SHOULD WE BE TESTING FOR BASELINE INTEGRASE RESISTANCE?

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This work was supported by the National Institutes of Health (R01 AI 042006; K01 HL123349 (EPH)), and by the Steve and Deborah Gorlin MGH Research Scholars Award (RPW).

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Poster #493

BACKGROUND

- Treatment guidelines recommend a standard genotype to guide selection of antiretroviral therapy (ART) in patients newly diagnosed with HIV.
- Integrase strand transfer inhibitors (INSTIs) are recommended in most first-line ART regimens, yet standard genotypes do not assess for INSTI-resistance (INSTI-R).
- Prevalence of transmitted INSTI-R virus is low (0-0.1%) in published and presented studies from the U.S. and Europe.
- Treatment with dolutegravir (DTG)-based ART can result in suppression of INSTI-R virus in some patients.
- It is not clear if testing for INSTI-R prior to ART initiation improves clinical outcomes or if it is cost-effective.

OBJECTIVE

- To examine the conditions under which INSTI-R testing at ART initiation might improve clinical outcomes and be cost-effective compared to current standard of care (no testing).

METHODS

Model structure (Figure 1)

- We designed a decision tree model to simulate an HIV-infected, ART-naïve patient presenting for baseline lab work and genotype, as per 2016 DHHS guidelines [1].

Strategies of care (Figure 1)

- ***No testing (current standard of care):*** Genotype only prior to ART initiation.
  - At ART initiation, all patients start DTG-based ART.
  - At 12-wk, patients reassessed; those not virologically suppressed undergo standard genotype and INSTI-R testing.
  - At 12-wk, patients with INSTI-R virus start darunavir/ritonavir (DRV/r)-based ART.
- ***Testing:*** Genotype and INSTI-R testing prior to ART initiation.
  - Patients with INSTI-susceptible (INSTI-S) virus start DTG-based ART.
  - Patients with INSTI-R virus start DRV/r-based ART.

Input parameters

- ***ART efficacy, Quality of life, ART costs (Table 1)***
- ***Cohort characteristics*** **[2]**
  - Mean age, 43 years.
  - 84% male.
  - Mean CD4 count, 339 cells/mm^3 (95% CI, 321-358 cells/mm^3).
- ***INSTI-R virus prevalence***
  - 0.1% among ART-naïve [3-10].
- ***Additional costs***
  - Genotype test 351 USD; INSTI-R test 175 USD [11].

Outcomes (96 weeks):

- ***Clinical outcomes:***
  - Suppressed.
  - Not suppressed: viremia due to virologic resistance, poor adherence, or ART discontinuation due to adverse events.
  - Quality-adjusted life years (QALYs):
    - Health-related quality of life (QoL) values stratified by CD4 count and viral load, based on ACTG 5142 trial data [12].
- ***Costs*** (USD).
- ***Incremental cost-effectiveness ratio*** (ICER, ΔUSD/ΔQALY); cost-effective if ≤100,000 USD/QALY.

METHODS: INPUT DATA

Figure 1: Decision tree to evaluate the clinical benefits and cost-effectiveness of testing for INSTI-R virus compared to no testing prior to ART initiation.

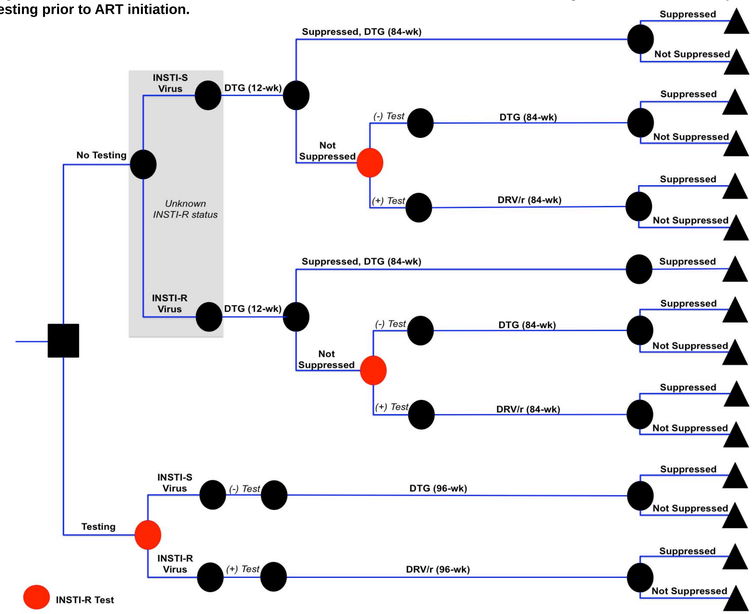


Table 1: Model input parameters for analysis of testing for INSTI-R virus compared to no testing prior to ART initiation.

	DTG-based regimen			DRV/r-based regimen		
	Base Case	Range (min-max)	Reference	Base Case	Range (min-max)	Reference
ART Efficacy (%)						
INSTI-S virus						
Suppression at 12-wk	90	30-100	[13]	–	–	
Suppression at 96-wk	80	30-100	[13]	71	30-100	[13, 14]
INSTI-R virus						
Suppression at 12-wk	35	0-100	[15]	71	30-100	
Quality of Life						
Virologically suppressed	0.954	–	[12]	0.954	–	[12]
Viremia	0.931	0.781-0.953		0.931	0.781-0.953	
QoL decrement for ART regimen	1	–		1	0-0.990	
Cost (USD)						
ART, annual	$38,150	$12,000-100,000	[16]	$42,661	$12,000-100,000	[16]

RESULTS

Table 2: Base case model output for testing for INSTI-R virus compared to no testing prior to ART initiation.

	QALY	Costs (USD)	ICER (USD/QALY)
No testing	1.788	$70,800	-
Testing	1.788	$71,000	DOMINATED

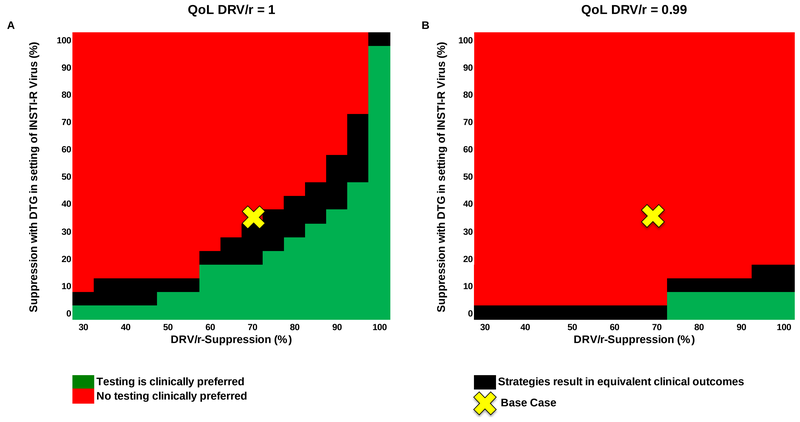
- In the base case, QALYs are equal between the two strategies, assuming a level of precision of 3 significant figures.
- The testing strategy costs more and is dominated.

Table 3: Univariate sensitivity analysis model outputs for INSTI-R testing compared to no testing prior to ART initiation.

	No testing clinically preferred	Testing clinically preferred
96-wk suppression with DTG-based ART (base case, 80%)	0-95%	>95%
96-wk suppression with DRV/r-based ART (base case, 71%)	0-85%	>85%
DTG-suppression in setting of INSTI-R virus (base case, 35%)	12-100%	<12%
QoL when viremic (base case, 1)	0-1	-
QoL on DRV/r-based ART (base case, 1)	0-1	-
Prevalence of INSTI-R virus (base case, 0.1%)	0-100%	-

- When one strategy is clinically preferred over the other, the differences in QALYs are extremely small (5.7×10^{-3} – 9.4×10^{-7}) and the differences in costs are also small (160-860 USD).
- Even when testing is clinically preferred, it is never cost-effective compared to no testing (ICERs > 40 million USD/QALY) unless 96-wk suppression with DTG-based ART is >95%.

Figure 2: Multivariate sensitivity analysis of the clinical impact (QALYs) of testing for INSTI-R virus compared to no testing at a prevalence of INSTI-R virus of 0.1% while varying the probability of suppression with DTG-based ART in setting of INSTI-R virus (y-axis) and suppression with DRV/r-based ART (x-axis).



Multivariate sensitivity analysis (Figure 2):

- When QoL for time spent on on DRV/r-based ART is equivalent to that on DTG-based ART (Panel A), ***testing*** is clinically preferred when suppression on DRV-based ART improves, even at higher probabilities of suppression on DTG-based ART for INSTI-R virus.
- When the QoL for time spent on DRV/r-based ART is 99% of that on DTG-based ART (Panel B), ***testing*** is only clinically preferred when:
  - DTG suppression in setting of INSTI-R virus is <10%.
  - DRV/r suppression is >75%.
- When one strategy is clinically preferred over the other, QALYs increase by 4.3×10^{-5} to 1.9×10^{-6}, an extremely small difference.

LIMITATIONS

- Our model-based analysis does not capture the impact of:
  - ***Transmissions***: patients with INSTI-R virus could infect others more frequently during the 12-wk of empiric DTG-based regimen (no testing strategy) compared to when INSTI-R testing occurs prior to ART initiation.
  - ***Time horizon*** (96-wk): suppression with different ART regimens could differ over longer time horizons (e.g., ART discontinuation or loss to follow-up due to adverse effects).
- Our study results are not necessarily generalizable to ***pregnant women*** or ***ART-experienced patients***.

CONCLUSIONS

- The results of our model-based analysis do not support the strategy of testing for INSTI-R virus prior to ART initiation.
- Testing for INSTI-R virus prior to ART initiation results in equivalent or worse clinical outcomes compared to a no testing strategy and costs more, assuming that:
  - DTG-based ART can suppress at least 17% of patients with INSTI-R virus [15].
- In base case and sensitivity analyses, testing for INSTI-R virus prior to ART initiation is never cost-effective compared to no testing.
- Prevalence of INSTI-R virus has minimal impact because:
  - Some patients with INSTI-R virus who start DTG-based ART will achieve suppression.
  - Patients with INSTI-R virus failing DTG-based ART wait a maximum of 12 weeks prior to switching to DRV/r-based ART in the no testing strategy.

REFERENCES

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