Host genotypes, inflammatory response and outcome of TBM Vietnam

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Tuberculous Meningitis (TBM)

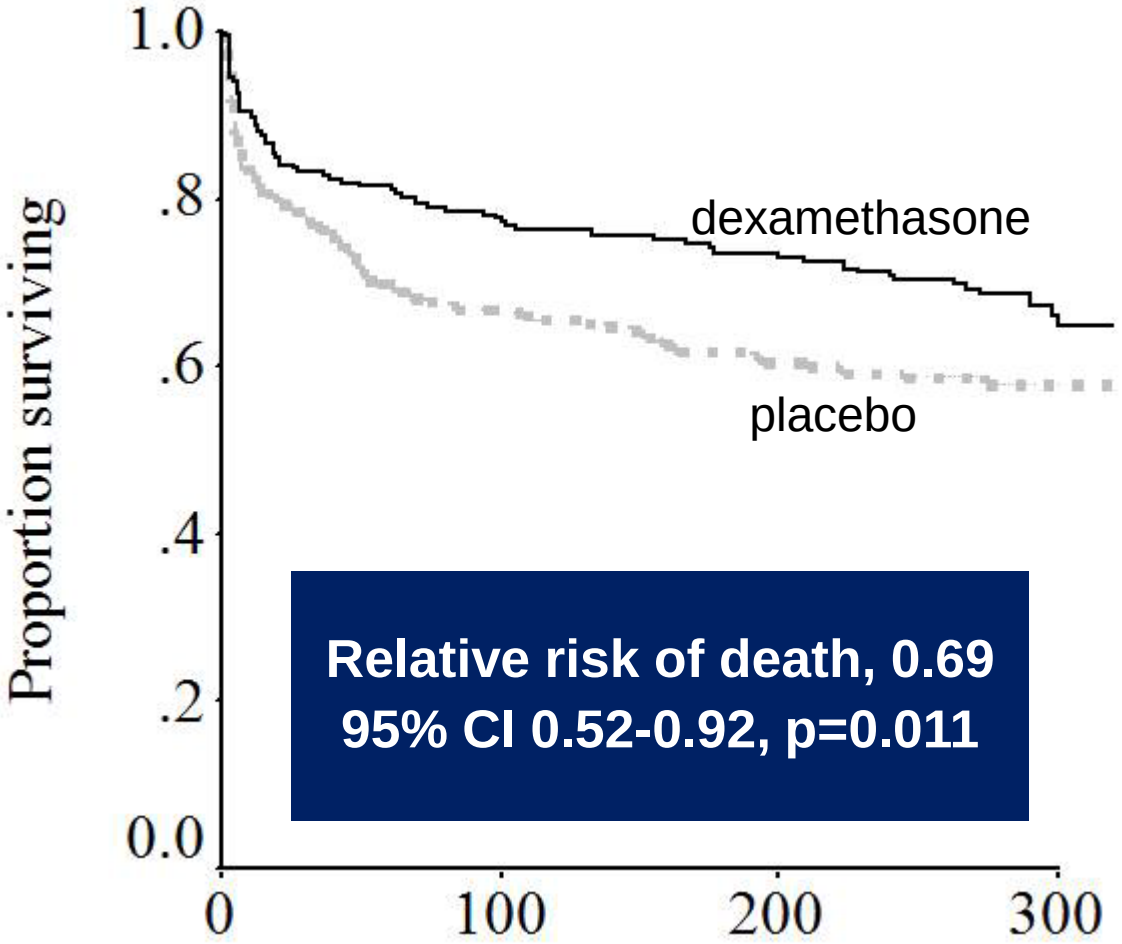
- Diagnosis remains difficult
- Delay in treatment associated with poor outcome
- Mortality of those treated (n=1700) is 23% in HIV-uninfected and 50% in HIV-infected.
- Common factors for mortality: HIV, severity, CSF lymphocyte count

Factors for death (HIV uninfected)	HR	95%CI	P value
Age [per +10 years]	1.24	1.15 - 1.34	<0.001
MRC Grade			
- MRC Grade I	1		
- MRC Grade II	1.36	0.87 - 2.13	0.17
- MRC Grade III	2.97	1.83 - 4.83	<0.001
Previous TB treatment : Yes	1.46	1.00 - 2.13	0.05
Focal neurological signs: Yes	1.80	1.22 - 2.64	0.003
CSF lymphocyte count [cells/ mm^3]	0.88	0.82 - 0.94	<0.001

Meta-analysis, unpublished, OUCRU

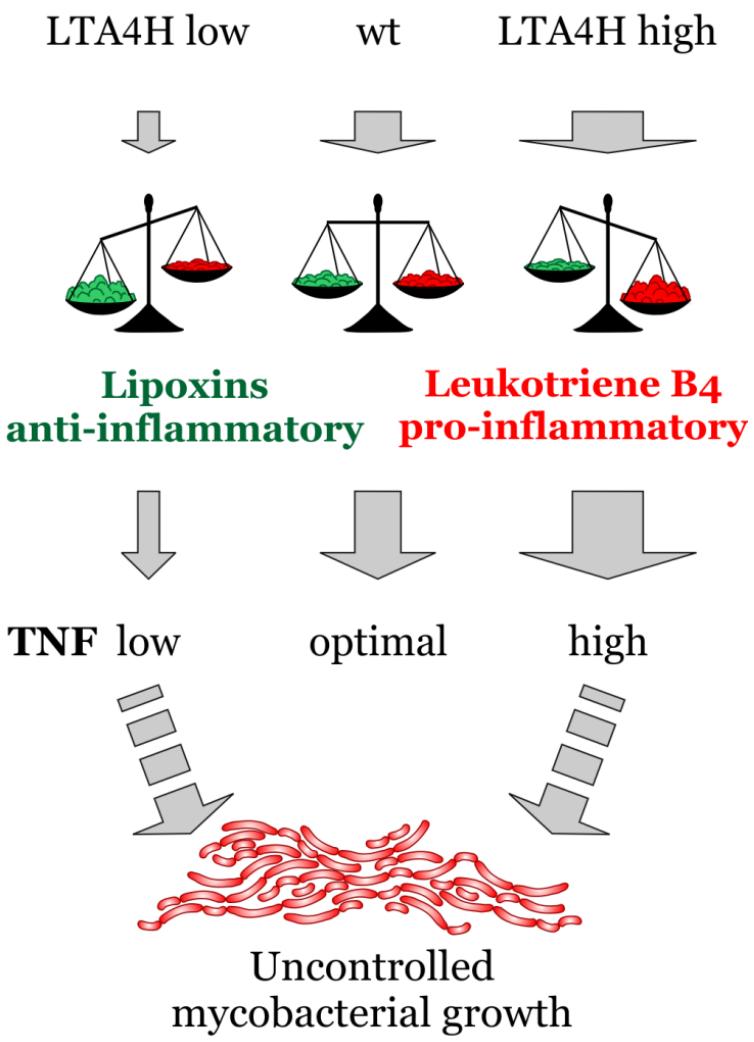
While we kill bacteria, should we also control the inflammatory response?

Anti-inflammatory dexamethasone reduces risk of death from TBM



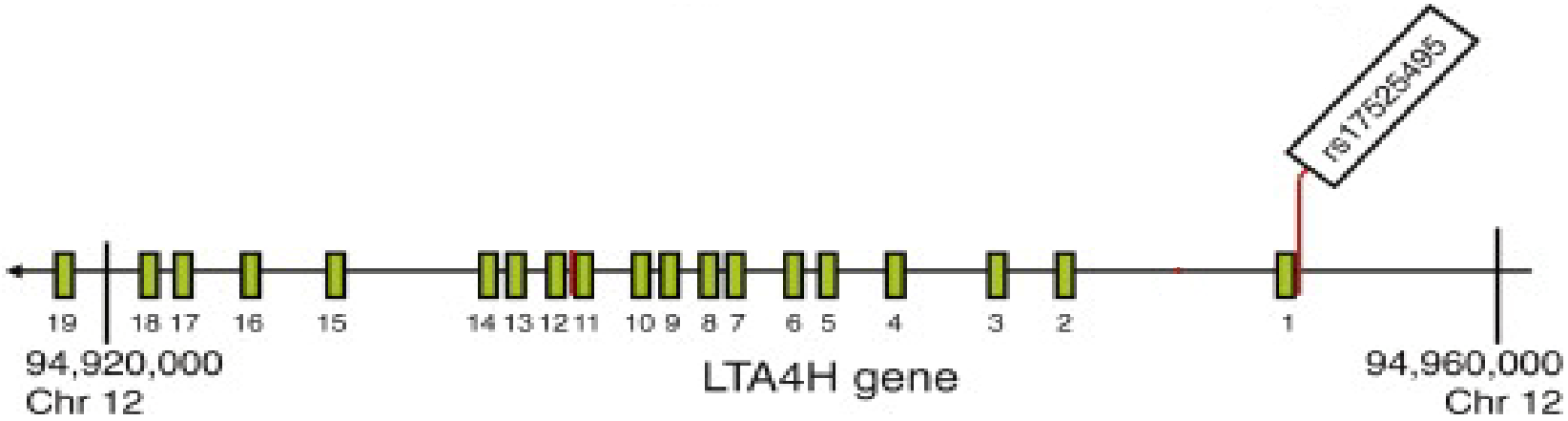
NEJM. 2004. 351:1741-1751

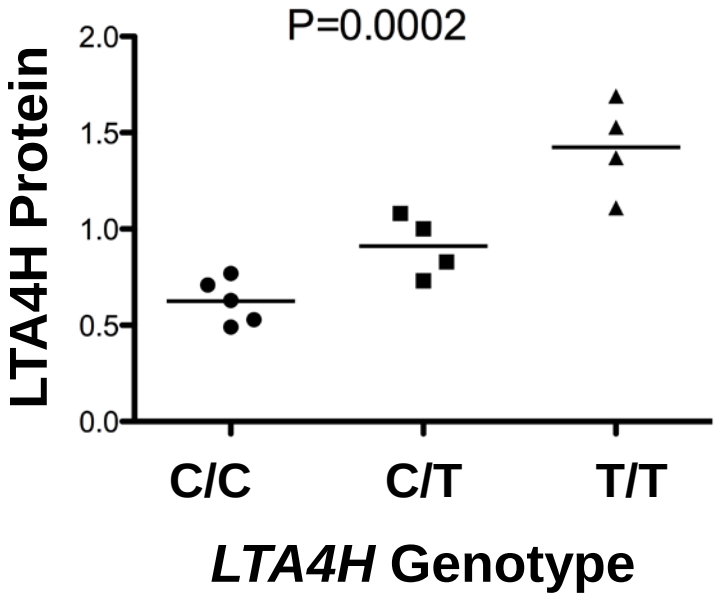
LTA4H deficiency and excess both increase TB susceptibility



Cell 2012. 148(3):434-46

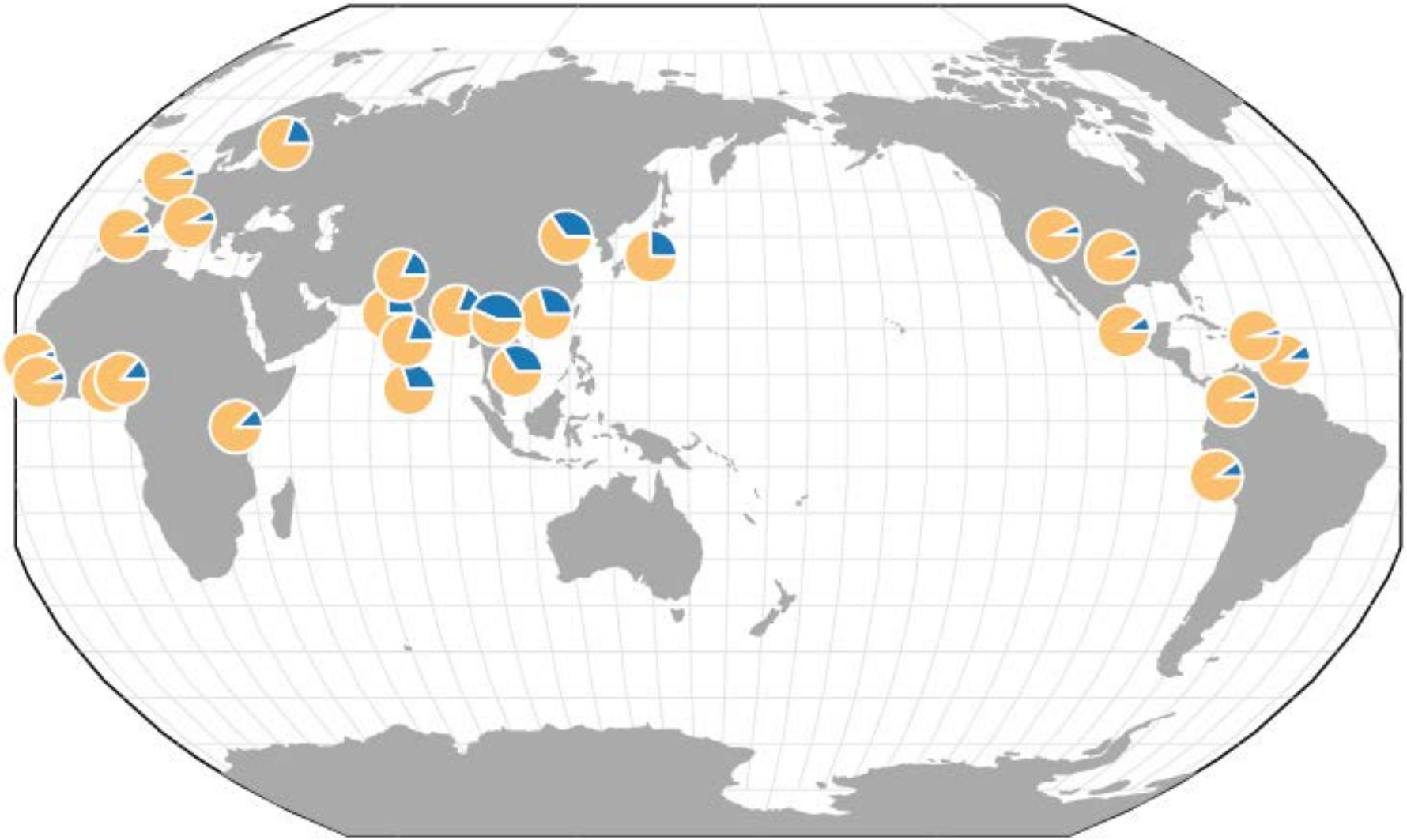
A human *LTA4H* promoter polymorphism regulates gene expression





Cell 2012. 148(3):434-46

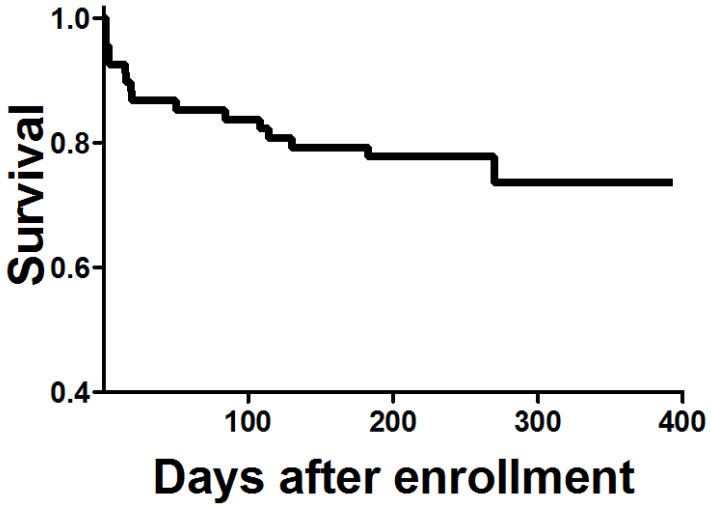
LTA4H rs17525495 Minor allele frequency



Geography of Genetic Variants Browser
Data from 1000 Genomes project

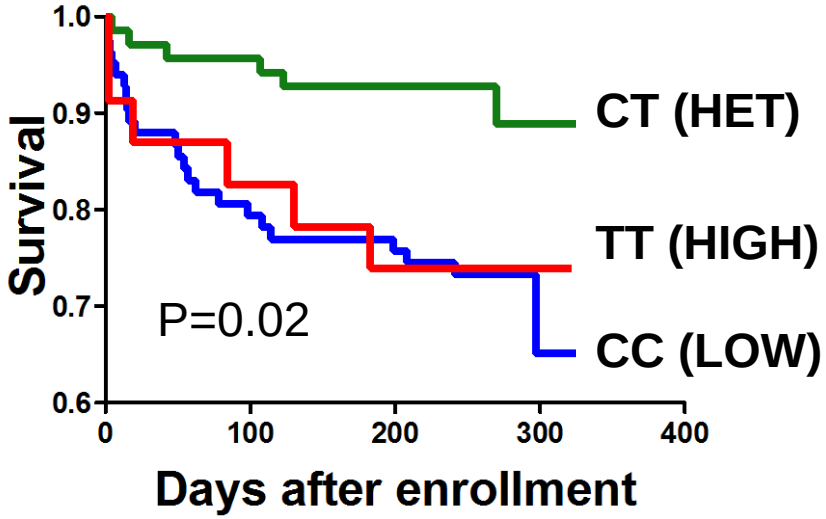
LTA4H genotype influences survival in TBM

Overall survival



NEJM. 2004. 351:1741-1751

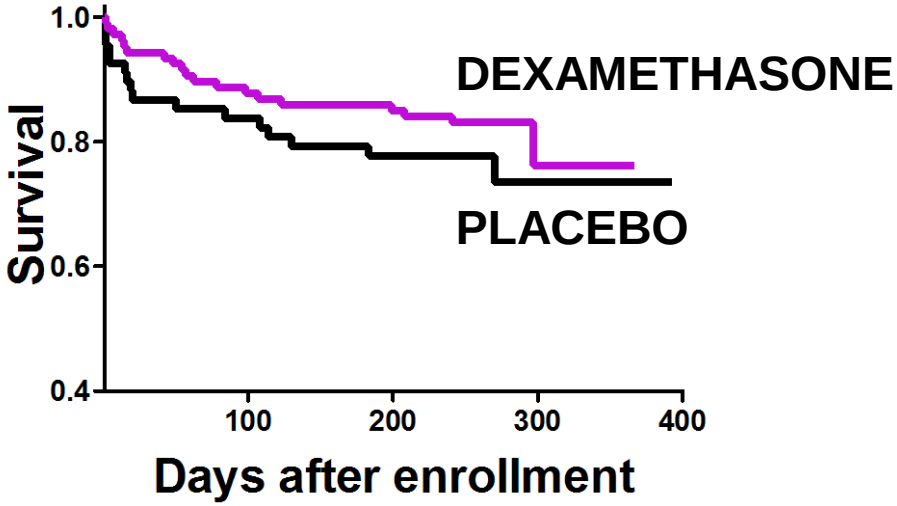
LTA4H Genotype-Adjusted Survival



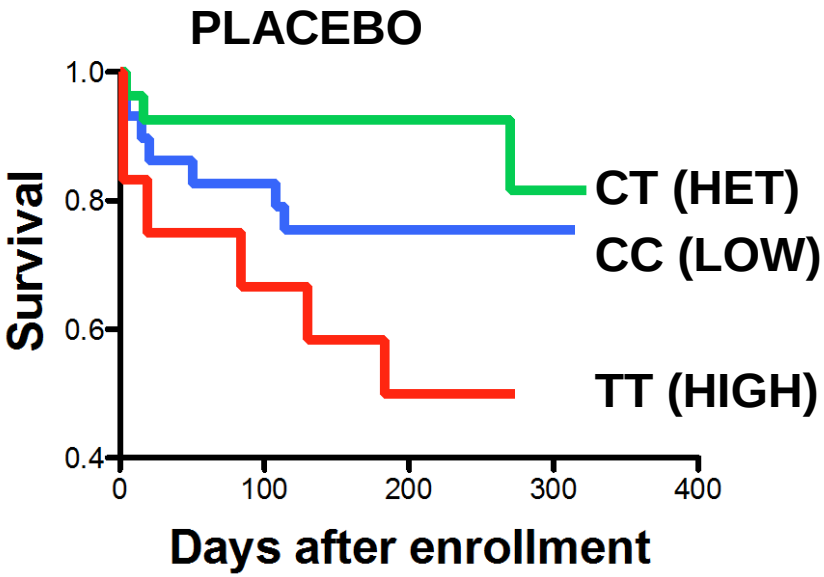
Cell 2012. 148(3):434-46

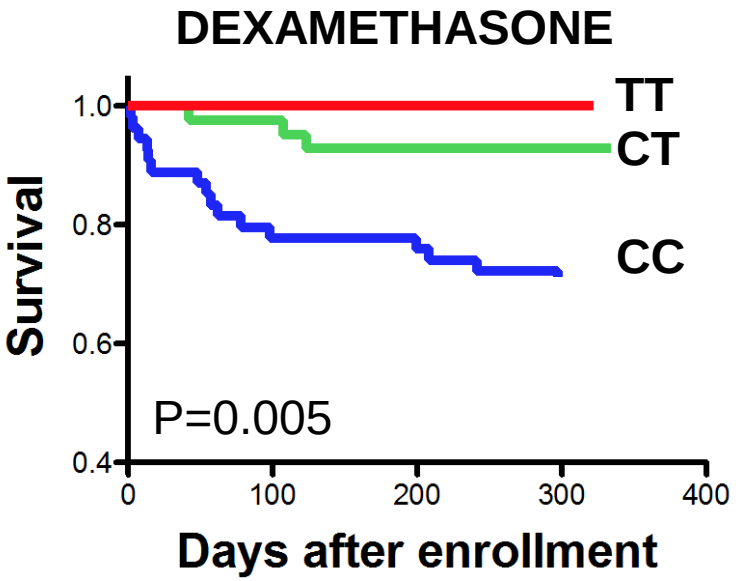
LTA4H genotype influences treatment response

Overall response



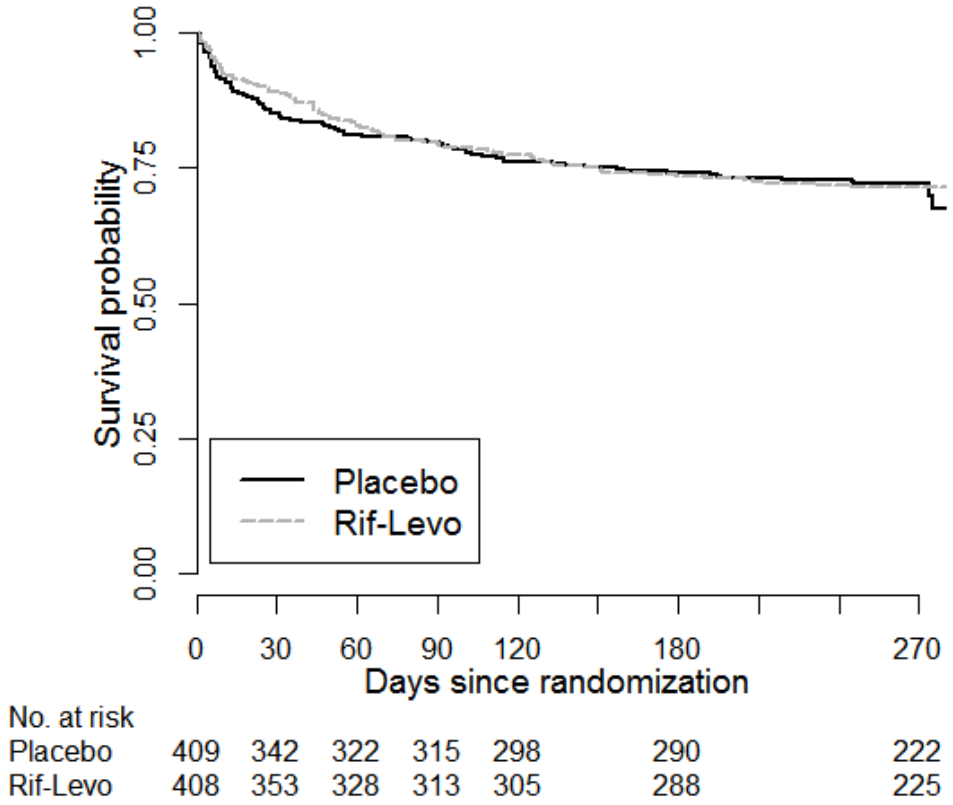
Genotype-adjusted response





Intensified anti-tuberculosis treatment did not improve outcome in TBM

- Randomised controlled trial
- All patients received adjunctive dexamethasone
- Data for death outcome with 9 months follow-up

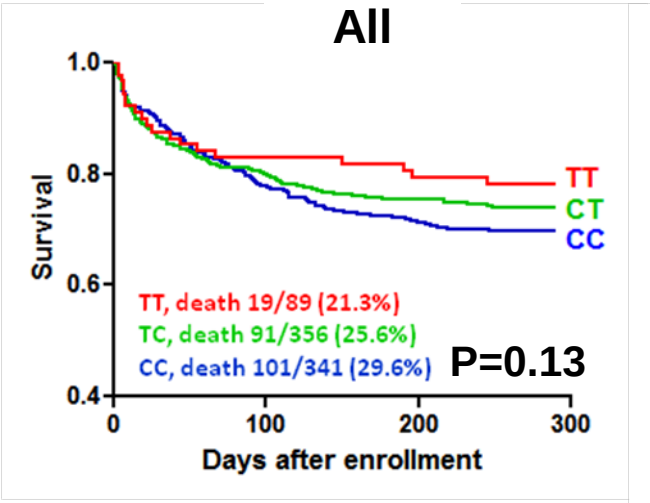


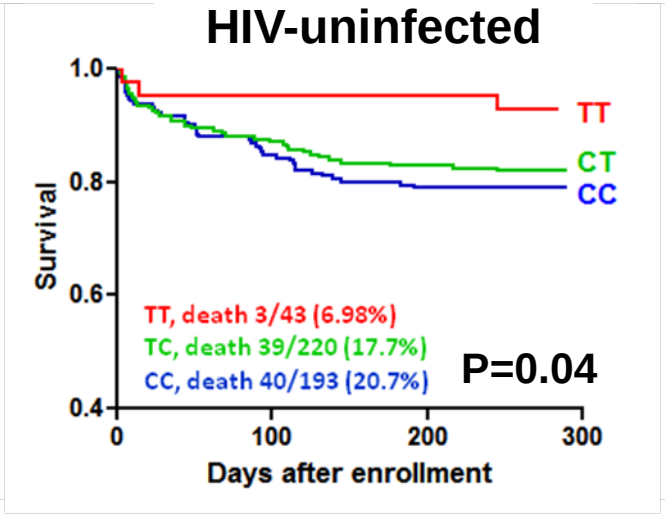
NEJM. 2016. 374:124-134

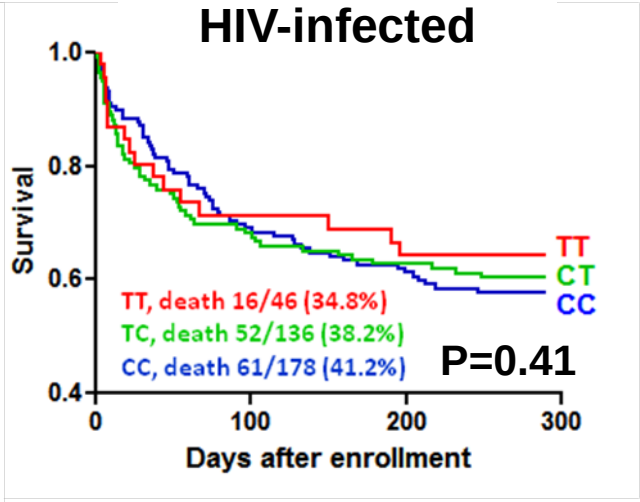
Inflammatory response – Hypotheses

1. *LTA4H* genotype predicts survival of TBM patients receiving corticosteroids
2. *LTA4H* genotype influences inflammatory phenotype
   - 2.1 *LTA4H* genotype influences cytokine production
   - 2.2 *LTA4H* genotype determines bacterial load
   - 2.3 *LTA4H* genotype regulates Lipoxin A4 level
3. Hyper-inflammation is associated with death
4. HIV infection is associated with an attenuated CSF inflammatory response

H1: *LTA4H* genotype predicts survival of TBM patients receiving corticosteroids



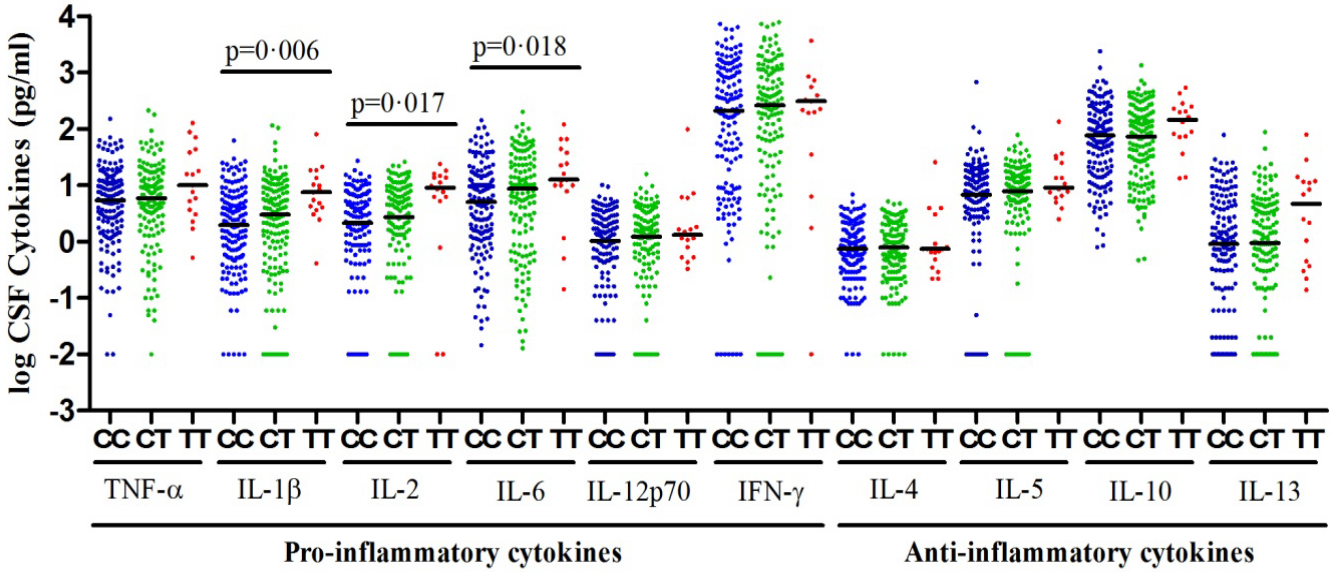




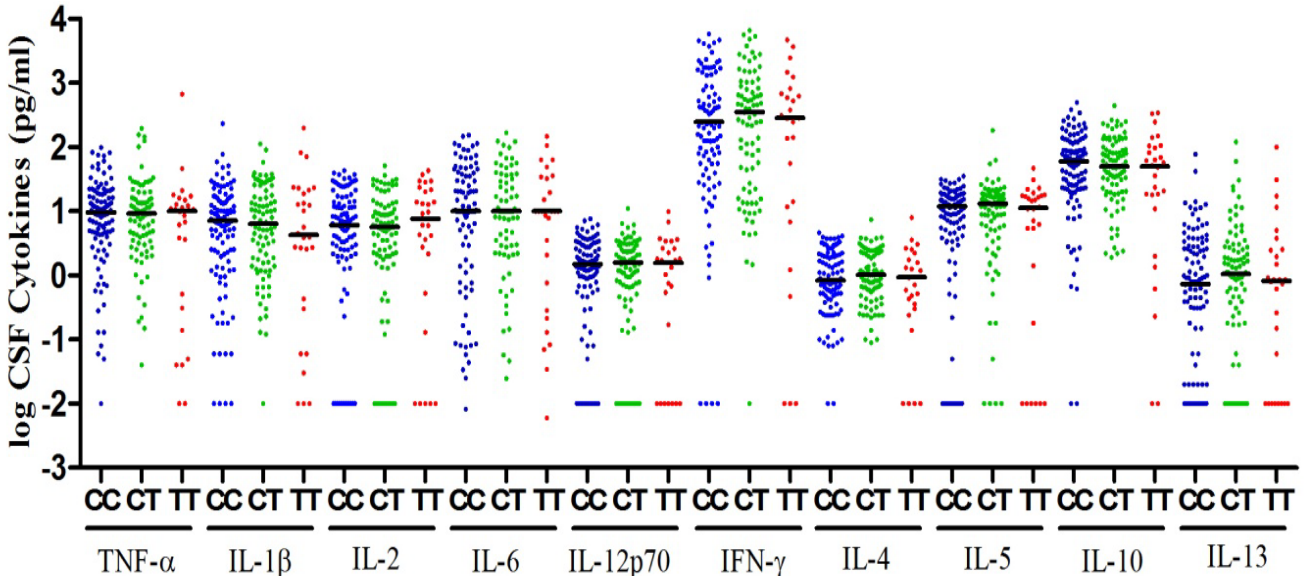
JID 2017. 215 (7): 1020-1028

H2.1: *LTA4H* genotype influences cytokine production

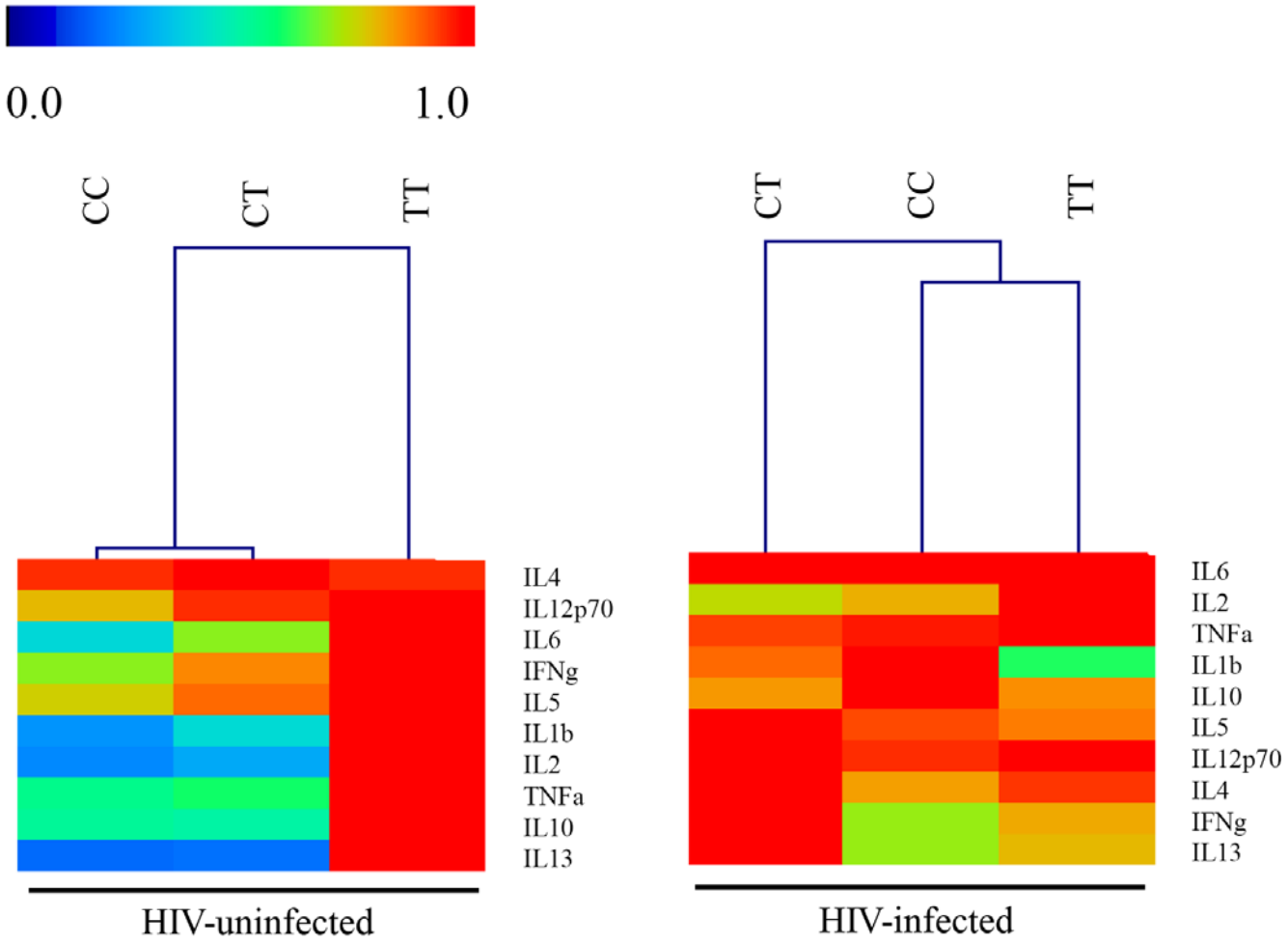
HIV uninfected



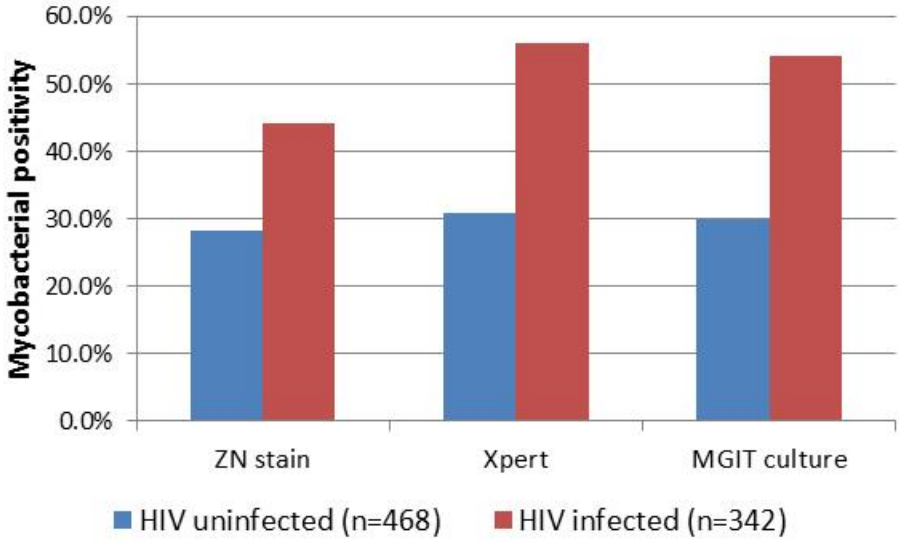
HIV infected

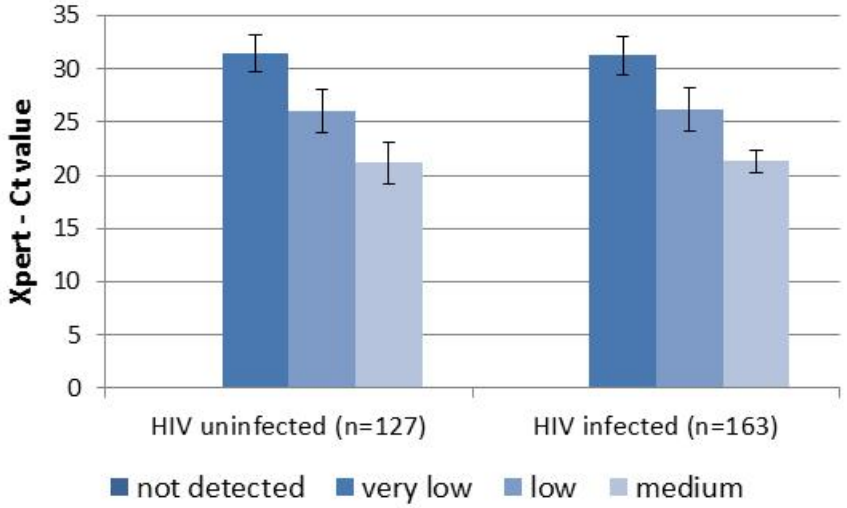


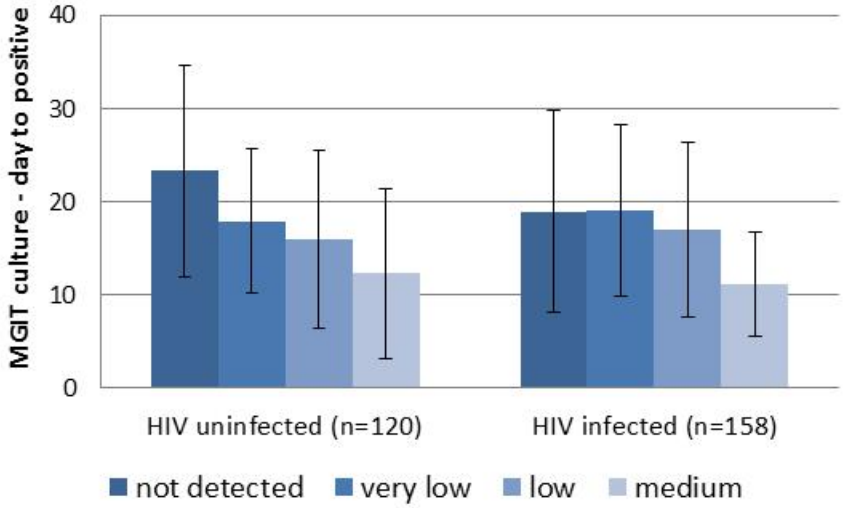
Cytokine expression by *LTA4H* genotype



Mycobacterial detection from CSF samples

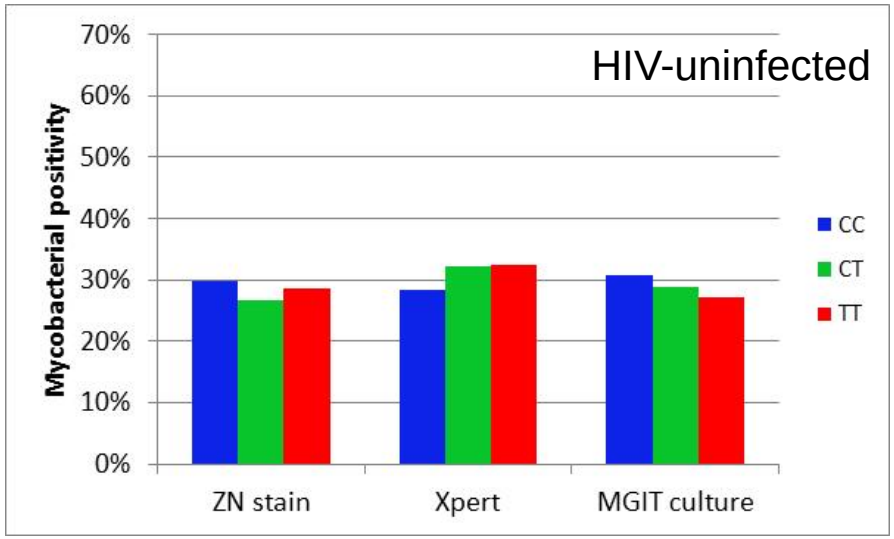


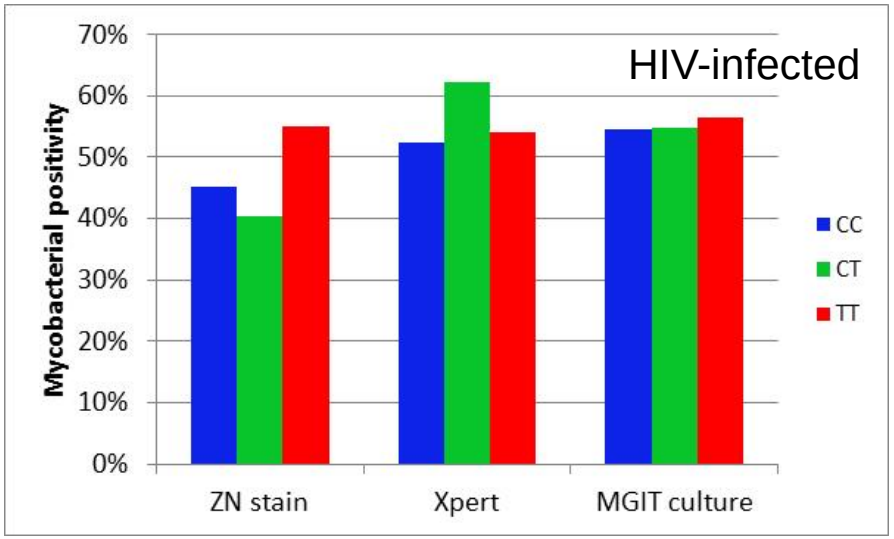


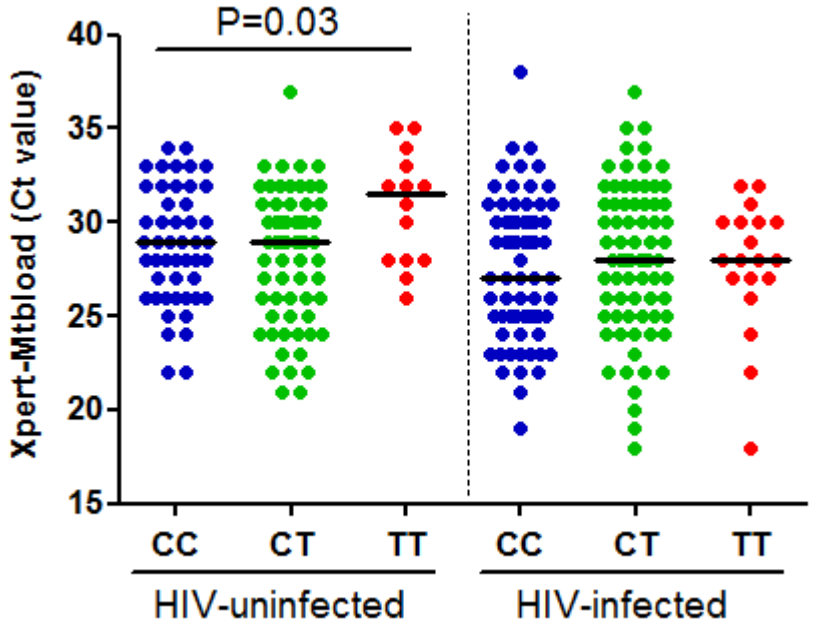


P trend <0.0001 for both comparisons

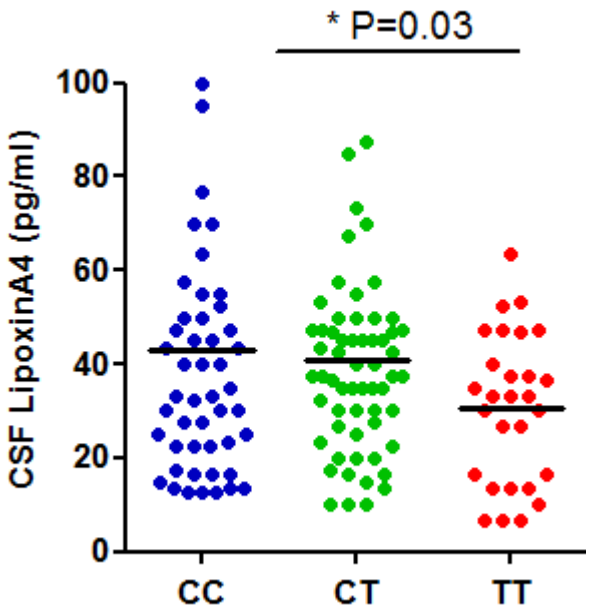
H2.2: *LTA4H* genotype determines bacterial load

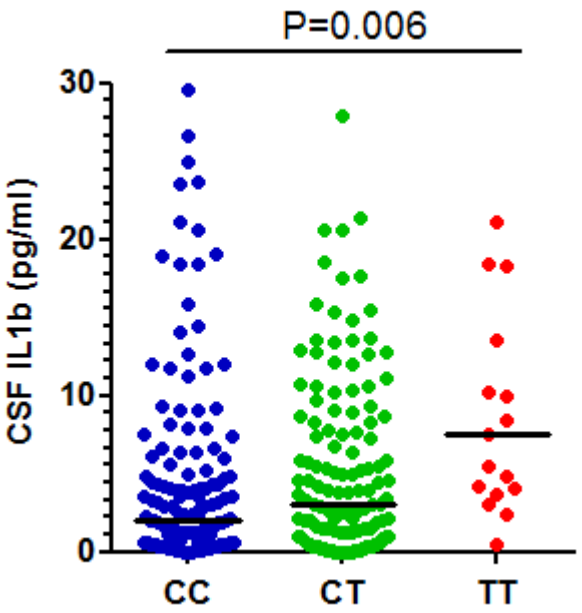


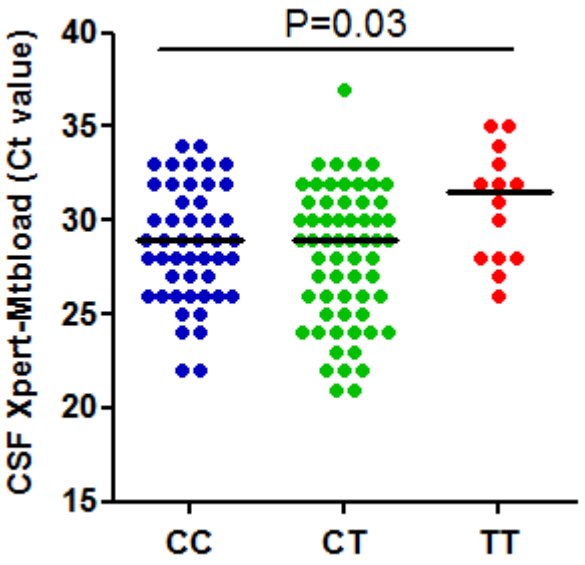




LTA4H genotype is associated with Lipoxin A4, cytokine response and bacterial load in HIV-uninfected



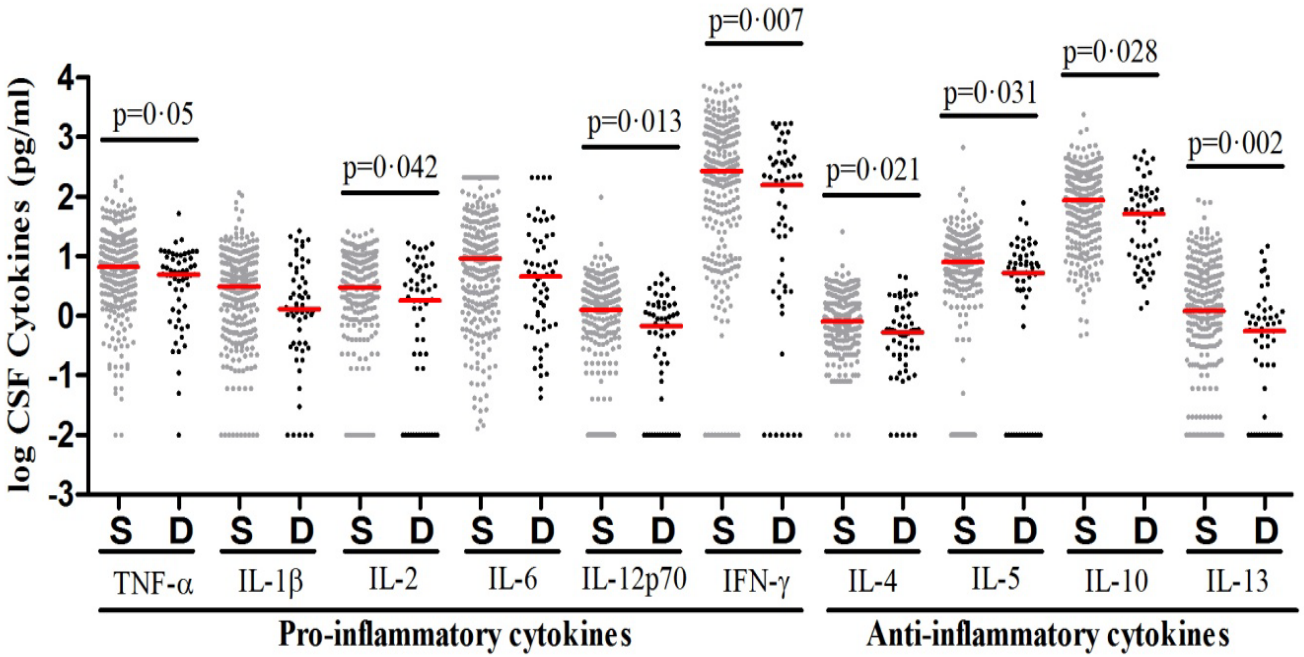




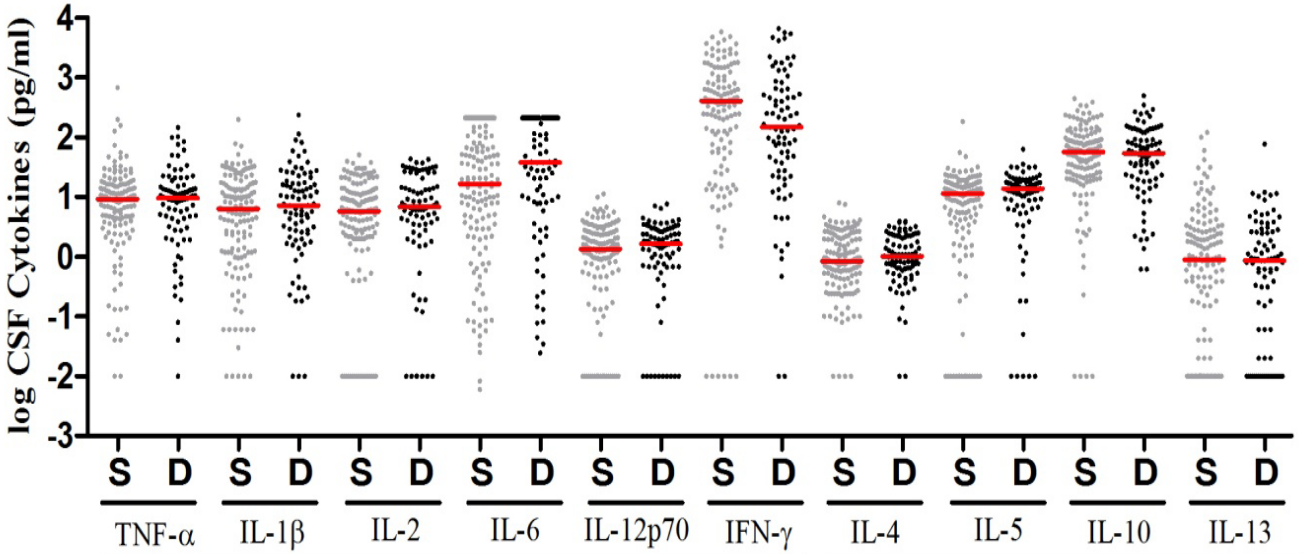
*(CC+CT) *vs* TT

H3: Hyper-inflammation is associated with death

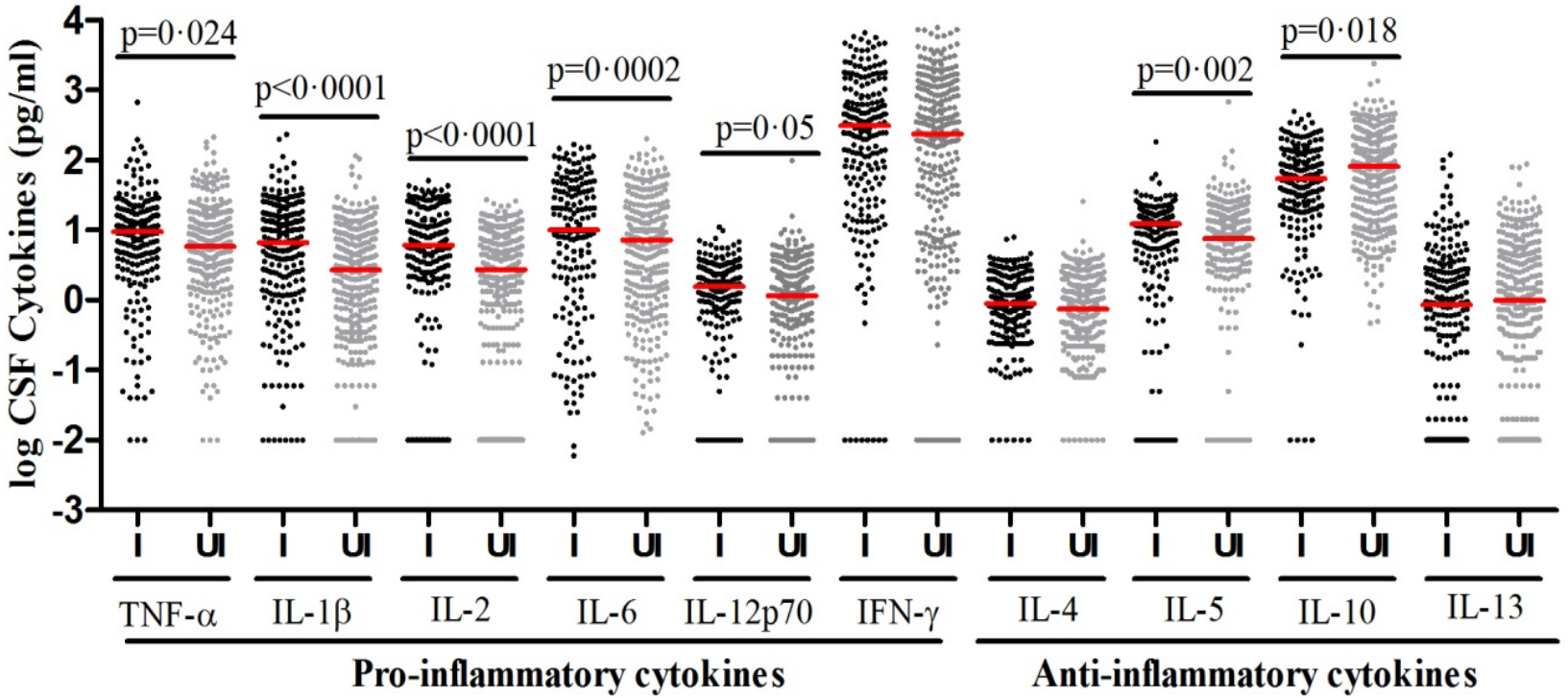
HIV uninfected



HIV infected



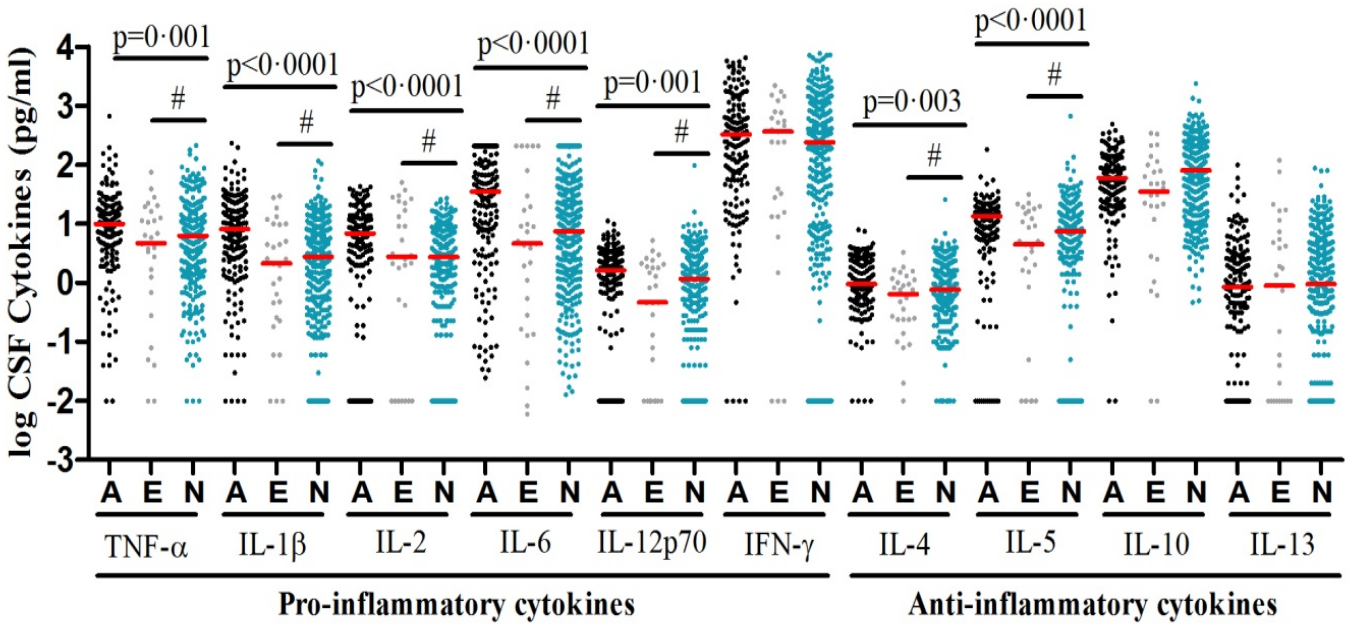
H4: HIV infection is associated with an attenuated CSF inflammatory response

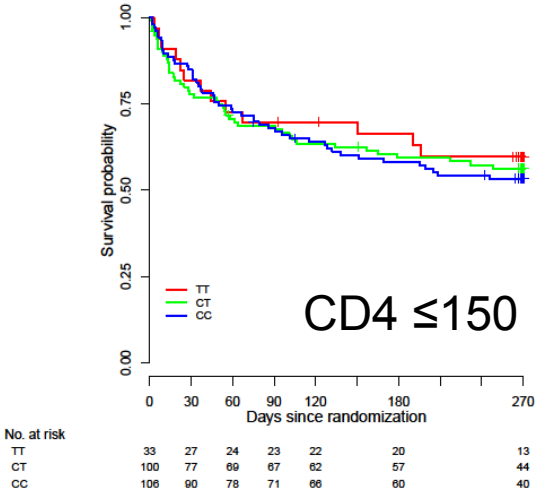


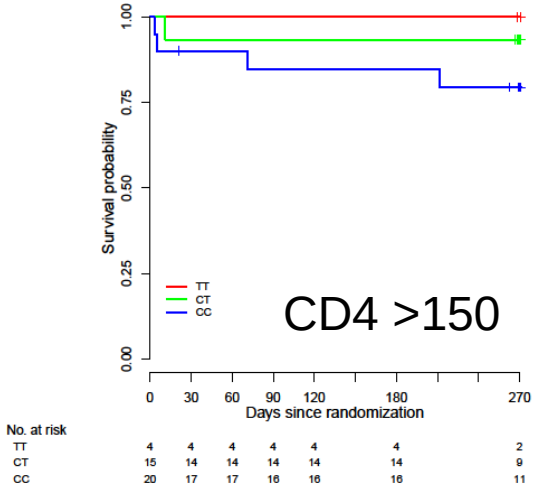
I = HIV infected
UI = HIV uninfected

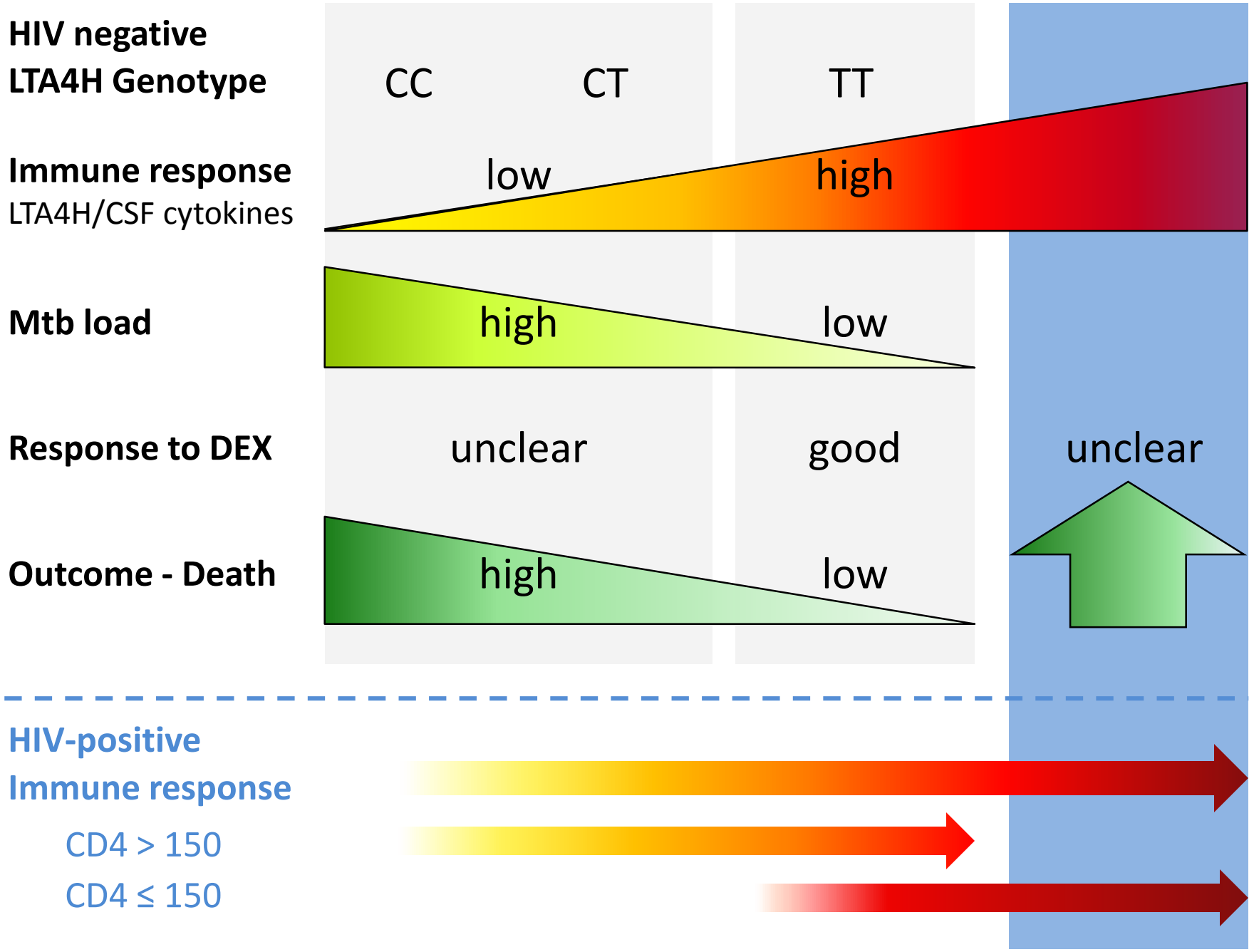
Inflammatory response in HIV-infected patients

CD4 ≤150
CD4 >150
HIV negative








HIV negative
LTA4H Genotype
CC
CT
TT
Immune response
LTA4H/CSF cytokines
low
high
Mtb load
high
low
Response to DEX
unclear
good
unclear
Outcome - Death
high
low
HIV-positive
Immune response
CD4 > 150
CD4 ≤ 150

We want to test the following hypotheses

In TBM HIV-uninfected:

Should adjunctive corticosteroid treatment be personalised according to *LTA4H* genotype?

In TBM HIV-infected :

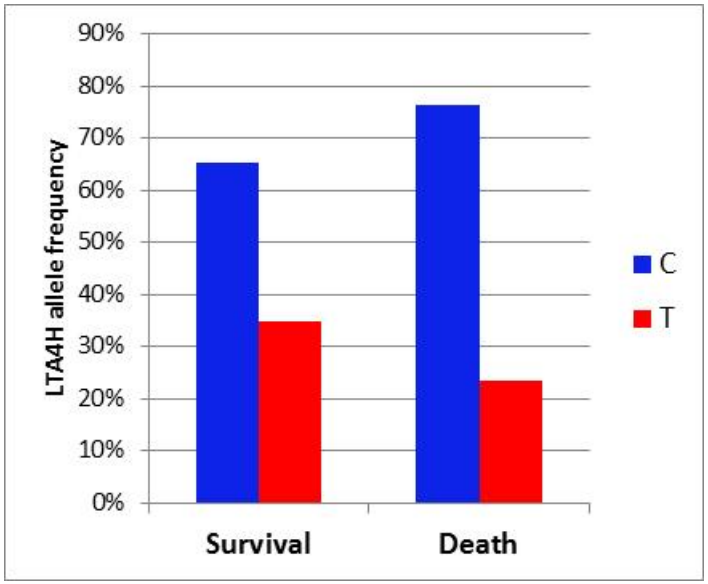
Do adjunctive corticosteroids improve outcome?

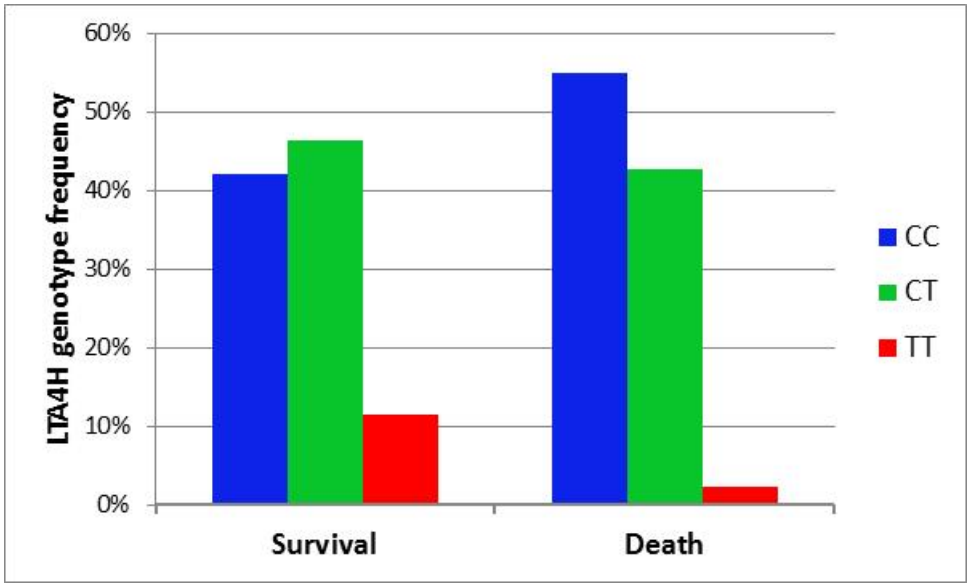
Host genetic markers for TBM outcome

- Deep-sequenced the whole gene region of the *LTA4H* gene and 78 genes involved in inflammatory response in 1000 TBM cases and 1000 controls
- 486 potentially functional variants (stop, frameshift, missense) identified
- Analyses include case *vs* control and survival *vs* death for each variant

Host genetic markers for TBM outcome

- 3 protective and 6 risk alleles in case *vs* control
- 4 protective and 2 risk alleles in survival
- *LTA4H* T allele is confirmed as a protective allele for survival in treatment with dexamethasone OR=1.73, p=0.004





Acknowledgments

OUCRU TB group

Collaborators:

Lalita Ramakrishnan
Mary-Claire King
David Tobin