The economic impact of non-adherence

Microsimulation modelling for HIV/AIDS in NZ

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Abstract

Failing to adhere to medical treatment programmes has significant impacts for patients and the economy. For patients, these impacts include reduced longevity and quality of life. For the economy, these impacts affect hospitalisation and treatment (medication) costs.

We developed a New Zealand-specific microsimulation model to estimate these impacts. Initial estimates of the impact of non-adherence to HIV/AIDS treatment to 2060 are increased hospitalisation costs of $8.2 million and 6,400 lost QALYs. Full adherence would imply $169 million in increased treatment costs.

**JEL Codes**: I10, C63

**Keywords**: Health, non-adherence, microsimulation
1. Introduction

A person who fails to follow the instructions for their medication is said to be non-adhering to their treatment programme. Non-adherence can result in earlier death as well as worse quality of life. There are also health care costs associated with non-adherence, such as more frequent hospitalisation events.

International studies suggest that these costs can be significant. Based on a review of seven studies of antipsychotic non-adherence, Sun et al (2007) estimated that the related hospitalisation costs from that non-adherence in the United States was US$1,479 million in 2005. Higgins et al (2009) found that total cost of care was 12.5 per cent lower for adhering patients than those than were non-adherent. The New England Healthcare Institute (NEHI, 2009) estimated that the cost of Drug-Related Problems (DRPs) in the United States was US$289 billion in 2008.

We are interested in developing an appropriate model to assess these impacts for New Zealand. This paper sets out the process followed to develop a New Zealand based microsimulation model (Adhealth), presents the costs associated with non-adherence for the HIV/AIDS disease, and discusses further research steps.

The following section sets out the findings from our literature review. The third section discusses the development of the Adhealth microsimulation model. Further sections outline the modelling approach, and estimates of the economic value of non-adherence to HIV/AIDS in New Zealand. We conclude by discussing the results and future research opportunities for the Adhealth model.

2. Literature review

A large body of international literature focuses on non-adherence to medication and other regimens prescribed to control diseases. The main points from the literature are:

- variation in the measurement of non-adherence and research methodologies means that further work is required to compare studies
- the barriers to adherence relate to the patient, the health care system and the condition
- some chronic illnesses have significant problems with adherence, for example, hypertension, diabetes, hyperlipidemia, asthma, HIV, and mental health
- while some studies consider the economic costs of non-adherence, most ignore the social costs

We have undertaken this literature review to get a general sense of the current understanding of non-adherence behaviour, and to investigate what data would be available for analytical research. This review summarises what is known about non-adherence. It also indicates where data is available and where it may be missing.

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1 Although the focus of the research brief is 'poor adherence', the quantitative estimate encompasses much more. From the appendix to the brief, 'Appendix I: Estimated Cost of Poor Adherence', the DRPs included: untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs, overdosage, adverse drug events, drug interactions, and drug use without indication.
2.1 Variation across studies means that comparing results requires some effort

Studies tend to adopt different measurements for adherence, which makes it challenging to compare research results. For example, some research measures adherence based on pill counts that measure the total amount of medication taken, while other research also considers the timing for taking prescribed medicine. This difference in assessment criteria can change the measured rate of non-adherence (Miravitlles et al., 2009). If a patient takes the right amount of medication at the wrong time, a study using pill counts as the only assessment criterion will record a higher adherence rating, while a study that takes timing into account will produce a lower rating. The different criteria across studies may result in some research finding an improvement in adherence after an intervention while another would find no improvement. Another key difference is whether a study includes dietary and lifestyle regimens as an assessment criterion (Patel & David, 2007).

The instrument for measuring adherence also differs across studies. Some studies use surveys or self-reporting to gather data. Other studies use more advanced electronic recording or the record from pharmacy databases to collect adherence data (Turchin, Kolatkar, Pendergrass, & Kohane, 2007). Differences in methods make it hard to compare results across studies and assess their success based on a common benchmark.

In a review article, Vermeire, Hearnshaw, Van Royen, & Denekens (2001) describe this variability:

The enormous amount of quantitative research undertaken is of variable methodological quality, with no gold standard for the measurement of compliance and it is often not clear which type of non-compliance is being studied. Many authors do not even feel the need to define adherence.

Working with the literature to systematise the descriptions and measurements is therefore not a trivial task. It is necessary, however, in order to develop a robust and consistent measure of the size of the non-adherence problem globally.

2.2 Causes of non-adherence are mostly psychological and sociological, rather than economic

Understanding the nature and determinants of non-adherence plays an important part in designing policy interventions that minimise the negative impact of non-adherence on individual health and social costs.

International literature suggests that the most important barriers to adherence are psychological and sociological factors rather than economic (Brown, Rehmus, & Kimball, 2006). The main barriers to adherence can be categorized as patient factors, health care

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2 This is an advanced and costly way of recording adherence. It records not only a patient's frequency of taking medicine but also the timing. It is done by an electronic meter attached to the pill box, which records the time and frequency when a patient opens the pill box.

3 This method assesses a patient's adherence by comparing his prescription record at the doctor's with the record from the pharmacy. However, the drawback of this method is that there is no way to know if the patient actually has taken the medicine, at the recommended frequency and time.

4 This literature tends to focus on developed economies. There is very little work on non-adherence in developing countries. The WHO (2003) stated, 'The magnitude and impact of poor adherence in developing countries is assumed to be even higher given the paucity of health resources and inequities in access to health care' (emphasis added). Later, the report discussed the two-way
system and provider factors, and condition related factors (Gellad, Grenard, & McGlynn, 2009).

Interventions designed to minimise non-adherence have mostly been proven effective, although evidence also suggests that interventions should be tailored to specific types of non-adherence to achieve the best outcome (Horne & Weinman, 2005). These factors and how they could impact on a patient’s adherence, as well as the possible interventions, are summarized in Table 1.

### Table 1 Main barriers to adherence and corresponding interventions

<table>
<thead>
<tr>
<th>Main barrier categories</th>
<th>Description of the barrier</th>
<th>Possible interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td>Disbelief in diagnosis and prescription</td>
<td>Develop, improve and disseminate self-management guidelines</td>
</tr>
<tr>
<td></td>
<td>Lack of knowledge, motivation and self-efficacy</td>
<td>Provide evidence of successful treatment</td>
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<td></td>
<td>Anxieties about possible adverse effects</td>
<td>Activate the patient and their community to build motivation</td>
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<td></td>
<td>Lack of support for behavioural change</td>
<td>Enhance health professionals’ role in providing information, promoting optimism and</td>
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<tr>
<td></td>
<td>Hopelessness and negative feelings</td>
<td>encouraging maintenance of health behaviours</td>
</tr>
<tr>
<td>Health care and provider system factors</td>
<td>Inadequate or non-existent reimbursement by health insurance plans</td>
<td>Health insurance system reform to ensure the affordability of essential medication</td>
</tr>
<tr>
<td></td>
<td>Ineffective cost-sharing system</td>
<td>while effectively preventing moral hazard from unnecessary doctor visits or prescriptions</td>
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<tr>
<td></td>
<td>Short consultation and over-worked health professionals</td>
<td>Tailored intervention to the particular illness-related and socio-economic demand</td>
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<tr>
<td></td>
<td>Weak capacity to educate patients and provide follow-up</td>
<td>Adherence management training for health professionals</td>
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<td></td>
<td>Inability to establish community support</td>
<td>Assessment tools such as patient interviews for adherence</td>
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<tr>
<td></td>
<td>Prior-authorization requirement and benefit caps</td>
<td></td>
</tr>
<tr>
<td>Condition and therapy related factors</td>
<td>Diagnosis specific non-adherence such as forgetfulness caused by depression</td>
<td>Tailored intervention to the needs of the patient of particular condition and therapy</td>
</tr>
<tr>
<td></td>
<td>Non-adherence caused by the complexity of the medical regimen, duration of treatment,</td>
<td>Special reminder pill packaging and prescription reminder</td>
</tr>
<tr>
<td></td>
<td>or frequent change in treatment</td>
<td>Provision of effective follow-up consultations and work with the patient's community</td>
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<tr>
<td></td>
<td></td>
<td>and carer if necessary</td>
</tr>
</tbody>
</table>

Source: NZIER, WHO (2003), Gellad et al. (2009)
Literature on adherence tends to focus on social factors rather than economic ones (Lamiraud & Moatti, 2006). For developed countries, most of the economic literature on the barriers to adherence relates to the cost-sharing system. Research by Gellad et al. (2009) found that increased cost-sharing for medication is associated with lower rates of initiation of prescriptions, poor adherence among users, and more frequent discontinuation of medication.

2.3 Studies on non-adherence focus on a number of chronic medical conditions

International literature on non-adherence focuses on a number of chronic medical conditions (Ingersoll & Cohen, 2008). These chronic illnesses include hypertension, diabetes, hyperlipidemia, asthma, HIV, and mental health. These are widespread, chronic diseases with high on-going costs. Studies show each disease has a unique characteristics and no universal intervention suits them all (Vermeire et al., 2001). Therefore, any assessment of the impact of non-adherence and the effectiveness of the interventions should also differentiate across diseases.

This section reviews the kind of information that is available for specific diseases. Data on adherence rates, their impacts on treatment outcomes, and possible treatments are available from the literature. Modelling would tend to follow the available data. Other diseases have not been studied as extensively, so estimates will be more difficult to produce.

Asthma

Research worldwide has documented poor adherence to treatment for asthma. Evidence showed that adherence rates for the regular taking of preventive therapies were as low as 28 percent in developed countries (Vermeire et al., 2001). The total cost of asthma as a single condition comprised up to one to two percent of health care expenditures in developed countries. Unscheduled acute care, indicating poor adherence, contributed to half of this expense (World Health Organization, 2003).

Hypertension

Research by WHO showed that poor adherence to therapy contributes to lack of good blood pressure control in more than two-thirds of people living with hypertension. Erhardt and Mourad (2008) estimates that non-adhering hypertensive patients have heightened risk of severe complications of 158 per cent over existing incidence rates for age, gender, and ethnicity, and 181 per cent heightened mortality risk over existing mortality rates for age, gender, and ethnicity.

Diabetes

WHO research showed health expenditure on type 2 diabetes contributed on average five percent of total health expenditure among the countries studies in the United States. Less than two percent of adults with diabetes performed the full level of care that had been recommended by the American Diabetes Association. Thus, the cost of non-adherence is likely to be substantial.

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Adherence rate is measured by the percentage of prescribed medications taken, serum theophylline levels, days of medications adherence, and percentage of patients who failed to reach a clinically estimated adherence minimum according to WHO.
Hyperlipidemia

Studies showed patients with hyperlipidemia had barriers to adherence to dietary recommendations and prescription requirements (Horne & Weinman, 2005). The non-adherence of prescription requirements is especially prevalent among elderly patients due to forgetfulness (Balkrishnan, 1998).

HIV

There is research designed to examine the factors associated with adherence to highly active antiretroviral therapy (HAART) in patients with HIV diseases. Research reported barriers including non-adherence to recommended medication and lifestyle (Vermeire et al., 2001).

Mental health

The research by WHO (2003) has identified depression as the type of mental illness that has the lowest levels of adherence. Studies showed that patients with depression had a significantly higher likelihood of non-adherence with all treatments, including diet, exercise and medications. Adherence was found to be negatively associated with the severity of depression symptoms, duration of illness and perceived risk of medication (Gellad et al. 2009).

2.4 Some economic costs are quantified, but social costs are not

Estimates of costs and outcomes are often expressed in hospitalization costs (Sun, Liu, Christensen, & Fu, 2007) or even the narrower term ‘hospital costs’, which does not include medical costs that happen outside hospital, such as ambulatory care and nursing home care (Higgins, Rubin, Kaulback, Schoenfield, & Kane, 2009). This often results in an underestimate of the true cost of non-adherence and its impact on society. To fully understand the impact of non-adherence and the benefit of adherence with proper intervention, it is appropriate to estimate the full cost of non-adherence. This may include:

- **Direct costs:**
  - **hospital costs:** health care and medicine costs that occurred due to increased morbidity and hospital visits as a result of non-adherence to medical instructions and recommendations (Cleemput, Kesteloot, & De Geest, 2002)
  - **hospital related costs:** costs outside the hospital setting that are caused by non-adherence, such as ambulatory care costs, nursing home care costs, laboratory tests costs, etc. (Salas, D. Hughes, Zuluaga, Vardeva, & Lebmeier, 2009).

- **Indirect costs:**
  - **productivity costs:** the costs incurred by the patient and society because of lost or impaired ability to work or engage in leisure activities due to morbidity and lost economic productivity due to early death (Elliott, Shinogle, Peele, Bhosle, & D. A. Hughes, 2008)
  - **social welfare costs:** costs to the social welfare system (e.g., Invalid’s Benefit) given an individual’s inability to work
- **personal costs**: costs to the patient due to loss of health and subsequent loss of income as a result of non-adherence (Schoenwetter, Dupclay, Appajosyula, Botteman, & Pashos, 2004)
- **costs to the patient’s family and friends**: costs to family members and other associates, such as time associated with caring for the patient
- **other associated costs**: all other negative externalities not covered above. For example, non-adherence with infectious diseases may cause public health problems if other patients are infected (Smith, Pagel, Utley, & Gallivan, 2008).

The estimate of indirect costs of non-adherence is currently a gap in the literature. It needs to be filled to assess the true impact of non-adherence and determine the scope of intervention. These costs can be measured in monetary terms (Cantrell, Eaddy, Shah, Regan, & Sokol, 2006) or utility terms, such as the Quality Adjusted Life Years (QALYs) gained (Cleemput et al., 2002).

Finally, another economic concern that needs further consideration is whether interventions are cost-effective. Certainly, many interventions have been shown to improve adherence. However, the benefits of increased adherence do not appear to have been sufficiently quantified to generate cost-efficacy or cost-efficiency estimates. Further analytical or modelling work is necessary to produce these estimates.
3. Developing Adhealth

Vermeire et al. (2001) pointed out a key deficiency in the adherence literature:

*Often absent in the research on compliance is the patient, although the concordance model points at the importance of the patient’s agreement and harmony in the doctor-patient relationship. The backbone of the concordance model is the patient as a decision maker....*

Our review of the non-adherence literature suggests that the individual is central to the issue. It is the individual who has a condition, the individual who is prescribed some set of medications, and the individual who adheres or not to the prescribed regimens. We therefore use an analytical method – microsimulation – centred on individuals to estimate the economic value of non-adherence and interventions to improve it. In the next sections we go into detail about microsimulation modelling and how it can and is being applied to health analysis, and in particular, non-adherence analysis.

3.1 Microsimulation

3.1.1 Background

Microsimulation is an advanced modelling technique that performs highly detailed analysis at the individual or ‘micro’ level. Rather than using simple population averages, a microsimulation model contains a large number of synthetic ‘people’, called agents. These agents use information, make decisions, experience consequences, and ultimately serve as a basis for measuring impacts. The results from the overall model are based on or calibrated to known population-level outcomes.

3.1.2 Microsimulation and health

Microsimulation is widely used in health care policy analysis. Agents make decisions such as whether to drink, smoke etc., or in this case, whether to adhere, or not, to medical treatment. They may experience negative health outcomes and disease. A microsimulation model uses information from a wide variety of sources to put probabilities on these life events. The impact of adherence on probability of a negative health outcome can then be modelled across the entire heterogeneous population.

The most prominent user of microsimulation in policy analysis is Statistics Canada, who over 20 years have developed a range of health-related microsimulation models. These models include risk factor exposures (such as drinking and smoking), health outcomes and the demographic characteristics of the Canadian population. Some examples are:

- Population Health model (POHEM) focuses on risk attributes and associated chronic diseases such as cancer and asthma
- cancer risk management model is a specific cancer model that can evaluate various cancer control strategies such as prevention, screening and treatment for lung and colorectal cancer
- physical activity model was jointly developed with the Public Health Agency of Canada to investigate how physical activity impacts on life course health outcomes
neurological disease model projects the incidence and prevalence of neurological conditions, and computes the direct treatment costs and indirect wage and tax costs.

3.1.3 Microsimulation and non-adherence

Non-adherence adds a decision or probability tree between treatment and outcome. Because the decision is at the individual level, this concords with the microsimulation framework. We have found a few examples where researchers have started to use microsimulation in just the last two years. Examples of health care policy analysis that have either included or focused on non-adherence include:

- Hiligsmann, Rabenda, Bruycre, and Reginster (2010) used a microsimulation model to investigate the clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients
- Broder, Chang, Bentley, Juday, & Uy (2011) investigated the cost effectiveness of atazanavir-ritonavir versus lopinavir-ritonavir interventions in HIV-infected patients, and specifically split out adherence rates
- Knudsen et al. (2010) analysed cost-effectiveness of computed tomographic colonography screening, and computed sensitivity testing for various levels of adherence.

In our review of the literature, we found no examples of microsimulation being used to assess multiple diseases, or to estimate national-level non-adherence impacts.

3.2 NZIER adherence health microsimulation model

The NZIER adherence health (Adhealth) microsimulation model is based on the Statistics Canada POHEM model. It is developed and computed within the Statistics Canada Modgen microsimulation software. Adhealth is a continuous, case-based dynamic microsimulation model. It is calibrated to the Statistics New Zealand medium term population projections. Adhealth models four diseases within the wider New Zealand population. This paper focuses on HIV/AIDS.6

3.3 Modelling adherence

3.3.1 Adherence as a dichotomous variable

We use a dichotomous variable for adherence. An agent adheres, or not. The status of adherence changes the relative risks of severe episodes of disease and mortality.

Both compliance and persistence data provide overlapping information about adherence. Compliance tells us the average level of adherence. Persistence tells us the proportion of patients adhering at a given time.

3.3.2 Adherence probability curves

We use compliance and persistence data to develop adherence probability curves (APCs). The APC shows the probability of adherence over time from first point of treatment. We

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6 The remaining diseases are hypertension/cardiovascular disease, cancer (breast and colorectal), and depression (bipolar disorder and major depressive disorder).
use a standard Weibull survivorship curve so that we can define the APC \( A(t) \) simply by two parameters, \( \lambda \) and \( \beta \), according to the following:

\[
A(t) = e^{(-\lambda t)^\beta}
\]

The APC is used as input into the model (via \( \lambda \) and \( \beta \)). It determines the duration of adherence for each agent.

Data limitations mean that we typically do not have perfect information about compliance and persistence. We apply the available information where possible. Any gaps are filled by assumptions which are based on expert opinion and the literature.

### 3.4 Key output metrics

Our key output metrics for the analysis of the impact of non-adherence are health care costs, deaths and quality-adjusted life years (QALYs). For each disease we also consider prevalence and incidence rates where appropriate.

#### 3.4.1 Costs

Non-adherence impacts health care costs in a number of ways. We consider impacts on:

- treatment costs – the changes in the costs of treating the disease due to non-adherence
- hospitalisation costs – the changes in hospitalisation costs of non-adherence. In the case of AIDS we consider hospitalisation events that are due to opportunistic diseases.

Both metrics can be calculated annually, for a given year, or across a number of years e.g. from 2012 to 2060.

We report 2012 results and long term impacts which are the net present value of the costs from 2012-2060. We use a rate of 3.5% based on the United Kingdom social discount rates used by the National Institute for Health and Clinical Excellence (2011).

There are other health care costs that we have not considered in the analysis due to insufficient data. We have focused on hospitalisation costs as these are the most costly events. NEHI (2009) estimate that hospitalisation cost savings account for about 70% of total health care cost savings available from adherence.

#### 3.4.2 Deaths and quality-adjusted life years

Non-adherence reduces longevity and quality of life. We measure this through two ways:

- deaths – change in the number of deaths across the entire population due to non-adherence
- quality adjusted life years (QALYs) – the change in the number of QALYs across the entire population due to non-adherence. A count of deaths or life years lost does not provide any indication of any losses in quality-of-life due to non-adherence. QALYs calculate the amount of time in a particular health state, and multiply it by the quality of life during that time. One year lived at full health is 1 QALY.

Both metrics can be calculated annually, for a given year, or across a number of years e.g. from 2012 to 2060. When summing over a number of years, it is typical to discount the QALYs.

We report 2012 results, and long term impacts which are the net present value of the costs from 2012-2060. We use a rate of 3.5% as per above.
4. Modelling HIV/AIDS adherence in NZ

To develop a model for HIV/AIDS, we first consider:

- background epidemiology. This summarises how HIV/AIDS transitions from mild to severe states over time, and if remission between states is possible
- New Zealand context. This details the current situation of HIV/AIDS within New Zealand, such as prevalence rates and treatments.

We then develop a modelling approach to represent a simplified version of HIV/AIDS epidemiology. The key data we used to parameterise HIV/AIDS are:

- incidence. The number of new cases of HIV/AIDS each year
- adherence probability curves, as described earlier
- impact of non-adherence risk ratios. The relative risk ratio parameter determines the impact of non-adherence on the progression of severity of HIV/AIDS – from HIV to AIDS to death. Because it is a critical parameter for determining the overall impact of non-adherence, we consider a sensitivity that alters the relative risk associated with the impact of non-adherence by ±20%
- quality-of-life weightings. The benefits from adherence in HIV/AIDS are an increase in life expectancy which we will capture through QALY values. The QALY values are calculated based on a disability weighting for each state of each disease. These disability weights reflect the severity of the disease across a range from 0 (completely healthy) to 1 (deceased)\(^7\)
- hospitalisation and treatment costs. In the baseline, we assume no change to hospitalisation or treatment costs over time. We consider a sensitivity that linearly alters the hospitalisation and treatment costs so that they reach ±20% of today’s value in 2060. The worst case scenario for this sensitivity is if hospitalisation costs are low and treatment costs are high. The best case scenario for this sensitivity is if hospitalisation costs are high and treatment costs are low.

4.1 Background epidemiology

HIV is a disease that attacks the immune system making an infected person more susceptible to other diseases and infections. There is no cure for HIV, but patients can survive for up to 38 years after infection if on-going treatment is maintained.\(^8\)

Body Positive (2010) summarises the progression of HIV through four stages. First, when a person is first infected they may experience a flu-like illness which may be accompanied by a rash. This illness is known as a ‘seroconversion illness’, but not all infections present with this illness.

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\(^7\) We calculate Quality of life (Q) weightings from WHO disability weightings (D) according to the formula \(Q = 1 - D\). This is a standard approach as per Sassi (2006).

\(^8\) Collaborative Group on AIDS incubation and HIV survival including the CASCADE EU concerted action (2000) and (Bangsberg et al., 2001) suggests that adhering to HIV treatment can increase lifetimes by up to 38 years.
The second stage is when HIV is asymptomatic. This stage can last for a number of years with the infected person remaining well. Symptomatic illnesses signify the third stage and can include diarrhoea, minor skin or oral conditions, and persistently swollen glands.

The fourth stage is the advanced disease. As the immune system continues to weaken it becomes vulnerable to severe symptoms or opportunistic illnesses. Some of these illnesses only occur when the immune system is very weak. This group of illnesses are known as AIDS defining conditions, and their diagnosis is used to define the progression of the HIV disease to AIDS.

### 4.2 Modelling approach: the health path of HIV/AIDS

We summarise the HIV/AIDS disease epidemiology as follows:

- an agent is initially diagnosed with HIV, as in stage 1 above. HIV is the mild state of the disease, which includes stages 2 and 3 above.
- HIV transitions to AIDS. AIDS is the severe state of the disease
- AIDS transitions to death
- there is no remission from either HIV or AIDS
- the duration of HIV and AIDS can vary significantly
- the key impact of adherence is to lengthen the duration of HIV (prolong the transition to AIDS), and lengthen the duration of AIDS (prolong the time to death).

The disease transitions are shown in Figure 1.

#### Figure 1 Modelled progression of HIV/AIDS

![Modelled progression of HIV/AIDS](image)

**Source:** NZIER

### 4.3 New Zealand context

#### 4.3.1 Prevalence in New Zealand

In 2010, 185 New Zealanders were diagnosed with HIV ((AIDS Epidemiology Group, 2011). The number of people newly diagnosed with HIV in New Zealand each year between 1985 and 1999, varied between 60 and 130 with no noticeable growth trend. From 1999 to 2005 the number of newly diagnosed people grew steadily from around 60
to approximately 180 per year. Since then the number of newly diagnosed has stabilised around this number.

New Zealand males of the European/Pakeha ethnicity had the largest number of HIV diagnoses between 1996 and June 2011, accounting for 45.9% of total diagnoses. Following them were African men and women (9.8% each), and then Asian men (8.4%).

The number of AIDS related deaths peaked in New Zealand in 1992 at approximately 65, and has steadily decreased since then. In 2009 less than five New Zealanders died from AIDS (UNGASS, 2010).

Ministry of Health public hospital discharge data shows that 28 people were, on average, hospitalised for HIV/AIDS related illnesses between 2005/06 and 2008/09. The length of hospital stay for these people was, on a weighted average, 17.2 days. This hospital data included seven significant hospital stays. When these outliers were removed, the weighted average length of stay fell to 3.4 days.

4.3.2 Treatments

The available treatment for HIV/AIDS in New Zealand is a combination of antiretroviral (ART) drugs, of which there are six drug classes. The New Zealand treatment guidelines suggest a combination of at least three drugs from at two of these classes. As of 2010, PHARMAC, New Zealand’s drug buying agency, subsidises 27 drugs across these classes. PHARMAC data suggests that the average annual cost per patient is approximately $17,000 for these drugs.

The optimal drug combination for each person may be different. This could be due to a range of factors including the drug resistance of that particular strain of HIV, and the side effects of the drug on that person.

HIV weakens the immune system, which makes it easier for patients to be exposed to ‘opportunistic’ illnesses. Some patients may also take treatments to prevent the onset of these illnesses. These treatments are known as ‘prophylaxis’ and in New Zealand are usually given to people with very weakened immune systems or who have had an AIDS-defining illness.

The Ministry of Health provided hospital cost data by procedure. When grouping HIV/AIDS related procedures together and multiplying by the average length of stay we estimated the hospitalisation costs associated with the disease to be approximately $20,000.

4.4 Parameters

4.4.1 Disease incidence

New Zealand HIV incidence rates are based on diagnosis statistics provided by the University of Otago. HIV statistics are collated by the AIDS epidemiology group at the University of Otago. Annual HIV diagnosis levels have been supplied. Combining these levels with New Zealand population estimates yields HIV incidence rates. These calculated rates are shown in Figure 2.

Since 2005 the number of newly diagnosed has stabilised. For this reason we have based our incidence estimates on the average incidence rate for age cohort between 2008 and 2010. We assume these rates remain constant for our projections.
The adherence probability curve for HIV/AIDS is shown in Figure 3. It shows a 12 month adherence probability of 95%. Lamiraud et al (forthcoming) suggest that compliance rates are typically between 60 and 70% when using a 95% cut-off. However, if we use rates of 60-70%, the model predicts much greater numbers of deaths due to AIDS than the AIDS epidemiology data for New Zealand shows. Recall that we use a dichotomous variable for adherence. The status of adherence changes the relative risks of severe episodes of disease and mortality.

There is some conjecture about the compliance cut-off for HIV/AIDS. Our initial premise for HIV/AIDS was that 95% of the prescribed HIV medicines were required to maintain suppression of the viral replication, based on Paterson et al., (2000) and the WHO (2008). However, research by Bangsberg et al. (2001) suggests that the cut-off compliance value for HIV/AIDS may be much lower than 95%, and closer to 50%.

This observation raises the hypothesis that the level of adherence required to produce clinical benefit may be lower than that required for viral suppression. If true, this hypothesis would explain the apparent contradiction between the dramatic declines in AIDS-related mortality throughout the developed world after the introduction of HAART, in spite of both suboptimal adherence and viral suppression in most clinical cohorts.

We assume high adherence rates (as shown in Figure 3), based on a lower compliance cut-off threshold, consistent with the Bangsberg et al. observation.
4.4.3 Impact of adherence

HIV treatment adherence increases the duration between an agent’s diagnosis with HIV and transition to AIDS. It also increases the duration between that transition and the agent’s death. Combining the work of the Collaborative Group on AIDS incubation and HIV survival including the CASCADE EU concerted action (2000) and (Bangsberg et al., 2001) suggests that adhering to HIV treatment can increase lifetimes by up to 38 years.

Based on these studies and expert consultation we calculate a survivorship curve for adhering and non-adhering agents, which is shown in Figure 4.

Source: NZIER

Source: NZIER
4.4.4 Health care costs

Annual treatment costs for adhering patients are estimated to be $17,000 based on Pharmac (2011) data. Non-adhering patients also have some treatment costs. We assume that 60% of non-adhering patients moderately comply with treatment, based on Bangsberg et al (2001), incurring treatment costs of $5,000 per annum.

Hospitalisation costs for HIV or AIDS are not considered, but those associated with concomitant diseases are. We assign concomitant disease hospitalisation costs to AIDS patients, but not to HIV patients.

Ministry of Health hospital discharge and cost data (MOH 2011a) suggests the average length of hospital stay is 15 days at an approximate cost of $20,000. The number of hospitalisations in this data suggests that approximately 5 per cent of AIDS patients are admitted to New Zealand hospitals each year. We do not have specific concomitant disease hospitalisation events in the model, so we apply an average cost of $1,000 to all AIDS patients.\(^\text{11}\)

We do not distinguished concomitant disease hospitalisation costs between adhering or non-adhering patients. Adherence reduces concomitant disease hospitalisation costs by reducing the prevalence of AIDS.

<table>
<thead>
<tr>
<th>State</th>
<th>Treatment costs</th>
<th>Hospitalisation costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild adhere</td>
<td>$17.0</td>
<td>$0.0</td>
</tr>
<tr>
<td>Mild non-adhere</td>
<td>$5.0</td>
<td>$0.0</td>
</tr>
<tr>
<td>Severe adhere</td>
<td>$17.0</td>
<td>$1.0</td>
</tr>
<tr>
<td>Severe non-adhere</td>
<td>$5.0</td>
<td>$1.0</td>
</tr>
</tbody>
</table>

Source: NZIER

4.4.5 Disability weight tables

The WHO (2008) average disability weights for HIV are:

- HIV: 0.135
- AIDS with ART treatment: 0.167
- AIDS without treatment: 0.505.

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\(^\text{11}\) This is calculated from 5% (proportion of patients who have a hospitalisation) multiplied by $20,000 (average cost of hospitalisation)
5. Results

5.1 Prevalence

Non-adherence reduces the average time from contraction of HIV to death. Adhealth shows that non-adherence reduces HIV/AIDS prevalence by around 700 people in 2060. The falling prevalence is a negative outcome as it is associated with reduced life expectancy.

Non-adherence reduces the prevalence of HIV (mild) by over 1,350 in 2060. This is a negative outcome because it suggests that, due to non-adherence, more people have transitioned from HIV to AIDS than if they had adhered.

Non-adherence increases the prevalence of AIDS (severe) by over 650 in 2060. This is due to the increased number of patients transitioning from HIV to AIDS. AIDS related deaths also increase, but is smaller than the increased numbers transitioning from HIV to AIDS, leading to an overall net increase in the prevalence of AIDS.

This net prevalence of HIV/AIDS falls because the decrease in the number of people with HIV and the increase in the number of AIDS related deaths outweighs the increasing prevalence of people with AIDS.

Figure 5 Impact of non-adherence on HIV/AIDS prevalence

![Graph showing impact of non-adherence on HIV/AIDS prevalence](source: NZIER)

5.2 Deaths

Non-adherence results in 22 more AIDS related deaths on average per year.
5.3 Costs and quality of life

5.3.1 2012

In 2012, non-adherence increases hospitalisation costs by $0.06 million. Non-adherence increases the prevalence of AIDS patients who, in the model, have hospitalisation events.

In 2012, non-adherence reduces treatment costs by $2.1 million. Non-adherence reduces the number of drugs taken, and therefore the costs of drug medications across HIV and AIDS patients.

In 2012, non-adherence reduces quality-of-life of patients by 41 QALYs. The cost to improve quality-of-life through adherence is $48,600 per QALY.

5.3.2 Long term

Over the period from 2012 to 2060, non-adherence increases hospitalisation costs by $8.2 million in net present terms. Treatment costs are reduced by $169.0 million, and total costs are reduced by $160.8 million.

Over this period, non-adherence reduces quality-of-life of patients by 6,351 QALYs. The cost to improve quality-of-life through adherence is $25,300 per QALY.

5.3.3 Sensitivity analysis

Sensitivity analysis suggests the long term results are robust. The cost per QALY remains within the range of $21,800 and $28,900 under different assumptions about the impact of non-adherence and trends in the hospitalisation and treatment costs.
Table 3 HIV/AIDS long term results and sensitivity
$NZ million unless otherwise stated

<table>
<thead>
<tr>
<th></th>
<th>Impact of non-adherence</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>-20%</td>
</tr>
<tr>
<td>Hospital costs</td>
<td>$8.2</td>
<td>$7.6</td>
</tr>
<tr>
<td>Treatment costs</td>
<td>$169.0</td>
<td>$174.7</td>
</tr>
<tr>
<td>Total costs</td>
<td>$160.8</td>
<td>$167.2</td>
</tr>
<tr>
<td>QALYs</td>
<td>6,351</td>
<td>5,996</td>
</tr>
<tr>
<td>$/QALY (thousands)</td>
<td>$25.3</td>
<td>$27.9</td>
</tr>
</tbody>
</table>

Source: NZIER

6. Conclusions

6.1 Non-adherence is costly and resolution requires resources

The net present value of increased hospitalisation costs from non-adherence between 2012 and 2060 is $8.2 million. Non-adherence impacts can also be measured in other ways. The modelling estimated a loss of approximately 6,400 QALYs as a result of non-adherence for HIV/AIDS.

Non-adherence in HIV/AIDS reduces fiscal spending by $161 million, because treatment cost savings are significantly greater than increased hospital costs. This suggests that resolving HIV/AIDS non-adherence will need additional resources. These resources have the opportunity to provide additional QALYs for $25,300 per QALY.

6.2 Demonstration of methodology

An important outcome of the research is the model itself. There are few other attempts to use microsimulation in this area, and none have attempted the work at this scale. By developing this model, we have:

- taken data from diverse sources and combined them in a new way. This work both draws extra value from existing information, and allows data from disparate sources to become comparable
- tested findings from existing studies. We could not reconcile the observed prevalence with the adherence and efficacy rates in the published literature. As a result, we confirmed the findings of later research on the adherence rates required to achieve effective control of the condition.
- quantified the impacts of non-adherence. Importantly, this includes both the current impacts of non-adherence, in terms of dollar costs and lost QALYs, but also the cost increase that would result from better adherence. This work goes much further towards a full cost-benefit assessment than other current research
- developed an extensible model. The key extension we can make to this model is interventions to improve adherence. We have the framework to incorporate
such activities and estimate their value. The model can also be extended to other diseases and other countries.

6.3 Further research opportunities

The microsimulation model is a full representation of the New Zealand population. This allows analysis of specific sub-populations e.g. ethnicities or age cohorts that might be especially susceptible to disease and adherence issues. The model projects the New Zealand population out to 2060, so it can explicitly estimate the impact of ageing. This allows analysis of how adherence and the burden of disease interact over time. The model performs highly detailed analysis at the individual or 'micro' level. This means that the model can be extended to include individual behaviours that drive adherence. This allows a detailed analysis of adherence across the entire heterogeneous population.

A further key value in model building is enforcing consistency across data and analysis. In the case of this research, it became clear that comparable, consistent data is difficult to obtain for the conditions/diseases modelled. As an example, microsimulation modelling requires that we construct a life-path for each simulated person, with probabilities associated with contracting diseases, adhering, and becoming either sicker or healthier. The data for HIV/AIDS initially available were inconsistent. That is, we could not reconcile the observed prevalence with the adherence and efficacy rates in the published literature. As a result, we confirmed the findings of later research on the adherence rates required to achieve effective control of the condition. These kinds of inconsistencies point to key areas where future research could have great benefit in understanding the impacts of non-adherence.
7. References


