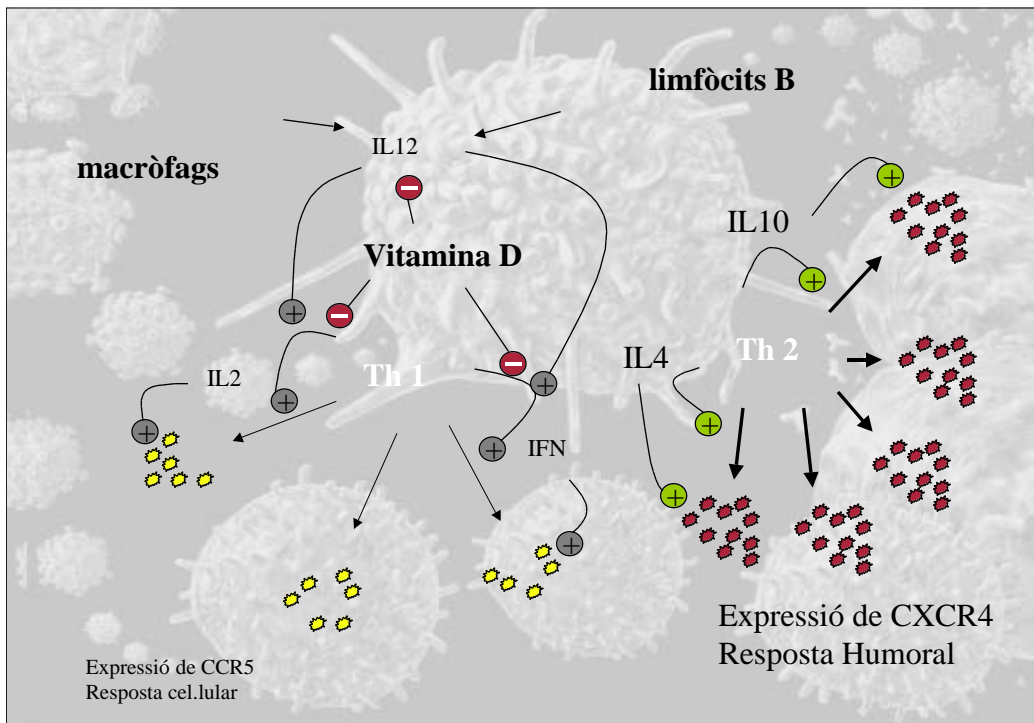


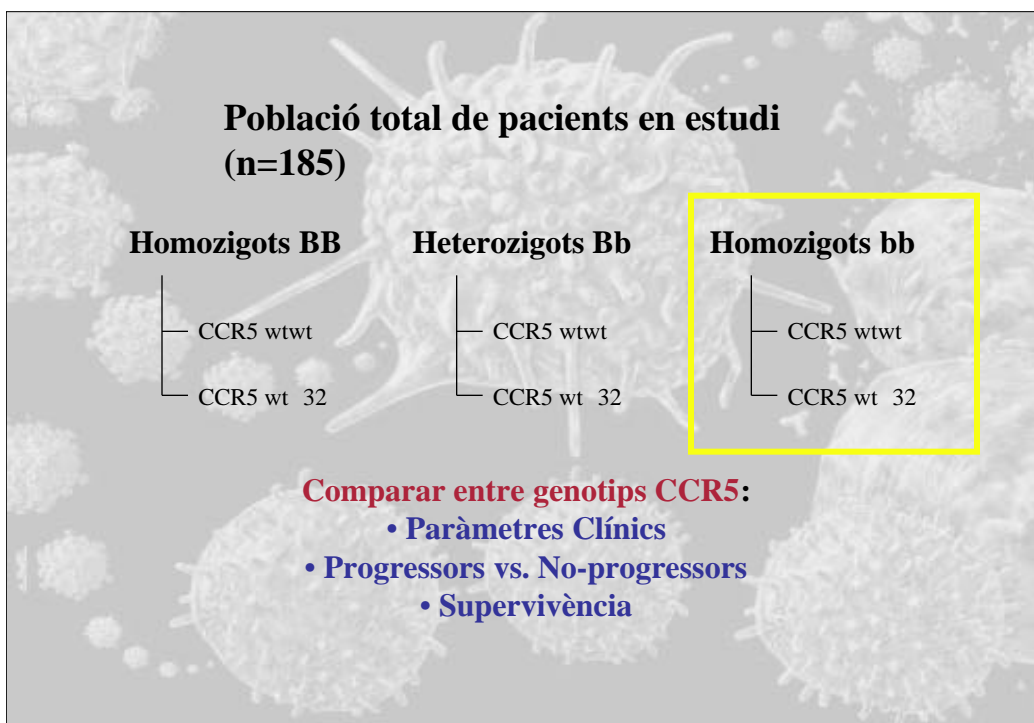
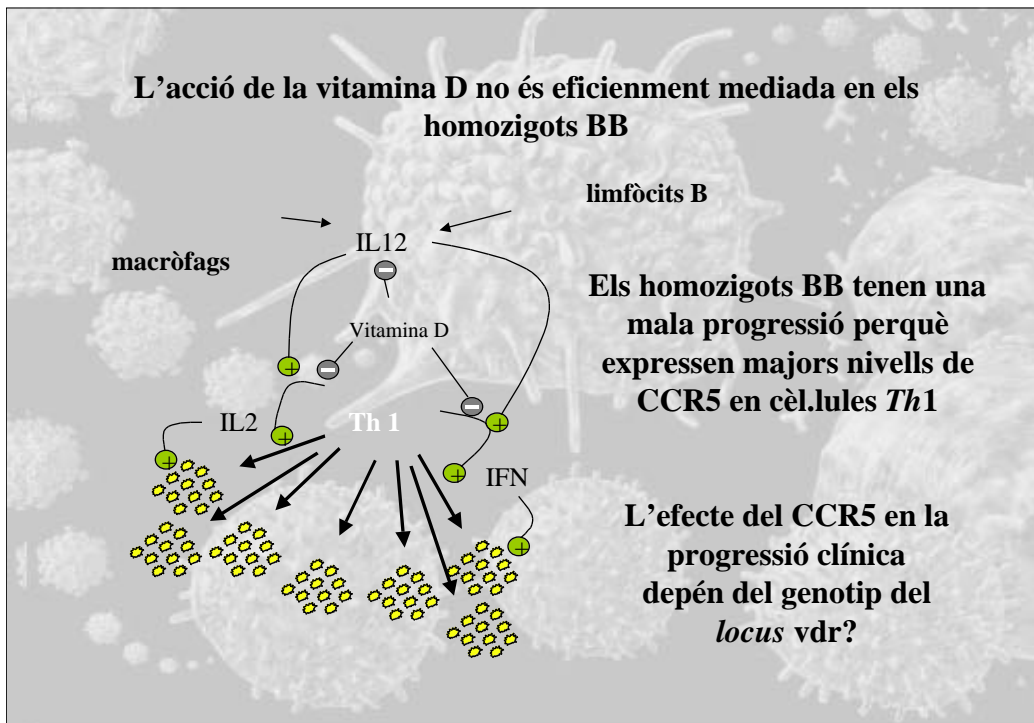
Time from first HIV-1 positive test

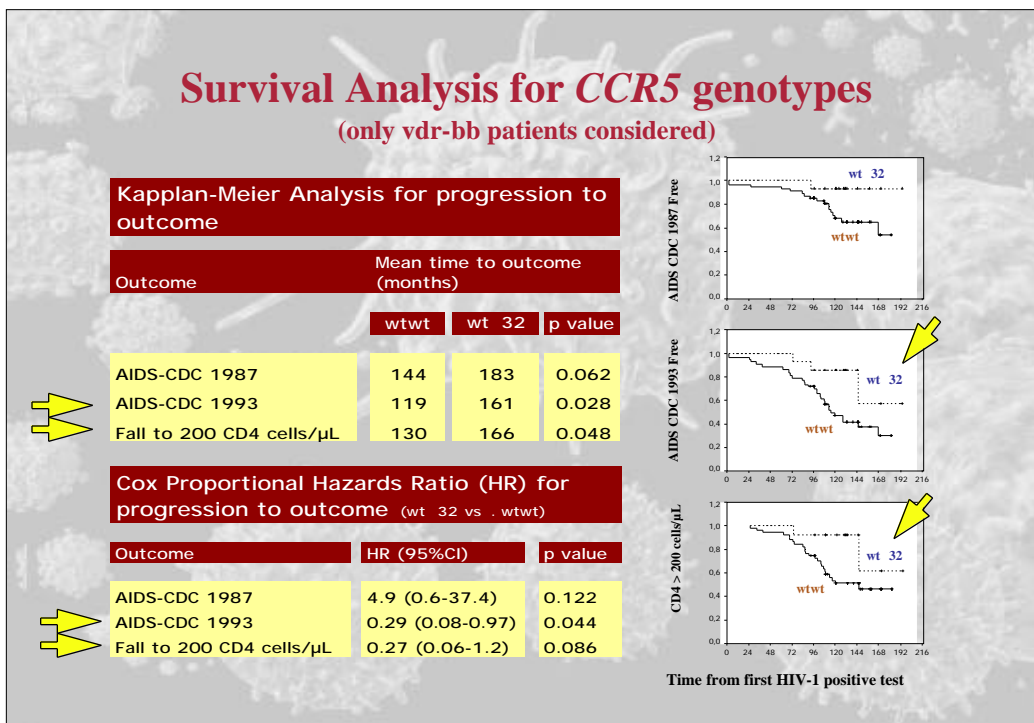
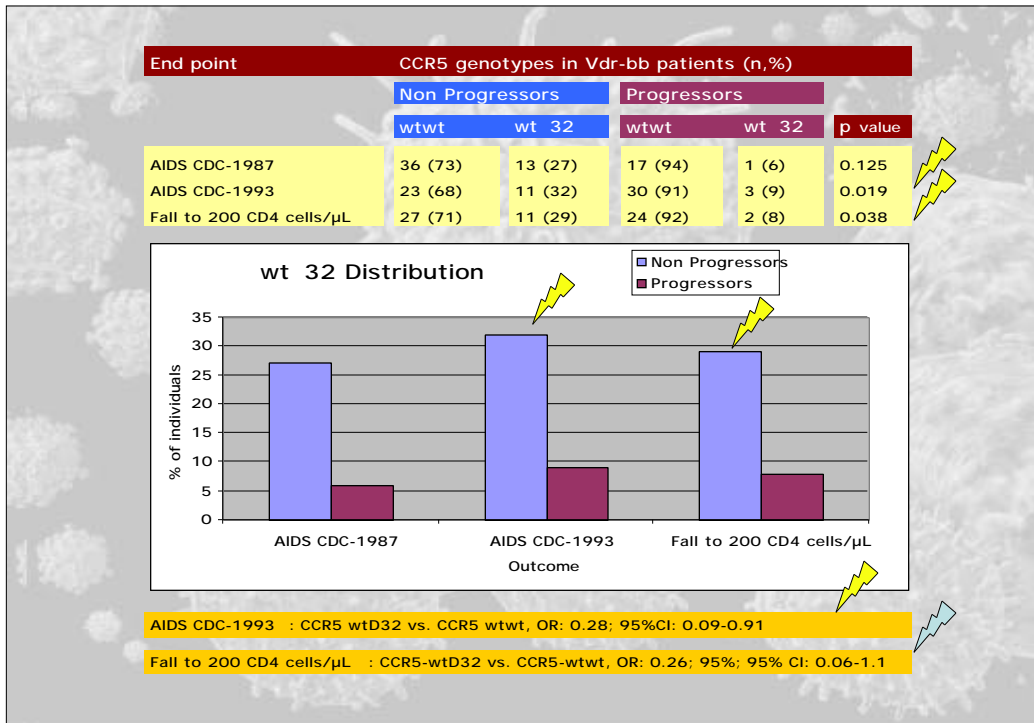
CCR5: Fenotip/Genotip



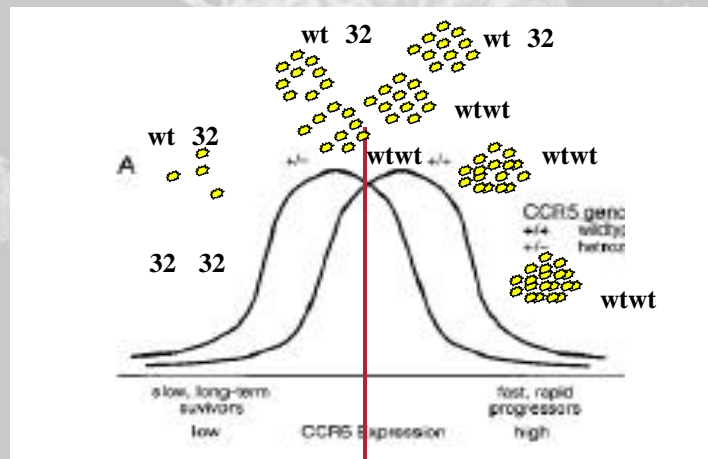






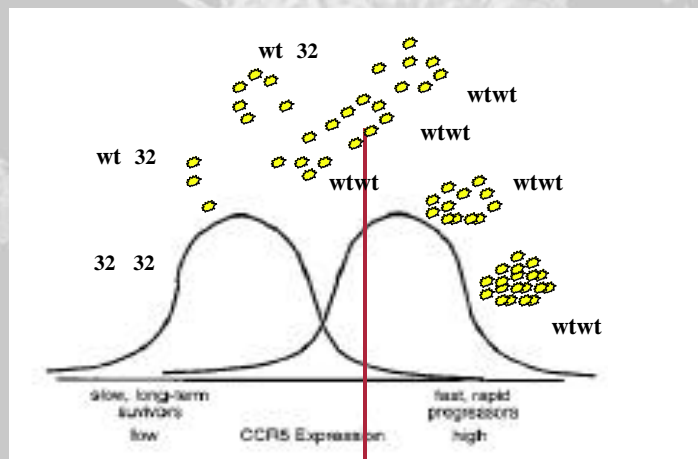


Com podem explicar la interacció CCR5-VDR ?



Llindar d'infectivitat
(10.000 molec/cell)

En un fons genètic bb



Llindar d'infectivitat
(10.000 molec/cell)

En població IVDU / HIV-1 (+)

La susceptibilitat a la infecció

- No està afectada per la variabilitat en el locus VDR
- Els heterozigots 32 no mostren resistència a la infecció

La progressió clínica a SIDA

- No és significativament diferent entre genotips del *locus* CCR5
 - Els heterozigots 32 mostren una millor progressió clínica
- Els homozigots *vdr*-BB progressen més ràpid i pitjor que els no-BB
- La progressió clínica dels heterozigots 32 és significativament millor en els pacients que són homozigots bb
- **La progressió dels malalts HIV+ a SIDA està influenciada per la variabilitat del *locus* VDR**