Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation

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Objectives: Determining the relationship between antiretroviral adherence and resistance accumulation is important for the design and evaluation of adherence interventions. Our objective was to explain heterogeneity observed in this relationship.

Methods: We first conducted a systematic review to locate published reports describing the relationship between adherence and resistance. We then used a validated computer simulation to simulate the patient populations in these reports, exploring the impact of changes in individual patient characteristics (age, CD4, viral load, prior antiretroviral experience) on the shape of the adherence–resistance (A–R) curve.

Results: The search identified 493 titles, of which 3 contained relevant primary data and 2 had sufficient follow-up for inclusion (HOMER and REACH cohorts). When simulating HOMER, the A–R curve had a high peak with a greatly increased hazard ratio (HR) of accumulating mutations at partial compared to complete adherence (simulation, HR 2.9; HOMER, HR 2.7). When simulating REACH, the A–R curve had a shallow peak with a slightly increased hazard of accumulating mutations at partial adherence (simulation, HR 1.2; REACH, HR 1.4). This heterogeneity was primarily attributable to differences in antiretroviral experience between the cohorts.

Conclusions: Our computer simulation was able to explain much of the heterogeneity in observed A–R curves.

Keywords: AIDS, HAART, effectiveness, efficacy

Introduction

Combination antiretroviral therapies have transformed HIV to a chronic disease, decreasing mortality rates from 3- to 10-fold.1,2 Because numerous studies have demonstrated that high levels of adherence to antiretroviral therapies are required in order for these therapies to be successful, promoting adherence has become one of the highest priorities in HIV care.3,4 It has been postulated that the relationship between adherence and mutation accumulation has an inverse-u shape (Figure 1),5,6 with minimal rates of mutation accumulation when adherence levels are very low (because selection pressures are low) or very high (because viral replication is suppressed), and a maximal rate of mutation accumulation when adherence levels are intermediate (because selection pressures accompany brisk viral replication).

Defining this relationship is important for informing the design and evaluation of adherence interventions. Whereas the short-term impact of adherence interventions can be estimated based upon known associations of adherence with virological and clinical outcomes,7 their long-term impact is more difficult...
Adherence and mutation accumulation

Figure 1. Hypothetical resistance–adherence curve.

Increasing adherence may change the rate at which drug-resistant virus emerges, which consequently may impact clinical outcomes in the long term.

Data describing the relationship of adherence to resistance have recently emerged, and although they broadly support the inverse-u hypothesis, their shapes differ substantially. Bangsberg et al. found a gently descending slope between the peak and the right side of the curve, with little difference in mutation accumulation between perfect adherence and commonly observed levels of adherence (70–90%), whereas Harrigan et al. found a steeply descending slope, with large differences in mutation accumulation. Furthermore, these differences occur across a heavily populated region of the curve, magnifying their clinical implications.

Because the factors which determine the shape of the A–R curve are important yet are not fully understood, we have used a previously validated computer simulation of adherence and resistance accumulation in HIV to explore why this curve may be shaped differently for different patient populations.

Methods

We first describe our literature review, and then how we used our computer simulation to explore what factors may have caused the variation in observed results.

Literature review

We conducted an electronic literature search using MEDLINE, starting from 1996 (when combination antiretroviral therapies first came into common use) and ending in March, 2005. Our search strategy required at least one of the following terms to identify adherence (text words adherence or compliance), at least one of the following terms to identify resistance (text words mutation, mutations, genotype, genotypic, phenotype, phenotypic and resistance; or subject headings mutation, genotype, phenotype and drug resistance including its viral subheadings), and at least one of the following terms to identify antiretroviral medications (text words antiretroviral therapy, combination therapy, HAART, or subject headings drug therapy, combination and antiretroviral therapy, highly active). Titles and abstracts were then manually reviewed, and manuscripts were obtained if they included primary data delineating an A–R curve that were based on prospective and longitudinal measurements of genotypic mutations, or if they included models that aimed to estimate these curves. Letters to the editor, comments, editorials and review articles were excluded during manual review of titles and abstracts. Research that was only published in abstract form was excluded. The search was not limited by language of publication, as all abstracts were available in English.

Computer simulation

We have developed a probabilistic simulation of the natural history of HIV disease in the current treatment era of combination antiretroviral therapies specifically designed to model HIV drug-resistance mutation accumulation by level of adherence. Our simulation generates HIV mutations at a rate proportional to viral replication, and models the accumulation of these mutations in the viral population based on the presence of selection pressure produced by antiretroviral drug regimens. It separately tracks the number of accumulated mutations that may confer resistance to each of the three constituent drug categories in antiretroviral therapy: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. It then uses this information to determine the likelihood of phenotypic resistance to combination therapies (Figure 2).

Each simulated patient proceeds through the model separately. The adherence that each of these events can occur is based on a random draw from a probability distribution that reflects the characteristics of the particular patient. For example, the overall probability of adhering to medications is a specified characteristic; however the adherence at any one particular time is probabilistic and therefore may vary greatly. Similarly, the observed viral load at any one particular time may vary greatly. Because each hypothetical patient may have a distinct clinical trajectory, the simulation can mirror the heterogeneity that is present in true populations.

This simulation has been calibrated by ensuring that it could reproduce Kaplan–Meier curves describing survival and the time to failure of rounds 1, 2 and 3 of combination antiretroviral therapy in a large multi-site observational cohort study, and has been validated by demonstrating that it could predict mortality for a separate clinical cohort and by verifying that the mutation accumulation and non-adherence rates producing the best model fit were well within the ranges of clinical observations. Additional details of the simulation are described elsewhere and in the Appendix [available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. It is important to emphasize that the model does not directly represent the relationship between adherence and resistance accumulation. Rather, it models directly the relationship of adherence to HAART efficacy, which, in turn, affects viral load and accumulated mutations. Therefore, A–R curves presented in this paper are ‘emergent properties’ of the model, and are not derived from direct statistical modelling of the relationship between adherence and resistance.

Cohorts simulated

Based on the results of our literature search, we simulated two cohorts with contrasting A–R curves, the HOMER and REACH cohorts (Table 1). The HOMER cohort consists of 1191 antiretroviral-naive individuals initiating antiretroviral therapy. Genotype testing was a prospectively defined outcome measure that was performed approximately four times per year on any individual with a detectable viral load. Adherence was estimated by identifying the ratio of filled-to-prescribed medication orders. Adherence–resistance (A–R) analyses in REACH cohort consists of 148 individuals without permanent housing, the majority of whom were antiretroviral experienced. Genotype testing was also a prospectively defined outcome measure, and was performed at least twice over an interval of at least 6 months. Adherence was estimated by study personnel, who interviewed enrollees on an unscheduled and unannounced basis, and conducted pill counts during the interview.
Viral replication

combination therapy, using values for age and CD4 count based on
experienced cohort of individuals who were starting a new round of
the patient population of REACH, we simulated an antiretroviral-
load and CD4 count based on that cohort (Table 2). To approximate
therapy, using baseline (pre-treatment) values for median age, viral
interactions and interrelated feedback loops, many components of which have
been calibrated from separate, unrelated studies. Unlike observational studies, the relationship between adherence and resistance
mutation accumulation, concordant with clinical observation. Therefore,
or who are not taking any antiretroviral drugs are likely to have low levels of
viral loads while taking antiretroviral drugs are likely to have high levels of
mutations to accumulate. For this reason, persons who have poorly suppressed
viral replication, but also directly impacts the selection pressure for new
Adherence, therefore, impacts not only the extent to which therapies reduce
resistance directly: the simulation models the relationship as the culmination
of a complex series of underlying relationships. At the start of the simulation,
patients may start with either the ‘wild-type’ HIV virus or may start with a
strain already containing mutations due to previous treatment experience or
through inoculation (infection) with a resistant strain. With each passing day,
the virus replicates based on a specific replication rate; the actual rate is
negatively affected by therapy (the more effective the therapy, the lower the
replication rate). As the virus replicates, mutations are randomly generated
through a combination of the mutation rate and replication rate: the higher the
mutation rate or the higher the replication rate, the more mutations are created.
However, all new mutations do not necessarily accumulate: selection pressure
determined by the medications being taken is required to produce accumulated
mutations above and beyond the baseline mutation rate. For those individuals
on treatment, the therapy will have an effectiveness given the current resistance pattern in the virus and the particular regimen the patient is taking.
Adherence, therefore, impacts not only the extent to which therapies reduce
viral replication, but also directly impacts the selection pressure for new
mutations to accumulate. For this reason, persons who have poorly suppressed viral loads while taking antiretroviral drugs are likely to have high levels of
mutation accumulation, whereas patients who have undetectable viral loads
or who are not taking any antiretroviral drugs are likely to have low levels of
mutation accumulation, concordant with clinical observation. Therefore,
unlike observational studies, the relationship between adherence and resistance
is an emergent property of the simulation: a result of a complex series of
interactions and interrelated feedback loops, many components of which have
been calibrated from separate, unrelated studies.

To approximate the HOMER cohort, we simulated an antiretroviral-naive cohort of individuals who were starting antiretroviral
therapy, using baseline (pre-treatment) values for median age, viral
load and CD4 count based on that cohort (Table 2). To approximate
the patient population of REACH, we simulated an antiretroviral-
experienced cohort of individuals who were starting a new round of
combination therapy, using values for age and CD4 count based on

Figure 2. Influence diagram of relationships between adherence and resistance
in the computer simulation. Observational studies such as HOMER and
REACH estimate the A–R relationship by measuring adherence and viral
resistance directly: the simulation models the relationship as the culmination
of a complex series of underlying relationships. At the start of the simulation,
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experienced cohort of individuals who were starting a new round of
combination therapy, using values for age and CD4 count based on

Table 2. Parameters in computer simulation

NA, not applicable because population is mostly treatment experienced.

Table 1. Characteristics of clinical populations

<table>
<thead>
<tr>
<th></th>
<th>HOMER</th>
<th>REACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1191</td>
<td>148</td>
</tr>
<tr>
<td>% Male</td>
<td>84.3%</td>
<td>85.1%</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>Median CD4 count (cells/mm³)</td>
<td>280</td>
<td>336</td>
</tr>
<tr>
<td>Pre-treatment viral load (copies/mL)</td>
<td>120 000</td>
<td>NA</td>
</tr>
<tr>
<td>Antiretroviral naive at baseline</td>
<td>100%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Regimen includes protease inhibitor</td>
<td>74.3%</td>
<td>61.5%</td>
</tr>
<tr>
<td>Overall adherence to antiretrovirals (%)</td>
<td>80%</td>
<td>64.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters in computer simulation</th>
<th>Simulating HOMER</th>
<th>Simulating REACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37³</td>
<td>43³</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>280³</td>
<td>336³</td>
</tr>
<tr>
<td>Pre-treatment viral load (copies/mL)</td>
<td>120 000³</td>
<td>120 000³</td>
</tr>
<tr>
<td>Resistance-associated mutations at baseline</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Log viral load decrement with complete adherence and no resistance</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Probability of new mutations per month with complete adherence and no resistanceb</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Probability that a resistance-associated mutation causes resistance</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Probability that NRTI mutation causes resistance to other NRTIs</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td>Probability that NNRTI mutation causes resistance to other NNRTIs</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Probability that PI mutation causes resistance to other PIs</td>
<td>0.43</td>
<td>0.43</td>
</tr>
</tbody>
</table>

NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

bBased on observed characteristics in clinical cohorts.
³This seldom occurred when simulating the REACH cohort due to extensive resistance at baseline.

Table 2. Parameters in computer simulation

Outcome measures

To summarize simulation results, we chose outcome measures that
resembled those used by the corresponding clinical cohort. When
simulating the HOMER cohort, we examined hazard ratios (HRs) for
mutation accumulation at each adherence stratum relative to the
accumulation rate in the highest adherence stratum, and we examined
the proportion of individuals having new resistance to any, ≥2 or
≥3 antiretroviral drug classes at the end of 1 year, irrespective of
Adherence and mutation accumulation

adherence. HOMER divided NRTI mutations into two separate groups (M184V versus other) whereas our simulation does not make this distinction. For this reason, our definitions for \( \geq 2 \) classes and \( \geq 3 \) classes do not correspond exactly.

We performed analyses both with and without an adjustment factor that compensated for pharmacy refill data’s overestimation of adherence (odds ratio for missed doses, actual adherence compared to pharmacy refill estimate, 3.0). This adjustment factor was based on two studies that compared the adherence estimated by pharmacy refill or other medication inventories with a more resource-intensive but precise method of measuring medication doses based on recording whether pill bottles were opened at the appropriate times (Medication Event Monitoring System, or ‘MEMs caps’). Choo et al. \textsuperscript{13} compared MEMs caps with pharmacy refill measurements among 286 patients receiving antiretroviral therapy, and the corresponding odds ratio for non-adherence according to MEMs caps versus medication inventories was 3.1. Liu et al. \textsuperscript{14} compared MEMs caps with clinic-based pill inventories among 108 HIV-infected adults receiving protease inhibitors, and found that the odds ratio for non-adherence according to MEMs caps versus medication inventories was 2.9.

When simulating the REACH cohort, we examined the mean number of new mutations in each adherence stratum. Because strata were defined on the basis of quintiles, we chose to simulate adherence levels that corresponded to the midpoint of each adherence quintile. As REACH measured adherence in the context of unscheduled and unanticipated interviews, overestimation of adherence was less likely, and we did not use the adjustment factor.

We tested the goodness of fit between A–R relationships reported by each study and A–R relationships specified by the corresponding simulation runs using the \( \chi^2 \) goodness-of-fit statistic.

Sensitivity analyses

We performed analyses to determine how our results would vary with different assumptions regarding patient and treatment characteristics.

Patient characteristics. To determine whether differences in clinical characteristics would impact our results, we varied age, viral load, CD4 counts and extent of antiretroviral experience (as indicated by numbers of resistant mutations at baseline) across clinically plausible ranges, and examined the effect of these changes on the overall risks of accumulating mutations and on the shapes of the A–R curves.

Treatment characteristics. We also varied assumptions regarding the relationship between adherence to antiretroviral therapy and viral load suppression, alternatively assuming a relationship that may be typical of NNRTI-based regimens \textsuperscript{14} (low levels of adherence producing little or no viral load suppression and moderate levels of adherence producing complete viral load suppression) and a relationship that may be typical of unboosted protease inhibitor-based regimens (viral load suppression incomplete even at high levels of adherence). Our baseline assumption regarding this relationship, a linear correlation between adherence and the logarithm of viral load suppression, was that which was most consistent with the simulation’s previous calibration and validation. \textsuperscript{15}

Results

We first conducted a literature review for studies that might further elucidate the characteristics of A–R curves. We then used a validated computer simulation of adherence and resistance accumulation in HIV to explore how the shape of this curve would vary with differing patient characteristics, and a preliminary exploration of how it would vary with different antiretroviral regimens.

Literature review

The electronic search identified 493 titles, of which 8 met our inclusion criteria during manual review. \textsuperscript{6,8,9,15–19} Of these 8 articles, 3 contained primary data that allowed construction of an A–R curve. \textsuperscript{8,9,15} 2 had additional primary data but with insufficient detail to allow construction of an A–R curve \textsuperscript{6,17} and 3 employed statistical or mathematical modelling to gain insights about the A–R curve. \textsuperscript{6,18,19} Of the three articles that constructed A–R curves from primary data, one (Hopkins) \textsuperscript{13} estimated adherence over a brief timeframe (3 days), whereas two (HOMER and REACH) \textsuperscript{6,18} estimated adherence over the duration of the study. HOMER studied an antiretroviral-naive cohort and used pharmacy refill data to estimate adherence, whereas REACH studied an antiretroviral-experienced cohort and employed unannounced pill counts to estimate adherence. The HOMER and REACH groups had contrasting A–R curves, with the HOMER cohort finding a steep descent in mutation accumulation rates between commonly observed levels of adherence and complete adherence, and the REACH cohort finding only a slight descent. The A–R curve constructed from Hopkins data was more similar in shape to the HOMER curve than to the REACH curve. Because its estimations of adherence were based on very brief patient-reported timeframes (3 days) and very few individuals reported <60% adherence, which suggests that underreporting may have been frequent, we decided to focus our simulations on the HOMER and REACH cohorts.

Of the three modelling papers, two were published by the group of REACH investigators \textsuperscript{6,18} and used statistical methods to explore the impact on the A–R curve of the type of antiretroviral therapy and the assumed probability of viral load suppression with complete adherence. These papers concluded that the A–R curve would have a more prominent peak if individuals were on a regimen with greater likelihood of viral load suppression with perfect adherence. The third modelling paper was performed before any clinical data were available, \textsuperscript{15} and its predictions were sufficiently discordant from subsequent clinical results that it will not be described further (>60% adherence would prevent any mutations from accumulating).

Computer simulation

Because our model allows us to define the simulated population by specifying a wide range of characteristics such as age and CD4 count, we were able to simulate an antiretroviral-naive cohort with characteristics similar to HOMER cohort as well as an antiretroviral-experienced cohort with summary characteristics similar to the REACH cohort.

Mutation accumulation rate. The simulation was able to closely reproduce the overall mutation accumulation rates of each cohort. In HOMER, 17%, 6% and 1% of individuals had new mutations to any, 2 or more and 3 or more drug classes at the end of 1 year, respectively. The corresponding estimates for the simulation were 21%, 6% and 1%, respectively. HOMER did not analyse the mean number of mutations accumulated per year; the simulation estimated this value to be 0.28 mutations per year.

REACH did not stratify mutation accumulation by number of drug classes; however the simulation estimated that 58%, 27% and
11% of hypothetical individuals with characteristics similar to the REACH cohort would have new mutations to 1, 2 and 3 or more drug classes at the end of 1 year. REACH determined that the mean accumulation rate was 0.96 mutations per year. The corresponding estimate from the simulation was 1.00 mutations per year.

**Adherence–resistance curve.** The simulation was able to reproduce a large amount of the variation in A–R curves between these two cohorts, estimating mutation accumulation rates that were often within the confidence intervals of the HOMER cohort (Figure 3), and were always within the confidence intervals of clinical observations in the REACH cohort (Figure 4). In particular, when the simulation reproduced the HOMER cohort, the A–R curve had a high amplitude peak with a greatly increased hazard of accumulating mutations with partial adherence compared with the highest adherence category (simulation, HR 2.91; HOMER, HR 2.73). Without adjusting for the tendency of pharmacy refill data to overestimate adherence, the simulation curve was shifted leftward compared with the clinical cohort curve, with the maximum risk of mutation accumulation occurring at ~60% adherence rather than at ~85% adherence. However, after adjusting for this overestimation, this shift was no longer substantial, with both peaks occurring in the range of 60–70%, and the two curves were not statistically distinguishable ($P = 0.84$).

In contrast, when the simulation reproduced the REACH cohort, the A–R curve had a low amplitude peak, with only a small increased hazard of accumulating mutations with partial adherence compared with the highest adherence category (simulation, HR 1.15; REACH, HR 1.42). There was no apparent shift of the simulation curve compared with the clinical cohort curve, with the maximum risk of mutation accumulation occurring at ~80% adherence for both curves. The two curves were not statistically distinguishable ($P = 0.99$).

**Variation of A–R curve with prior antiretroviral exposure.** Prior antiretroviral exposure impacts HIV outcomes by leading to genotypic mutations. We explored how the shape of the A–R curve varies with increasing antiretroviral exposure by increasing the number of genotypic mutations at the start of the simulation, and holding all other patient characteristics constant (Figure 5). When a cohort starts with no genotypic mutations (corresponding

![Figure 3. Comparison of simulated and observed adherence–resistance curves for the HOMER cohort. When adherence data are not adjusted for the overestimation of adherence by pharmacy refill (upper panel), the simulated curve appears to be shifted to the left. However, after adjustment, the simulated curve (lower panel) no longer appears shifted. Both simulated and observed curves corresponding to the HOMER cohort have high peaks, with substantially greater mutation accumulation at partial adherence compared to full adherence.](image-url)
to a fully antiretroviral-naive population), the curve has a high amplitude peak and then a relatively steep downward slope over commonly observed adherence levels, and the overall rates of mutation accumulation are low. Therefore, its characteristics generally resemble those from the HOMER cohort. Prior antiretroviral exposure and pre-existing drug resistance lead to a lower amplitude peak and a more shallow downward slope over commonly observed adherence levels. The net effect suggests greater population levels of drug resistance, and resembles the A–R characteristics from the REACH cohort.

Variation of A–R curve with other patient characteristics. Other patient characteristics had a much smaller impact on the A–R curve. Variations in age and CD4 count did not change its shape appreciably. However, baseline viral load had a significant impact on its magnitude, with higher viral loads amplifying the peak of the curve. When we assumed that an antiretroviral-naive population started the simulation with a low baseline viral load (10 000 copies/mL), the peak mutation accumulation rate (0.132 mutations per year) was only 1.6 times as large as the rate with complete adherence (0.085 mutations per year). In contrast, when we assumed that an antiretroviral-naive population started with a high baseline viral load (1 000 000 copies/mL), the peak accumulation rate (0.533 mutations per year) was 4.4 times as large as rate with complete adherence (0.120 mutations per year).
Another important factor influencing the shape of the A–R curve was the presumed relationship of adherence to viral load suppression. For our base case analyses, we assumed that adherence had a linear relationship with the logarithm of viral load suppression, as this assumption was most compatible with our previous calibration and validation of the simulation. However, we also explored the impact of two contrasting but plausible alternative forms for this relationship, based on previously observed variations with the type of antiretroviral regimen. When we assumed that low levels of adherence produced little or no viral load suppression and moderate levels of adherence were sufficient to produce complete viral load suppression, as may be typical of NNRTI-based antiretroviral regimens, the peak of the A–R curve shifted to the left, moving from ~60% adherence to ~40% adherence. When we assumed that viral load suppression was not complete even at high levels of adherence, as may be typical of unboosted protease inhibitor-based antiretroviral regimens, the peak of the A–R curve shifted to the right, moving from ~60% adherence to ~80% adherence.

Discussion

We used a previously validated computer simulation of HIV disease to gain insights about which factors lead to the variation in A–R curves that has been observed clinically. We were able to replicate many of the contrasting features of the A–R curves between populations by varying the level of exposure to prior antiretroviral therapy.

For antiretroviral-naive individuals, simulated and observed results both suggest that the likelihood of accumulating new mutations will increase sharply with even small departures from perfect adherence, with a rise to 1.9 times higher for individuals with 90% adherence and to 2.4 times higher for individuals with 80% adherence. Indeed, the maximum likelihoods of accumulating mutations occur at some of the most commonly observed adherence rates (60–80%). This implies that many antiretroviral-naive individuals may benefit substantially from adherence interventions not only because of the short-term benefit that accrues from greater viral load suppression, but also because a long-term benefit would accrue due to preservation of future drug options. Therefore adherence interventions may be particularly effective at preventing drug resistance over this range of adherence. In contrast, for antiretroviral-experienced individuals, simulated and observed results both suggest that the likelihood of accumulating new mutations will increase only slightly with small departures from perfect adherence. Therefore, the main benefit of adherence interventions in this group may stem from the short-term gain of greater viral load suppression, rather than the long-term gain of preserving future drug options.

There are plausible biological reasons for why the A–R relationship should vary with prior antiretroviral exposure. Pre-existing mutations confer partial resistance to combination therapies, and therefore viral replication continues at a brisk pace even if adherence is perfect. Because this replication occurs under circumstances of great selection pressure, mutations will accrue rapidly even with perfect adherence. In contrast, if there is no resistance at baseline, perfect adherence will strongly suppress viral replication, so even though selection pressures are strong, mutations will accrue slowly.

Our results expand upon but are broadly consistent with other models of adherence and resistance among individuals with HIV. Bangsberg et al.14 used statistical modelling to explore varying assumptions about how effectively antiretroviral therapy would suppress viral load with complete adherence. They found that if suppression was assumed to be rare, the A–R curve would rise monotonically and lose its inverse-u shape, whereas if suppression was assumed to be guaranteed, the curve would have a nearly symmetric inverse-u shape with steep ascending and descending slopes. Our simulation produced similar changes when we varied the amount of antiretroviral experience, a major determinant of viral load suppression with complete adherence. Kagay et al.20 estimated the cost-effectiveness of directly observed therapy (DOT), and estimated that it would be ineffective at preventing resistance because many individuals were on the ascending slope of the A–R curve. In our simulation, comparably adherent individuals would not benefit from DOT unless the effect size was extremely large. Bangsberg et al.14 modelled the impact of different types of antiretroviral regimens on the A–R curve, and found that NNRTI-based regimens were associated with a leftward shift of the peak of the A–R curve, also consistent with our results. Lastly, a manuscript that was published after we performed our systematic review, King et al.,21 described the relationship between mutation accumulation and adherence in 653 antiretroviral naive HIV patients. They also found that the A–R curve had a high amplitude peak in naive patients, with a greatly increased risk of accumulating mutations at partial compared with complete adherence.

Our work has important limitations. Adherence is characterized only by the proportion of doses consumed, and pattern of non-adherence is not considered even though adherence pattern may be an important modulator of the A–R curve. Modelling was based on unboosted protease inhibitor regimens rather than the boosted protease inhibitor regimens that have largely replaced them and that may protect from the emergence of drug-resistance mutations more effectively. Treatment experience is only likely to explain variance in the A–R curve if there is cross-resistance between HAART regimens; if newer HAART regimens were developed with entirely distinct resistance patterns, our results would no longer be generalizable. Finally, although we explored many possible factors that may account for the heterogeneity in clinical data, it is always possible that unexamined factors may have played an important role. However, this analysis has the unique strength of being based on a simulation that has been extensively validated,10,11 and that was able to estimate overall mutation accumulation rates from cohorts with greatly differing characteristics.

In summary, we have used a validated computer simulation of mutation accumulation in HIV disease to replicate the differences in A–R curves that have been observed clinically. Because current clinical data on A–R curves is limited to very few sources, future research is needed to define these curves in additional populations, as well as the degree of virological and clinical benefit of effective adherence interventions.

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Adherence and mutation accumulation

Transparency declarations

Drs R. S. B., S. S., M. S. R., A. S. and A. C. J. have none to declare. Dr D. R. B. has received honoraria from Abbott, Pfizer and GlaxoSmithKline as well as grants from Abbott and Pfizer. Dr P. R. H. has worked in the pharmaceutical industry (Glaxo Wellcome) and HIV diagnostic industries (Virco). He has received fees for consulting, honoraria, owned stock, acted as a consultant and received grants from a range of companies including Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Roche, Northern Lipids, Merck, Pfizer and Virco.

Supplementary data

The Appendix is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References