Simulation Modeling of Adherence and Resistance on Long-Term Outcomes in HIV

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Introduction

Suppression of plasma HIV RNA (vRNA) below the limit of detection remains a chief goal of highly-active antiretroviral therapy (HAART) in both naïve and experienced patients[1]. Antiretroviral (ARV) drug resistance is a major contributor to the failure to initially achieve and maintain virologic suppression. A key mechanism for the development of resistance is adherence, and poor adherence has been linked to the risk of virologic failure[2].

Recent evidence suggests that the relationship between adherence and the likelihood of resistance and/or failure may vary for protease inhibitors (PIs), boosted PIs, and non-nucleoside reverse transcriptase inhibitors (NNRTIs)[3,4]. We use a simulation model of HIV disease to estimate the impact of adherence on time to first failure and survival for individuals initiating HAART with a boosted PI- or NNRTI-containing regimen.

Methods

Model Structure:

- HIV disease progression was modeled as a function of CD4+ cell count and virologic suppression (vRNA < 50 copies/mL). CD4+ cell count trajectories in the presence of virologic suppression and failure were derived from clinical trials and cohort studies[5-8].
- Outcomes were estimated using a Monte Carlo simulation of 10,000 individuals for 40 years. Demographics of the modeled cohort were based on Walmsley et al (2006) and are shown in Table 1[9].

Treatment Regimens:

- Individuals were assumed to receive ≤ 5 HAART regimens over their lifetimes, starting with either an NNRTI (NNRTI First cohort) or a boosted PI plus 2 NRTIs (Boosted PI First cohort).
- Initial NNRTI regimens were followed with a boosted-PI and vice versa. **In order to illustrate the impact of adherence, not potency, on outcomes, these 2 regimens were assumed to have equal efficacy.**
- Efficacy for the 3rd regimen ("3 Class Experienced") was based on Study AI424-045 to reflect patients with exposure to the 3 main classes of ARVs[10]. Regimens 4 and 5 were salvage regimens consisting of optimized background (OB) and OB + T-20, respectively, following the TORO trials[11,12]. These regimens contained boosted PIs but not NNRTIs
- Efficacy parameters for the 5 regimens are shown in Table 2.

Adherence & Resistance:

- Published data from King et al (2005) and Bangsberg et al (2006) were used to determine probabilities of virologic suppression and subsequent failure based on adherence rates for patients on boosted PI- and NNRTI-containing regimens, respectively.
- Table 3 shows the relative risks of initial suppression and subsequent failure by adherence quartile and ARV class used in the model. Risks shown in italics are based on assumption.
- Adherence quartiles reported in Bangsberg et al (2006) were denoted as "Excellent" (≥95%), "Good" (77 - 94%), "Fair" (49 - 76%), and "Poor" (≤48%). **All risks are calculated relative to the Excellent group.**

Table 1. Demographics of the Modeled Cohort[9]

Age (yrs), mean (SD)	38 (9.3)
Male gender, proportion	80
White race, proportion	57
Baseline vRNA (copies/mL), mean (SD)	4.91 (3.77)
Baseline CD4+ count (cells/mm^3), mean (SD)	259 (145)

SD = standard deviation. vRNA = plasma HIV RNA.

Methods (cont'd)

Adherence & Resistance (cont'd):

- For NNRTIs, a relative risk of suppression by 48 weeks for different rates of adherence was estimated based on the proportion of patients with vRNA < 50 copies/mL; relative risk of subsequent failure was based on the proportion of patients with detectable and resistant virus[4].
- For boosted PIs, relative risks of suppression for adherence levels of 95%, 90%, 80%, and 70% were mapped to the quartiles shown in Table 3 [3]. **Risks of subsequent failure were not available. In the base case analysis, we conservatively estimated these risks to be equal to those for un-boosted PIs[4]. As a sensitivity analysis, we also examined outcomes when the relative risk of failure was assumed equal to 1.0, meaning that the risk of failure was unrelated to adherence.** The actual relative risks of failure for boosted PIs can be reasonably expected to lie in this range.
- Explicit data for NRTIs were unavailable. However, the PI and NNRTI data were based on regimens that contained NRTI backbones. Thus, relative risks of suppression and failure were assumed equal to 1 for all adherence quartiles to avoid overestimation of failures.

Model Outcomes:

- Median time to first failure among initially suppressed patients, mean expected survival, and mean quality-adjusted life years (QALYs) were estimated by adherence group and initial regimen. Utility weights for the derivations of QALYs were taken as an average from several published sources [13-15].

Table 2. Efficacy Parameters for Modeled Treatments

Line	Regimen	CD4+ Change[1]	Pr (< 50)[2]	Source(s)
1 or 2	NNRTI + 2 NRTIs	204	87%	Assumption
1 or 2	Boosted PI + 2 NRTIs	204	87%	Assumption
3	3 Class Experienced	110	52%	[10]
4	OB	110	52%	[11, 12]
5	OB + T-20	91	23%	[11, 12]

1. Change from baseline at 48 weeks, cells/mm^3.
2. Proportion with vRNA < 50 copies/mL) at 48 weeks.
OB = optimized background.

Results

- Simulation results for the base case are shown in Table 4. Estimated survival and QALYs as a function of adherence were similar for both the NNRTI First and Boosted PI First cohorts, but time to first failure patterns were not.
  - Time to first failure for individuals with "Excellent", "Fair", and "Poor" adherence were the same for both cohorts (12.25, 6.00, and 2.00 years, respectively).
  - For individuals with "Good" adherence, time to failure was longer for the Boosted PI First cohort compared to the NNRTI First cohort (11.25 vs 7.00 years). **This information should be evaluated carefully, as the risk of failure on boosted PIs could not be extrapolated from available data and was assumed to be the same as un-boosted PIs**.
  - Estimated survival and QALYs for individuals with at least "Fair" adherence was approximately 23 – 25 years when initiating HAART at CD4+ counts near 259 cells/mm3. For individuals with "Poor" adherence, these estimates were reduced by 60-64%.

Table 3. Rates and Relative Risks of Suppression and Failure by Adherence Quartile and ARV Class[1]

	Adherence Group			
	Excellent 95 – 100%	**Good 77 – 94%**	**Fair 49 – 76%**	**Poor 0 – 48%**
Suppression, rate (relative risk)				
NNRTIs	0.80 (1.00)	0.57 (0.71)	0.50 (0.63)	0.08 (0.10)
Boosted PIs	0.86 (1.00)	0.80 (0.97)	0.66 (0.44)	0.47 (0.13)
Failure with Resistance, rate (relative risk)				
NNRTIs	0.20 (1.00)	0.43 (2.14)	0.50 (2.50)	0.92 (4.62)
Boosted PIs[(2)]	*n/a (1.00)*	*n/a (1.00; 1.10)*	*n/a (1.00; 1.49)*	*n/a (1.00; 1.71)*

1. **Relative risks are calculated relative to the 95 – 100% adherence quartile.** Rates of suppression for boosted PIs were based on adherence rates of 95%, 90%, 80%, and 70% and were mapped to the 95 – 100%, 77 – 94%, 49 – 86%, and 0 – 48% quartiles, respectively.
2. **N/a = Data not available. Relative risk assumed to fall within 1.0 and the relative risks associated with un-boosted PIs (see Methods).** The rates of subsequent failure for un-boosted PIs are 0.58, 0.64, 0.87, and 1.00 for the Excellent, Good, Fair, and Poor adherence groups, respectively.

Sources: [3,4]

Table 4. Modeled Outcomes by Adherence Group

	Adherence Group							
	NNRTI First				Boosted PI First[1]			
	Excellent 95-100%	**Good 77 - 94%**	**Fair 49 - 76%**	**Poor 0-48%**	**Excellent 95-100%**	**Good 77 - 94%**	**Fair 49 - 76%**	**Poor 0-48%**
Time to 1st failure[2] (yrs), median	12.25	7.00	6.00	2.00	12.25	11.25	6.00	2.00
Survival (yrs), mean (SD)	25.33 (11.86)	24.92 (11.94)	23.11 (11.78)	9.26 (8.95)	25.34 (11.87)	25.14 (11.81)	22.87 (12.02)	9.35 (8.93)
QALYs, mean (SD)	15.11 (5.75)	14.85 (5.84)	13.84 (5.86)	5.95 (5.14)	15.12 (5.75)	15.01 (5.74)	13.65 (6.02)	6.03 (5.16)

1. Relative risk of subsequent failure for boosted PIs = relative risk of failure for un-boosted PIs.
2. Time to first failure excludes individuals who never achieved initial viral suppression or never met the endpoint due to death or other event.
Yrs = years. SD = standard deviation. QALYs=quality-adjusted life years.

Table 5. Sensitivity Analysis on Relative Risk of Failure for Boosted PIs

	Adherence Group							
	NNRTI First				Boosted PI First[1]			
	Excellent 95-100%	**Good 77 - 94%**	**Fair 49 - 76%**	**Poor 0-48%**	**Excellent 95-100%**	**Good 77 - 94%**	**Fair 49 - 76%**	**Poor 0-48%**
Time to 1st failure[2] (yrs), median	12.25	7.00	6.00	2.00	12.25	12.25	12.25	12.25
Survival (yrs), mean (SD)	25.30 (12.02)	24.94 (12.01)	24.93 (11.88)	23.16 (12.59)	25.30 (12.02)	25.15 (11.88)	25.19 (11.69)	24.28 (11.81)
QALYs, mean (SD)	15.07 (5.84)	14.86 (5.86)	14.84 (5.80)	13.65 (6.33)	15.07 (5.84)	15.02 (5.76)	15.04 (5.66)	14.49 (5.58)

1. Relative risk of subsequent failure for boosted PIs = 1.0 for all adherence groups.
2. Time to first failure excludes individuals who never achieved initial viral suppression or never met the endpoint due to death or other event. Yrs = years.
SD = standard deviation. QALYs=quality-adjusted life years.

Results (cont'd)

- Results of the sensitivity analysis where the relative risk of failure for boosted PIs was assumed equal to 1.0 for all adherence groups are shown in Table 5. NOTE: Estimated outcomes for the NNRTI First cohorts differ between Tables 4 and 5 because 3rd and later lines of therapy contain boosted PIs (and exclude NNRTIs).
  - As would be expected, times to first failure under this scenario were substantially greater for the Boosted PI First group when adherence was less than Excellent, compared to the NNRTI First cohort.
  - Estimated survival and QALYs were again similar for both the NNRTI First and Boosted PI First cohorts, but differences across adherence groups within each cohort largely disappeared.
- In both the base case and the sensitivity analysis, expected QALYs were lower than expected survival times due to adjustment for quality of life.

Discussion

- **Our analysis confirms the importance of adherence on patient outcomes with HAART. With excellent adherence, individual life expectancy is high compared to the pre-HAART era, although still short of normal life expectancy (e.g., estimated life expectancy for 40 year old males in the US was 37.3 years in 2003)[16].**
- **Time to first failure results are consistent with the view that regimens containing boosted PIs may be more successful compared to NNRTIs when adherence is relatively high (77 – 94%).**
- **Although failure times varied somewhat between NNRTI- and boosted PI-containing regimens, overall survival was similar since individuals were assumed to be treated with both classes early in the course of treatment.**
- **For every adherence level, mean QALYs were roughly 40% lower than raw survival estimates, highlighting the impact of HIV on patients' quality of life in comparison to the loss in survival associated with poor adherence.**
- **This analysis is subject to the following limitations:**
  - **Relative risks of failure with boosted PIs were conservatively estimated by assuming risks equal to those of un-boosted PIs[4]. We would expect actual boosted PI outcomes fall within the ranges reported in Tables 4 and 5.**
    - **While failure with resistance can occur more rapidly with NNRTIs vs boosted PIs, the development of resistance in the model is not time-dependent; i.e., resistance does not develop faster for NNRTIs compared to boosted PIs for a given level of adherence.**
  - **We were unable to model resistance to NRTIs as a function of adherence or the use of boosted PIs or NNRTIs.**
  - **Efficacy for the first 2 regimens was assumed to be equal in order to focus on the adherence/resistance relationship. Since individuals received both regimens, increasing the potency for one of the regimens would not affect the results.**

Conclusions

- **Even relatively small improvements in adherence among patients with low adherence to therapy have the potential to significantly improve life expectancy with HAART.**
- **Additional data are needed to better understand the impact of small changes in adherence on resistance and long-term outcomes in HIV.**
- **To achieve maximal survival benefit from HAART, providers should consider regimens based the likelihood for success, monitor for signs of poor adherence, and make appropriate adjustments prior to failure.**

References

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