

Resistance Data Revolution: Insights, Challenges and FDA Compliance Implementation

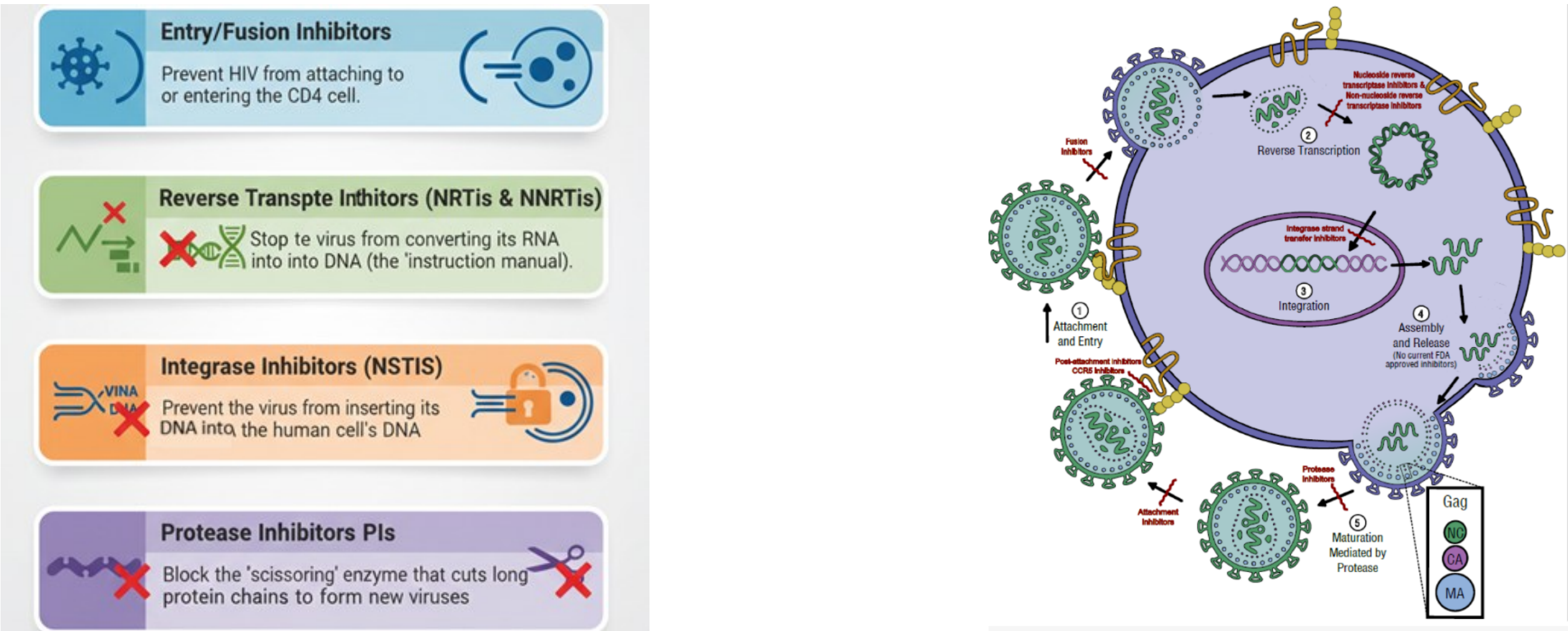
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HIV/AIDS: HIV (human immunodeficiency virus) is a virus that attacks the body's immune system. Without treatment, it can lead to AIDS (acquired immunodeficiency syndrome).

ART: Anti-Retroviral Therapy is a combination of daily medications that work together to prevent HIV from making copies of itself. By suppressing the "viral load" (the amount of virus in the blood), ART allows the immune system (CD4 cells) to recover and prevents the progression to AIDS.

HIV must complete several steps to infect a cell and replicate. Different classes of ART drugs target different stages of this cycle:



Drug resistance occurs when HIV changes its genetic structure (mutates) in a way that makes a specific drug less effective. Because HIV replicates rapidly and makes many "mistakes" during the process, it is naturally prone to mutations. Resisting testing is done by 2 methods

1. Genotypic Testing

Sequencing These Genes

- Utilizes DNA sequencing to find (e.g., M184V)
- Faster, Cheaper, Widely Available
- Predicts resistance based KNOWN mutations

2. Phenotypic Testing

Measures actual viral growth in lab

- Creates Pseudovirus
- Creates viral growne of ART drugs

Sanger Sequencing and NGS testing are the popular methods of Genotypic resistance testing.

Sanger Sequencing:

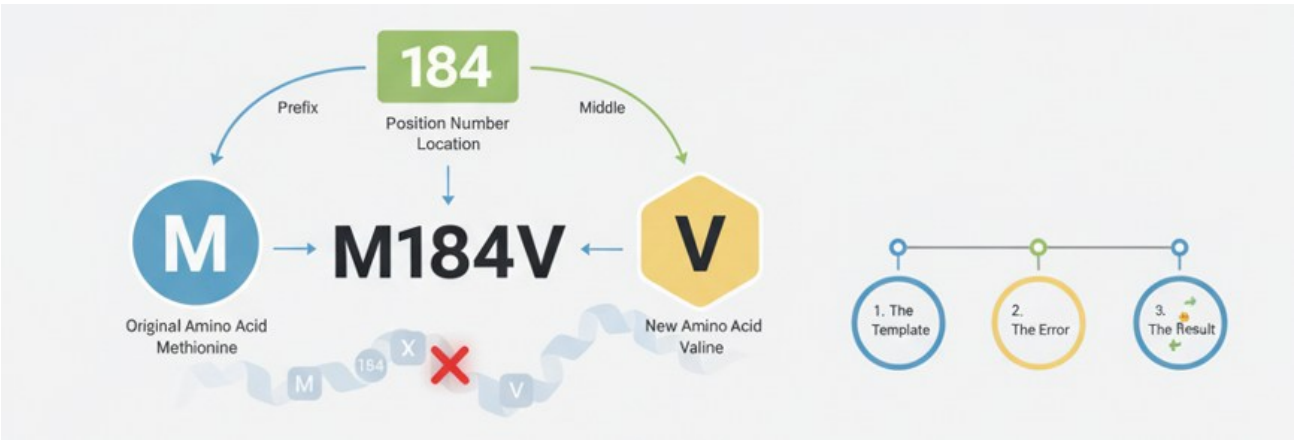
Sanger sequencing is a "population-based" method. It reads the most dominant genetic sequence in a sample to create a single consensus sequence. Sanger can only detect a mutation if it exists in at least 15-20% of the sample.

NGS Data Testing (The High-Sensitivity Method):

Next Generation Sequencing is "massively parallel" meaning it sequences millions of individual DNA fragments at the same time. This allows it to detect rare mutations (down to 1% or less) that Sanger would miss.

Example of Genotypic Mutation data:

Subject	Isolate	Accession	NRTIs	NNRTIs	NRTI Mut	NNRTI Mut	Common	Unusual
ACTG5288_1	ACTG5288_1_1		ABC, AZT, D4T, DDI, 3TC	NVP	S68G	Y181YC, H221HY	K166KR, E169D, D177E, E194ED, G196E, T200TI, R211G, V276I, A288S, K311R, I326V, I329L	
	ACTG5288_1_2		ABC, AZT, D4T, DDI, 3TC, TDF, FTC	NVP	S68G	V90VI	K166KR, E169D, D177E, G196E, T200TI, R211G, V276I, A288S, K311R, I326V, I329L	
ACTG5288_10	ACTG5288_10_1		AZT, TDF, 3TC	NVP	M41L, D67N, K70R, V75M, M184V, T215F, K219Q	K103N, E138Q, P225H, K238T	V35T, T39A, V60I, I94L, D121Y, K122E, I135T, S162A, K173S, Q174K, D177E, I178M, V179I, T200A, E203D, Q207A, R211S, V245K, D250E, T286A, I293V, P294A	
ACTG5288_100	ACTG5288_100_1		AZT, TDF, FTC, 3TC	NVP	M41L, D67N, K70R, M184V, T215Y, K219Q	A98G, Y181C	V35I, T39D, V60I, I94L, K101Q, D121Y, K122E, I135T, T139R, S162A, K173T, D177G, T200A, Q207N, R211K, D219E, L228H, V245Q, A272P, K281R, T286A, T290TS, E291D, I293V, T296TN, E297R	



Classification of Mutations:

The classification of **Major** (Primary) and **Minor** (Accessory) mutations is a scientific process that combines lab data with clinical observation. Organizations like the **IAS-USA** and the Stanford **HIVdb** use specific criteria to determine where a mutation belongs.^[1]

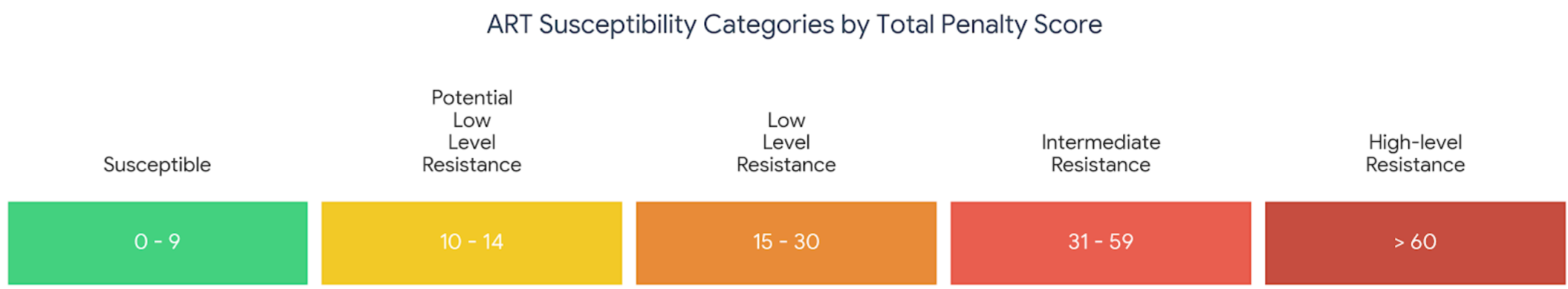
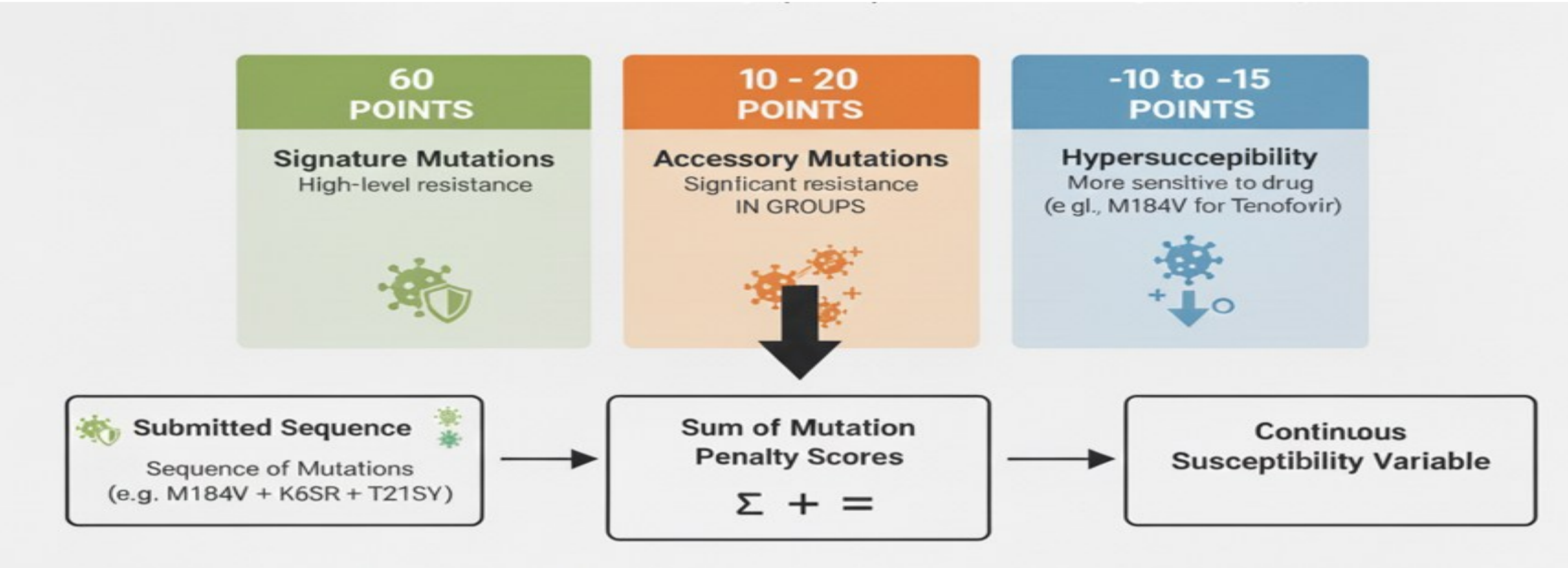
Genotypic Resistance Interpretation:

Resistance interpretations are implemented by a compiler – the algorithm specification interface (ASI). The ASI comprises an XML format for specifying an algorithm and a compiler that transforms the algorithm into executable code.

Penalty Scores:

Penalty scores are developed to reflect the effect of individual mutations on drug susceptibility and estimates of ARV susceptibility for the most commonly occurring patterns of ARV resistance mutations.

The algorithm assigns scores in multiples of 5, typically ranging from -15 to 60.



Analysis Dataset implementation: We can create Analysis dataset with PARAMCD – S-GSS, PARAM – Stanford Global susceptibility Score with AVALC – with Susceptibility score.

FDA recommendation for resistance dataset: **ADEFFOUT**

It should comprise a combination of patient demographics, current and prior ART medication, Background therapy, Treatment and study discontinuation, resistance Susceptibility scores and viral load efficacy measures.

Benefits of Resistance data in ART treatment:

- Prevents "First-Line" Failure:** By identifying **Transmitted Drug Resistance (TDR)** before treatment starts, clinicians can avoid prescribing drugs that are already ineffective for that specific patient.
- HIV drug resistance testing can guide individual therapy where available and help guide reaching the resistance data to “Undetectable” more quickly.
- Distinguishes Adherence from Resistance:** Testing confirms whether a rising viral load is caused by the virus mutating (biological failure) or by the patient missing doses (behavioral issues), preventing unnecessary and expensive drug changes.

References:

- [1] <https://cms.hivdb.org/prod/downloads/resistance-mutation-handout/resistance-mutation-handout.pdf>
HIV Antiretroviral Therapy <https://www.ncbi.nlm.nih.gov/books/NBK513308/>
HIV-1 Drug Resistance and Resistance Testing <https://pmc.ncbi.nlm.nih.gov/articles/PMC5136505/>
[Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus-1 Infection](https://www.fda.gov/oc/submitting-select-clinical-trial-data-sets-for-drugs-intended-to-treat-human-immunodeficiency-virus-1-infection)