Standardization and Clinical Relevance of HIV Drug Resistance Testing

Data Analysis Plan

Version 1.2

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Initiatives for developing and comparing genotype and phenotype interpretation systems

Foreword

Sequencing of the reverse transcriptase (RT) and protease (PR) genes is widely used in clinical care in order to assess to which drugs a patient's virus is most likely to be sensitive. The means of translating the sequence information into a predicted sensitivity for any given drug (the "interpretation system") has evolved gradually over the past 12 years. For most drugs this has principally been based on relating the genotype to the viral phenotype based on sensitivity to a drug in a recombinant virus assay. There are several different interpretation systems currently in existence. Most of these have been put together by experts in the field, based on such genotype/phenotype data and some limited data linking genotype to virologic response to a drug. For several combinations of potential resistance mutations these interpretation systems differ in the predicted drug sensitivity. This sometimes leaves the clinician with difficulty in deciding whether a drug should be used or not. There is an increasing recognition that, wherever possible, derivation of interpretation systems should be based on, or at least validated using, virologic response data.

In addition, it remains unclear how, given a large database of genotypes linked to virologic responses, interpretation systems in the future should be derived, due to the high number of dimensions of genetic data. Several approaches have been suggested, including linear/logistic

regression, regression trees and neural networks. A limitation of some of these methods is that they do not naturally lend themselves to situations in which other new drugs besides the one(s) under consideration are initiated at the same time, as the effects of these other drugs needs to be accounted for. Thus, there are immediate pragmatic issues regarding differences in current interpretation systems to be resolved and there are much longer term issues regarding appropriate methods for deriving interpretation systems in the future. The answers to these latter questions will likely be applicable to fields far outside HIV care.

Even for results from phenotypic tests, interpretation is not always straight-forward, in that it is not always clear what cut-offs should be used to categorise drug sensitivity. This is a particular issue with boosted PI regimens, whether the same cut-offs should be used as for the unboosted drug.

The Forum aims to try to address both the immediate pragmatic questions as well as beginning to look at the wider longer term perspectives concerning the methods. To this end there are two tracks to the Forum's work in this area, which will be developed in parallel. The proposal which follows is for a collaborative analysis project to investigate differences in interpretation systems for the drugs didanosine and abacavir; essentially arbitrarily chosen as drugs to begin the process. This aims to bring together data on large numbers of people who were failing a previous regimen and initiate a regimen containing didanosine or abacavir to try to resolve differences in the interpretation systems. This is intended as a pilot project that, if successful, will be extended to other drugs. In parallel with this, and for which there is a separate analysis plan, the subset of data/studies in which ddI or abacavir have been initiated without other drugs being started at the same time (eg add-

on studies or as monotherapy) will be used to compare the various different approaches for deriving interpretation systems.

PROPOSAL FOR A COLLABORATIVE DATA ANALYSIS PROJECT

REFINEMENT OF VIRAL GENOTYPE INTERPRETATION SYSTEMS FOR DDI AND ABACAVIR, BASED ON VIROLOGIC RESPONSE

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Outline

1. **Introduction**

2. **Outline plan**

3. **Endpoints**

4. **Data to be pooled**
   - 4.1. Inclusion / exclusion criteria
   - 4.2. Data items required

5. **Analysis Plan**
   - 5.1. Identifying differences between interpretation systems
   - 5.2. Comparing the performance of different interpretation systems
   - 5.3. Procedure if data set can be divided into derivation and test sets

6. **Appendix**
   - 6.1 Data Analysis Plan Development Group
   - 6.2 Project Planning Committee

1. Introduction

This document outlines a plan for a collaborative analysis which aims to resolve differences in genotypic interpretation systems for didanosine and abacavir, and potentially generate a new interpretation system. This will be done using data linking viral genotype at the time of starting a new regimen containing one or both of these drugs to the virologic response to the regimen. Since, in all but exceptional cases, there will be more than one new drug used in the new regimen this involves trying to tease out the independent effect of the drugs under consideration from the effects of the other drugs in the regimen. Such an exercise requires data on large numbers of people with genotypic resistance tests and information on drug regimen and viral load changes. The aim is therefore to pool data from many different sources (clinical trials and cohorts) in order to arrive at an interpretation system. Didanosine and abacavir have been chosen as the focus of this proposal but it is hoped that it will eventually be possible to do this for each antiretroviral drug. While we hope that data can be pooled, this analysis plan may prove useful to those groups or companies who are unable, at least in the short-term, to contribute their data for pooling and who want to analyse their own data using a pre-determined, standardized methodology.

2. Outline plan

For each of the two drugs under consideration, data will be pooled on all people who virologically failed a previous regimen and then started a regimen including the drug. Patients do not have to be treatment naïve to the drug as long as the last previous date of use was at least 6 months prior to the date started for the purposes of this analysis. The inclusion/exclusion criteria are set out in section 4. Thus, different pooled data sets will be put together for different drugs.

As a first objective, the data set will be used to try to resolve differences in existing genotypic interpretation systems and possibly arrive at a new interpretation system which is a hybrid of existing systems. No new codons besides those appearing in existing interpretation systems will be considered for this exercise. The procedure for this is described in section 5.2.

If the pooled data set is sufficiently large (if, for example, there are resistance/virologic response data on over 2000 people), it will be divided at random into two. The first (derivation) data set will be used to resolve differences in existing systems, as described above (and in section 5.2). In addition, a new interpretation system using linear/logistic regression - which makes no prior assumptions concerning which codons in RT to consider - will be derived. The procedure for this is described in section 5.3. Performance of all candidate interpretation systems will be tested and compared in the remainder of the data (test data set) (ie the procedures described in section 5.2 will be repeated on the test data set).

3. Endpoints

We plan to consider two measures of viral load outcome after the start of the new regimen, as follows.

Week 8 outcome

Change from baseline in viral load at 8 weeks (closest value to week 8 within a window of 4-12 weeks)

Those discontinuing or switching any of the drugs in the new regimen before week 12 will be excluded.

Week 24 outcome

Viral load < 50 copies/mL at 24 weeks (closest value to week 24 within a window of 16 – 32 weeks) or not.

Those discontinuing or switching any of the drugs in the regimen after week 12 and before the week 24 value will be dealt with in the analysis as either (i) included and not < 50 at week 24, (ii) excluded and (iii) excluded only if viral load < 50 before switch/discontinuation, otherwise treated as not < 50 at week 24.

Note: it is expected that week 24 viral load values will in most instances be measured using an assay which quantifies values down to < 50 copies/mL. If an assay lower limit of between 50 and 500 has been used then this value will be used instead of 50 to define the outcome in such cases.

4. Data to be pooled

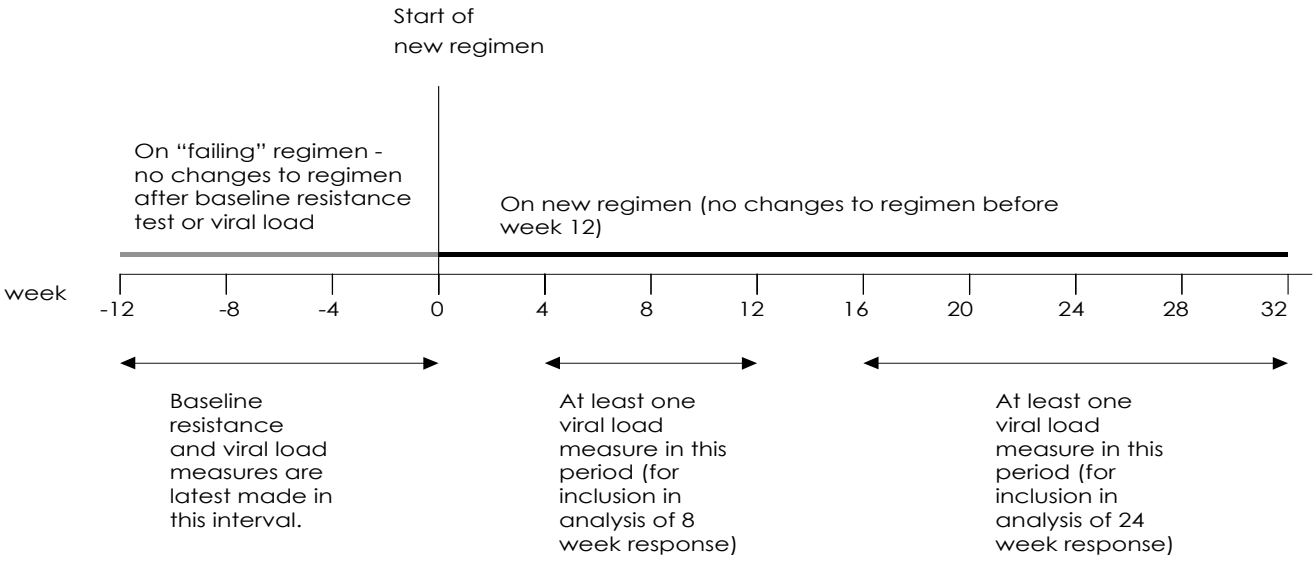
4.1. Inclusion criteria

Drug experienced people starting a new regimen including the drug under consideration are eligible for inclusion if the following criteria are met:

- Drug under consideration is started for the first time, or last used at least 6 months prior to the current start date
- Virologically failed the previous regimen (according to the clinician's judgement)

- An available genotypic resistance test on the previous regimen (measured < 12 weeks before start of new regimen) while on the previous regimen.
- An available viral load measure while on the previous failing regimen (which must also be < 12 weeks before start of new regimen). This is the baseline viral load. This viral load should be at least 500 copies/mL. At least one viral load measured between 4-12 weeks (the 8 week viral load) or between 16-32 weeks (the 24 week viral load) from the start of the new regimen (containing the drug under consideration)
- There are no changes in therapy between the time of the baseline viral load or resistance test and the start of the new regimen, nor between the time of the start of the new regimen and week 12.
- There is no evidence of inadequate adherence to the new regimen.

This is illustrated in the following figure.



4.2. Data items required

If items marked with an * are unavailable then patient is ineligible.

- Age at baseline (ie date of start of new regimen)
- Exposure category (msm, idu, heterosexual, other/unknown)
- Gender
- Race / ethnicity
- Previous use of each drug (yes/no) (If unknown, then previous use of each class (yes/no)) *
- Drugs in previous (virologically failing) regimen
- Drugs in new regimen – date of start of regimen *

- Genotypic resistance at baseline (< 12 weeks from baseline, taken while on previous regimen) (genotype as amino acid differences from HXB2/NL43) with date *
- Viral load at baseline (< 12 weeks from baseline, value taken while on previous regimen which is closest to start of new regimen) with date *
- CD4 count at baseline (< 12 weeks from baseline, value taken while on previous regimen which is closest to start of new regimen) with date
- Any previous AIDS disease at start of new regimen (yes or no)
- Minimum viral load ever pre-baseline with date (if available)
- Minimum CD4 count ever pre-baseline (measured before, or while off, antiretrovirals) with date (if available)
- Method used for viral loads (must be the same method for baseline and response-defining viral loads for any given person)
- Any previous resistance tests (data in format as above) with dates (if available)

- Previous virological failure of each drug (yes/no) (as well as knowing whether ever exposed to drug - possible in many cohorts)

Variables related to the endpoints

Patients may be eligible for analysis for one endpoint but not the other.

- Week 8 viral load (value taken closest to week 8, within 4-12 week window) with date. (* patient ineligible if neither week 8 or week 24 viral load is available)

- Week 24 viral load (value taken closest to week 24, within 16-32 week window) with date. (* patient ineligible if neither week 8 or week 24 viral load is available)
- Time of any change in regimen occurring between weeks 12-32. *
- If regimen changed between weeks 12-32: most recent viral load before change with date.

5. Analysis Plan

5.1. Identifying differences between interpretation systems

The first step for each of the two drugs will be to list interpretation systems (where these are explicit, rules-based systems) and their differences, in collaboration with groups who have devised such systems, to ensure the systems are correctly represented with the most up-to-date version.

Comparing the performance of different interpretation systems

8 week outcome

For each interpretation system, a regression model will be fitted of week 8 change in viral load on the following covariates.

- Sensitivity (as a three category variable scored as sensitive (S) / intermediate (I) / resistant (R) – with the resistant group as the base) for the drug under consideration based on the interpretation system. Interpretation systems containing more than 3 levels will be compressed into 3 levels. However, as a sensitivity

analysis, the analysis will be repeated treating the interpretation system as a continuous score.

- Baseline viral load (fitted as log transformed, as a continuous variable).
- Exact number of weeks from start of regimen to 8 week viral load measurement (fitted as a continuous variable, untransformed).
- Number of other drugs in the new regimen (those which are new or recycled – not those which were in the previous regimen) to which virus (at time of resistance test) is sensitive (see below for details).

The model will account for the censoring of viral load measurements due to assay lower limits by use of a program designed for parametric survival analysis models (eg PROC LIFEREG in SAS, using the DIST=NORMAL option). An appropriate distribution for the outcome variable will be selected based on analysis of residuals (Hughes et al, Stat Med 2000) from a model which includes all variables except the sensitivity for the drug under consideration, and for which the score for other drugs in the regimen is extended to include the drug of interest.

The effect of drug sensitivity as defined by different interpretation systems will be compared according to likelihood ratio test statistics for the sensitivity variable.

Addition of other covariates in the model will be considered. For example, prior drug history, no. of new drugs in regimen, no. of drugs in regimen, prior use of drugs of same class, and previous viral load < 500.

Number of other new drugs in the new regimen to which virus is sensitive

In the absence of a generally agreed interpretation system for other new (or recycled) drugs in the regimen, these will each be scored as sensitive (S) / intermediate (I) / resistant (R) *initially* according to an existing system which is transparent and in the public domain (eg the Rega system). The choice of this system is essentially arbitrary, but in order to account for the sensitivity of other drugs in the regimen it is essential to pick an interpretation system for use at this stage that will be used consistently for this purpose. The chosen system will be used to derive a score of the number of other (besides the drug under consideration) drugs being started in the new regimen to which the patient's virus is sensitive (score of 1 for each sensitive drug and 0.5 for each intermediate drug). This will continue to be the case for the other drugs in the regimen even if the chosen system does not perform as well as other systems for ddI and/or abacavir. If the data set is large enough it may be possible to fit each other drug as, for example, not newly initiated / newly initiated and R / newly initiated and I / newly initiated and S. Note that in situations where the drug under consideration has been added to the virologically failing regimen then this score=0 for all patients and hence would not be fitted.

24 week outcome

For each interpretation system, a logistic regression model will be fitted of the week 24 outcome on the following covariates

- Sensitivity (as a three category variable – with the resistant group as the base) for the drug under consideration based on the interpretation system.

- Baseline viral load (fitted as log transformed, as a continuous variable).
- Exact number of weeks from start of regimen of 24 week viral load measurement (fitted as a continuous variable, untransformed).
- Number of other drugs in the new regimen (those which are new or recycled – not those which were in the previous regimen) to which virus (at time of resistance test) is sensitive (as above).

Interpretation systems will be compared according to likelihood ratio test statistics for the sensitivity variable based on that system.

This will be done three times, once for each approach to dealing with those who switch/discontinue drugs between weeks 12 and 32 (see section 3).

Evaluating the impact of specific differences in mutations between interpretation systems

Where specific mutations for a drug differ between interpretation systems then the models can be fitted in a different way, such that the component of the interpretation system that is in common between the interpretation systems is fitted separately from the component that differs. This should allow more direct assessment of the role of the amino acid changes that differ between systems.

This process will allow us to arrive at the interpretation system which best predicts viral load response. This will possibly be modified from

the original, based on evidence for the impact of specific mutations, and hence a new hybrid interpretation system derived.

5.3. Procedure if data set can be divided into derivation and test sets

In the event of there being a sufficiently large pooled data set to divide into derivation and test sets (if, for example, there are resistance/viro response data on over 2000 people), the above procedure outlined in 5.1 and 5.2 will initially be performed in the derivation data set. Further, a new interpretation system, not based on any existing interpretation system, will be derived as outlined below, using an approach linked to that for comparing interpretation systems. All candidate systems will then be compared on the test set using the procedure described in section 5.2.

Generation of a new interpretation system

We will attempt to derive a new interpretation system based on the derivation data set, in the following way.

Step 1

Fit a regression model of week 8 change in viral load on the following covariates

- Baseline viral load (fitted as log transformed, as a continuous variable).
- Exact number of weeks from start of regimen of 8 week viral load measurement (fitted as a continuous variable, untransformed).

- Number of drugs in the new regimen (those which are new or recycled – not those which were in the previous regimen) to which virus (at time of resistance test) is sensitive (see below for details). This includes the drug under consideration.

The model will account for the censoring of viral load measurements due to assay lower limits by use of a program designed for parametric survival analysis models (eg PROC LIFEREG in SAS, using the DIST=NORMAL option). An appropriate distribution for the outcome variable will be selected based on analysis of residuals (Hughes et al, Stat Med 2000). This step is mainly to develop an appropriate model for the 8 week endpoint.

Number of other new drugs in the new regimen to which virus is sensitive

In the absence of a generally agreed interpretation system for other new (or recycled) drugs in the regimen, these will each be scored as sensitive (S) / intermediate (I) / resistant (R) *initially* according to an existing system which is transparent and in the public domain (eg the Rega system). The choice of this system is essentially arbitrary, but in order to account for the sensitivity of other drugs in the regimen it is essential to pick an interpretation system for use at this stage that will be used consistently for this purpose. The chosen system will be used to derive a score of the number of other (besides the drug under consideration) drugs being started in the new regimen to which the patient's virus is sensitive (score of 1 for each sensitive drug and 0.5 for each intermediate drug). This will continue to be the case for the other drugs in the regimen even if the chosen system does not perform as well as other systems for ddI and/or abacavir. If the data set is large enough it may be possible to fit each other drug as, for example, not newly

initiated / newly initiated and R / newly initiated and I / newly initiated and S. Note that in situations where the drug under consideration has been added to the virologically failing regimen then this score=0 for all patients and hence would not be fitted.

Step 2

Examine pair-wise correlations between the amino acid change binary variables which appear in at least 1% of resistance tests in the data set. Those highly correlated will not be considered for entry together in the models below. Initially, one will be arbitrarily chosen but it will be necessary to decide at a later stage which is the more appropriate to use, or whether indeed a variable indicating the presence of *either* amino acid change is more appropriate.

Step 3

Re-fit the model from step 1, excluding the drug of interest from the variable denoting the number of sensitive new drugs in the regimen. This basic model for the 8 week endpoint is used from this point on, adding covariates corresponding to various amino acid changes potentially related to the drug under consideration.

Step 4

Generate 100 bootstrap resamples of the data set, each consisting of the same number of people/resistance tests as the original data set. Steps 5 – 7 below are performed on each bootstrap sample.

Step 5

Using a stepwise procedure (using alpha=0.05 for inclusion/exclusion), try adding to the above model (the basic model [step 3] variables will be forced in the model) binary covariates for all amino acid changes in the relevant gene (ie PR or RT) which appear at least once in the data set (eg

binary variable for M184V: M184V = 1 means V is present at codon 184 (even as part of a mixture) and M184V = 0 means V not detected as present at codon 184. There would be another binary variable M184I, for example).

Note: If the number of amino acid changes being considered proves to be too large for computing reasons or, despite the bootstrapping approach used below, results in too large a problem with multiple testing, consideration will be given to including only those which occur in at least, for example, 1% of resistance tests in the data set.

Step 6

Perform an identical procedure to step 5 on the week 24 outcome, using a logistic regression model. Do this three times for each bootstrap sample, corresponding to the three approaches to dealing with those who switch/discontinue drugs between weeks 12 and 32.

Step 7

Amino acid changes that are selected in more than 75% (ie 75 / 100) of the models/bootstrap samples for week 8 viral load change or in more than 75% (ie 300 / 400) of the models for week 8 and week 24 (3 models), should be selected for inclusion in the final model.

Step 8

Repeat steps 5-7, with the difference that the amino acid changes selected above are forced in to the model (along with the basic model [step 3] variables). The candidate variables for inclusion in the model which are put into the stepwise procedure are those formed by the two way interactions between those amino acid changes included in the model at step 7.

Step 9

Now that the final set of amino acid changes (and any two way interactions) have been selected, this final model will be run on each of the bootstrap samples and the mean of the coefficient estimates taken.

Step 10

Returning now to the original data set, for each person, the mean coefficient estimates for the amino acid changes (and interactions) derived in step 9 are then used to derive a continuous "resistance score" for the drug of interest.

This score will then be fitted in the basic model instead of the specific amino acid changes. The coefficient estimate for this score indicates the predicted additional viral load reduction expected at 8 weeks per one unit lower score.

The disadvantage of an interpretation system based on exact coefficient estimates would be that it would not be simple to remember. We would also therefore consider using coefficient estimates which are simplified due to rounding.

Step 11 – sensitive / intermediate / resistant

Various approaches to deriving cut-offs to enable categorization of the score into sensitive/intermediate/resistant. One approach will be to use cut-offs corresponding to $< 0.2 / \geq 0.2$, $< 0.6 / \geq 0.6$ log additional viral load reduction at week 8. These cut-offs may depend on the drug under consideration.

Notes

This analysis plan is intended to give as much detail as possible about the intended approach. However, as with most analyses, modifications may need to be made in response to preliminary findings in the analysis.

The analysis may be repeated for those with repeat resistance tests. Amino acid changes would be scored according to whether the change was ever previously present on any resistance test, rather than just whether it was present on the resistance test measured at baseline for this analysis.

A particular problem with evaluating the impact of TAMS on ddI is that it is almost always used with zdv or d4t. We may need to consider interpretation systems for combinations of two nucleosides including ddI, rather than for ddI alone.

This is an approach which essentially assumes that the effect of one amino acid change does not influence the effect of another amino acid change, unless there is compelling evidence to suggest otherwise. This underlying assumption sets this approach apart philosophically from many of tree-based and neural network approaches. These latter approaches are not as yet suited to situations where several new drugs are being started at the same time.

Some Relevant References for the Statistical Approaches Adopted

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6. Appendix

6.1 Data Analysis Plan Development Group

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