Proofof-Principle Evaluation of Predictive Performance for Therapy Outcome of Baseline Estimated Fitness and Genetic Barrier Towards Resistance in a Clinical Cohort of HIV-1 Treated Patients

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Figure 2

BACKGROUND

Characteristics of the study population (n = 95)

• We have previously developed a computational method to reverse engineer, from clinical genotypes only, the fitness landscape experienced by HIV under treatment (Deforche K et al., XVIII Int. Drug Res. Workshop, Sibges, 2006) and applied it to NFV and the combination of AZT and 3TC.

• We demonstrated that the fitness landscape correlates with intrinsic resistance phenotype (Thays K et al., CRX 2007), and allows prediction of genetic barrier through simulated evolution (Deforche K et al., XVIII Int. Drug Res. Workshop, 2007).

OBJECTIVE

To evaluate, in an independent clinical cohort, a new genetic interpretation for AZT+3TC+NFV based on the estimated fitness landscape, for evolutionary response (at 3 and 6 months) of regimens containing these antiretrovirals. We used 3 commonly used interpretation systems (Rega, ANRS and Stavrids) as comparators.

METHODS

Patient Population (n = 95, Table 1)

• Patients were selected from the EuroSIDA cohort who started a new treatment with AZT+3TC+NFV and for whom a genotype was available at any time before initiation of this treatment.

• For these patients, two outcomes were studied:

  • Change in viral load (ΔVL) at 3 months (ΔVL ≤ 4000 copies/ml was considered undetectable).

  • Treatment failure (ΔVL ≥ 4000 copies/ml or treatment switch) at 3 months, according to the EuroSIDA consensus.

Genotypic Factors

Several genetic factors were computed from the estimated fitness Landscapes for NFV, AZT, and combination AZT+3TC:

• Estimated fitness (EF) during treatment.

• Higher replication capacity or higher resistance contribute to higher viral fitness during treatment.

• As measures of genetic barrier, the expected number of mutations (MR) or “genotypes” (GSS) before developing a major resistance mutation. Major resistance mutations according to antiretroviral drugs were defined as below:

  NFV: 30N, 88S or 90M

  AZT: 41L or 215Y/F

  AZT+3TC: 41L, 81A, 215Y/F or 219K

Therefore the smaller the value of MR (e.g. for AZT) the closer is a patient’s dominant virus to develop full resistance to AZT.

A genotypic score is a computed in a generalised linear model (Figure 1) that was used to simulate evolution on the fitness landscape. Therefore, GSS, compared to MR, reflects also the time needed to develop the mutations (with less time for a mutation with higher selective advantage).

• ROC analysis of treatment failure (VL>500 copies/ml or treatment switch) at 6 months:

• Comparison of methods to calculate the expected number of mutations (MR), estimated fitness landscapes (EF), genotypic scores (GSS), and fitness landscapes (NLG).

• Performance of genotypic factors to predict therapy outcome with the use of recorded sequences (ΔVL ≤ 4000 copies/ml, treatment success), the use of estimated sequences (ΔVL > 4000 copies/ml, treatment failure), or the use of both (ΔVL > 4000 copies/ml, treatment switch).

• Linear regression of ΔVL at 3 months, adjusted for baseline characteristics shown in Table 1 were performed:

  • Regression of ΔVL at 3 months, adjusted for previous treatment viral load.

  • ROC analysis of treatment failure (VL>500 copies/ml or treatment switch) at 6 months:

  • Linear regression of ΔVL at 3 months.

  • Logistic regression of odds of treatment failure at 6 months.

RESULTS

Table 1 shows the baseline characteristics of our study population.

• About half of the patient population (48%) was naive to treatment.

• Of the patients with treatment experience, 54% had failed previously on treatment with AZT, 75% with 3TC, and 20% with NFV.

• Figures 3 and 4 show the genotypic susceptibility as predicted by Rega and Table 1 shows variation in genotypic predictors computed from the estimated fitness landscapes.

• Figure 5 shows BOC curves for predicting failure at 6 months, for each of the four models.

Area under ROC tended to be higher for EF and MR and was similar to GSS or MR, but they were not significantly different (p>0.05).

The better performance of EF and MR compared to GSS was due to a larger increase in sensitivity when specifically dropped to values below 70%. Indeed, out of 5 patients with GSS=3, 24 (43%) did not experience treatment failure and 31 (56%) did experience treatment failure. For these patients, variation in EF and MR still tended to associate with treatment failure, although at lower levels of specificity.

Table 2 shows predictive performance for 3 months viral load reduction, for each genotypic factor within each of the four separate anaativational models (GSS, EF, MR, and GSS).

• Only greater susceptibility to AZT according to Rega was associated with a higher viral load reduction from pre-therapy levels (p<0.05).

• Greater estimated fitness (EF) for AZT+3TC was associated with a smaller viral load reduction (ΔVL 5.8 log per log 10 EF higher, p=0.04).

• Greater estimated fitness (EF) for NFV was also associated with a smaller viral load reduction (ΔVL 4.6 log per log 10 EF higher) although this difference in reduction was not significant. Combined analysis of both EF was not significant.

• Higher genetic barrier (MR and MRG) for AZT+3TC correlated with 0.49 (p=0.001) and 0.42 (p=0.001) greater viral load reductions respectively.

Table 3 shows the predictive performance for 3 months viral load reduction, for each genotypic factor within each of the four separate anaativational models (GSS, EF, MR, and GSS).

• Predictive performance of genotypic predictors in 5 models for odds of failure at 6 months are shown in Table 5.

• Adjusted analyses of correlation, adjusted for baseline characteristics shown in Table 1 were performed:

  • Linear regression of ΔVL at 3 months, adjusted for previous treatment viral load.

  • ROC analysis of treatment failure (VL>500 copies/ml or treatment switch) at 6 months:

  • Adjusted analyses of correlation, adjusted for baseline characteristics shown in Table 1 were performed:

  • Linear regression of ΔVL at 3 months.

  • Logistic regression of odds of treatment failure at 6 months.

CONCLUSION

No genetic predictor significantly outperformed any other (probably due to small sample size). In the analysis comparing methods according to their ability to classify patients with treatment failure, fitness landscape based predictors (EF and MR) showed as increased sensitivity (at specificity ≥ 70%) over expert interpretation systems for isolates which were scored by expert systems as fully susceptible. Therefore many patients were needed to repeat this exercise using a more rigid definition of treatment failure. It is indeed conceivable that a portion of patients with viruses susceptible to AZT+3TC+NFV were misclassified as failure at 6 months because of discordance to clinical excellence.

In all cases, previous treatment failure on 3TC was a better predictor for subsequent treatment failure than genotypic information. This could be due to the highly predictable emergence of 184IV under the pressure of a 3TC containing regimen, and the tendency to revert when patients are off 3TC.