Attachment to

Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency

Guidance for Submitting HIV-1 Resistance Data

DRAFT GUIDANCE

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For questions regarding this draft document contact Lisa K. Naeger at 301-796-0771.

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Guidance for Submitting HIV-1 Resistance Data[1]

Sponsors are encouraged to use the following sample format for submitting HIV-1 resistance data.

One dataset combines patient data, endpoint data, genotypic data, and phenotypic data. There are a number of ways datasets can be subdivided (i.e., by clinical study, baseline isolates, or virologic failure isolates) and this should be discussed with the Division of Antiviral Products (DAVP) before submission. To identify any potential formatting problems as early as possible, all sponsors are encouraged to submit preliminary (or mock) resistance datasets to the DAVP before assembling formal clinical trial resistance datasets.

For each study, we recommend constructing datasets as SAS transport files containing the following information:

- One record (row) per patient per isolate (e.g., baseline, failure, and other time points).

- Data in columns (with suggested column headings shown below) on all isolates.

- Genotypic data should be provided on the corresponding record for each patient isolate for baseline isolates of all patients in treatment-experienced studies, and the endpoint isolates of patients who are classified as virologic failures and discontinuations in all studies. In treatment-naïve studies, a baseline sample should be collected and stored from all patients for future phenotypic and genotypic analysis of virologic failures.

- Phenotypic data should be provided on the corresponding record for each patient isolate for baseline isolates and the endpoint isolates of patients who are classified as virologic failures and discontinuations. In treatment-experienced studies, it is recommended that baseline phenotypic data be obtained for all patients.

The specific criteria for defining virologic failures should be discussed with the DAVP and may include multiple primary and secondary protocol endpoints. The endpoints for virologic and resistance outcome analyses should be consistent.

Standardization of Column Headings and Variables for HIV-1 Resistance Datasets

Sponsors should consult with the DAVP in advance if considering alternative approaches to any of the recommended column headings, variables, or definitions.

Sponsors collecting and submitting next generation sequencing (NGS) data should consult with DAVP early in the experimental design process, as additional guidance will be necessary. To initiate discussions with DAVP, sponsors should provide the details of their planned NGS

[1] This guidance is being revised to provide the current format, recommended definitions, standardization of column headings and variables, and recommended data for submission of HIV resistance datasets.

analyses, including the performance characteristics of the assay and bioinformatics software to be used for analysis.

Information to Include With Suggested Column Headings

I. Patient Data:

- **USUBJID**: Unique subject identification number (ID number should be unique for all studies).

- **STUDYID**: Study identification number.

- **ARM**: Treatment group.

- **VISIT**: (e.g., SCREENING, BASELINE, DAY#, WEEK#, FOLLOWUP WK#). Visit windows should be as defined in the protocol or statistical analysis plan.

- **VISITDY**: Study day (planned), protocol-defined, relative to initiation of protocol treatment.

- **ISOLDY**: Study day (actual) of isolate, relative to initiation of protocol treatment.

- **ISOLID**: Unique identifier for isolate analyzed.

- **ISOLDTC**: Date of isolate.

- **EXTRTHIV**: Concomitant HIV-1 treatment drugs.

- **HIVHIST**: Previous therapeutic products (listing of all previous antiretrovirals (ARVs)).

- **PRVARV1**: Previous HIV-1 ARV product (e.g., AMPRENAVIR, ATAZANAVIR). Additional columns should be added as needed to provide information on multiple ARV exposures (e.g., PRVARV2, PRVARV3). NULL if no previous ARV products.

- **HIVGTSC**: HIV-1 clade/genotype at screening.

- **HBVCOINF**: Hepatitis B virus co-infected (Y or N).

- **HCVCOINF**: Hepatitis C virus co-infected (Y or N).

II. Endpoint Data:

- **HIVVLBL**: HIV-1 ribonucleic acid (RNA) (copies/mL) at baseline (identify assay in column heading description).

- **LOGVLBL**: HIV-1 RNA (log_{10} copies/mL) at baseline.

- **HIVVL**: HIV-1 RNA (copies/mL) at time points in protocol (e.g., Week 24 and Week 48); one row for each time point. HIV-1 RNA (copies/mL) from additional time points not specified in protocol can also be included.

- **LOGHIVVL**: HIV-1 RNA (log_{10} copies/mL) at all time points from protocol, one row for each time point. HIV-1 RNA (log_{10} copies/ml) from additional time points not specified in protocol can also be included.

- **HIVVL(TIME)**: Individual column headings for HIV-1 RNA measurements (copies/mL) at selected visit times as appropriate depending on trial design. Each column represents a single time point of interest. For example, Treatment Week 4 (HIVVLW4).

- **HIVVLEOT**: HIV-1 RNA (copies/mL) at end of treatment (including loss of virologic response; (i.e., virologic failure)) or discontinuation because of adverse event).

- **LOGVLEOT**: HIV-1 RNA (log_{10} copies/mL) at end of treatment (based on actual end of treatment, not planned end of treatment).

- **EFFICFL**: Achieved primary efficacy endpoint as defined in protocol and statistical analysis plan (Y or N).

- **NONRECAT**: Failure or Nonresponder category for currently tested therapy as defined by the protocol (e.g., REBOUND, NEVER SUPPRESSED, DISCONTINUED WHILE SUPPRESSED, DISCONTINUED BEFORE SUPPRESSED).

- **DISCTXFL**: A flag used to indicate subject discontinued from protocol treatment (Y or N).

- **DISCTXVL**: HIV-1 viral RNA load when subject discontinued protocol treatment.

- **DISCREAS**: Reason for early protocol treatment discontinuation (e.g., ADVERSE EVENT, DEATH, STOPPING RULE, LACK OF EFFICACY, LOST TO FOLLOW-UP, NONCOMPLIANCE WITH STUDY DRUG; PHYSICIAN DECISION; PREGNANCY; PROTOCOL VIOLATION; SCREEN FAILURE; WITHDRAWAL BY SUBJECT; OTHER); or NULL if no information available or not applicable. Reasons are defined according to protocol or statistical analysis plan.

- **VFFL**: A flag (Y or NULL) used to indicate the specific study visit in which the subject met the criteria for protocol-defined virologic failure (e.g., rebound, end of treatment).

- **VLMET**: HIV-1 RNA viral load assay name and version.

- **VLVEND**: Name of vendor, contract laboratory, or other central laboratory conducting HIV-1 RNA viral load assessments.

III. Genotypic Data:[2]

Genotypic data should be provided for the HIV-1 target, one amino acid per column, with the wild-type (WT) amino acid in the column heading. Changes from WT standard sequence should be indicated in the row (i.e., blanks indicate no change).

COLUMN HEADING FORMAT EXAMPLE:
For reverse transcriptase (RT), RTAXXX where A = amino acid code and XXX is amino acid position (e.g., RTK065, RTK103); for protease (PR), PRAXXX (e.g., PR I084, PRL090); for integrase (IN), INAXXX.

- Changes from the reference sequence should be indicated for each reported sequence (e.g., PRI084 change reported as "V"). Blank cells indicate no change from reference strain sequence. Mixed populations of WT/Variant or Variant/Variant should be reported as such (e.g., K65R/K reported as R/K; K103N/K reported as N/K).

- To report insertions in subject sequence data relative to the reference strain used to generate the dataset, additional columns should be added where appropriate. For example, a four-amino acid stretch that includes a two-amino acid insertion between RT position 69 and 70 should be reported under the column headings RTH069, RTH069A, RTH069B, and RTK070.

- To report deletions in subject sequence data relative to the prototypic reference strain used to generate the dataset, a dash (-) should be reported in cell for appropriate positions.

- For ambiguous amino acids (i.e., nucleotide information was present but amino acid could not be called due to non-interpretable translation), X should be reported for appropriate positions.

- Missing sequence data caused by poor sequence quality or other technical problems should be reported as a question mark (?) for appropriate positions. Efforts should be made not to have stretches of missing sequence information because of poor sequence quality or other technical problems.

- **GENOMET**: Genotypic assay name.

- **GENOFAIL**: A flag used to identify samples with sufficient HIV-1 RNA to be analyzed but results not reported because of poor sequence quality or other technical reasons (e.g., RT-PCR amplification not successful) (Y or NULL).

[2] Genotypic data should be provided for baseline isolates of all patients in treatment-experienced studies, and the endpoint isolates of virologic failures and discontinuations in all studies. In treatment-naïve studies, a baseline sample should be collected and stored from all patients for future phenotypic and genotypic analysis of virologic failures.

- **RESISTFL**: A resistance analysis flag used to identify any isolate/time point (including baseline, on-treatment, and during follow-up) with resistance analysis data reported. This flag should allow reviewers to pull out all reported resistance data (Y or NULL).

- **RESBLFL**: A flag used to identify baseline sample with resistance analysis data reported (Y or NULL).

- **RESEOTFL**: A flag used to identify the last on-treatment isolate/time point with resistance analysis data reported. The flag should indicate no more than one time point per subject (Y or NULL).

- **TOTCCR5**: Column with total number of CCR5 co-receptor antagonist substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTFI**: Column with total number of fusion inhibitor substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTINSTI**: Column with total number of INSTI substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTNNRTI**: Column with total number of NNRTI substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTNRTI**: Column with total number of NRTI substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTPI**: Column with total number of PI substitutions in subject isolate (for baseline and endpoint isolates). The specific substitutions to include should be discussed with the DAVP in advance.

- **TOTDRG**: Column with total number of target substitutions (or mutations for genome-targeting products) in subject isolate (for baseline and endpoint isolates) for a drug with a novel target. *DRG* is a placeholder for the three-character abbreviation of drug.

IV. Phenotypic Data:[3]

For the candidate drug, approved/investigational drug(s) in the same class, and approved/investigational drug(s) outside the candidate drug class with the same target protein (e.g., NNRTIs and NRTIs) or protein complex (e.g., gp120/gp41), sponsors should provide the following data:

- **DRGEC50** (i.e., DRUG ABBREVIATION EC_{50} value): EC_{50} values (µM) at baseline and post-baseline time points for candidate drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- **DRGECRF** (i.e., DRUG ABBREVIATION RF): Fold change values in EC_{50} value at time of assessment (BASELINE or ENDPOINT) compared to reference strain for drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- **DRGECBL** (i.e., DRUG ABBREVIATION BL): Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- **PHENOMET**: Phenotypic method or assay name.

- **PHENORF**: Reference strain.

- **PHENFAIL**: Phenotype analysis conducted but failed because of poor replication in phenotype assay (Y or NULL).

- **DRGIQ** (i.e., DRUG ABBREVIATION IQ): Inhibitory quotient (C_{min} value/serum or plasma adjusted EC_{50} value when available). DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

V. Protease Cleavage Sites (for protease inhibitors only):

- **NC/p1 Gag cleavage sites:** Sponsors should show amino acid and position of cleavage site of WT in column headings (as above for genotype) and indicate amino acid change if mutant in row

- **p1/p6 Gag cleavage sites:** Sponsors should show amino acid and position of cleavage site of WT in column headings (as above for genotype) and indicate amino acid change if mutant in row

[3] Phenotypic data should be provided for baseline isolates and the endpoint isolates of virologic failures and discontinuations. In treatment-experienced studies, it is recommended that baseline phenotypic data be obtained for all patients.

VI. Co-Receptor Usage (for all products targeting co-receptors):

- **TRPBL**: Co-receptor usage of baseline isolates. Sponsors should indicate R5, X4, D for dual-tropic, M for mixed-tropic, or D/M if the assay cannot distinguish between dual or mixed, in a column.

- **TRPBLR5**: Baseline R5 tropism assay value (e.g., RLUs).

- **TRPBLX4**: Baseline X4 tropism assay value (e.g., RLUs).

- **TRPEOT**: Co-receptor usage of virologic failures and end-of-study isolates (on therapy). Sponsors should indicate R5, X4, D for dual-tropic, M for mixed-tropic, or D/M if the assay cannot distinguish between dual or mixed, in a column.

- **TRPEOTR5**: R5 tropism assay value at failure or end of study (e.g., RLUs).

- **TRPEOTX4**: X4 tropism assay value at failure or end of study (e.g., RLUs).