Highly active antiretroviral therapy and survival in HIV-infected Injection drug users: implications for the critical role of adherence

Robert Hogg, PhD
BC Centre for Excellence in HIV/AIDS and Simon Fraser University
Learning objectives

• Determine the impact of HAART on life expectancy and survival
• Evaluate the impact of HAART adherence on survival
• Describe barriers to HAART adherence
• Review guidelines for HAART initiation
Life expectancy and survival
# Life Expectancy

## Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies

**The Antiretroviral Therapy Cohort Collaboration***

### Summary

Background: Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population level the effect on life expectancy is not well understood. Our objective was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy.

Combination antiretroviral therapy was introduced in high-income countries in 1996, and has led to improvements in life expectancy. Hogg et al. (2008) estimated that the life expectancy of individuals on combination antiretroviral therapy in high-income countries increased by 10-15 years compared to those not on therapy.

### Mortality rates (per 1000 person-years)

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
<th>Injecting drug users</th>
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</tr>
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<tr>
<td>Overall</td>
<td>12.9 (12.3-13.6)</td>
<td>9.1 (8.2-10.1)</td>
<td>20.7 (19.0-22.5)</td>
<td>10.5 (10.0-11.6)</td>
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<td>Between the ages 20 and 44 years</td>
<td>10.3 (9.7-11.1)</td>
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<td>18.4 (16.9-20.6)</td>
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### Mortality rates per 1000 person-years (33% CI)

- **20-44 years:**
  - Overall: 12.9 (12.3-13.6)
  - Men: 14.2 (13.6-14.8)
  - Women: 9.1 (8.2-10.1)
  - Injecting drug users: 20.7 (19.0-22.5)
  - Non-injecting drug users: 10.5 (10.0-11.6)

- **45-54 years:**
  - Overall: 8.3 (7.6-9.0)
  - Men: 9.8 (9.1-10.6)
  - Women: 5.5 (4.7-6.3)
  - Injecting drug users: 14.4 (12.7-16.6)
  - Non-injecting drug users: 5.2 (4.5-5.9)

- **55-64 years:**
  - Overall: 5.7 (5.0-6.5)
  - Men: 7.2 (6.5-7.9)
  - Women: 4.0 (3.3-4.8)
  - Injecting drug users: 11.5 (10.2-12.9)
  - Non-injecting drug users: 3.9 (3.2-4.6)

- **65+ years:**
  - Overall: 4.2 (3.6-4.9)
  - Men: 5.6 (5.0-6.3)
  - Women: 3.0 (2.5-3.6)
  - Injecting drug users: 8.0 (7.1-8.9)
  - Non-injecting drug users: 2.9 (2.4-3.5)

### Mortality rates are deaths per 1000 person-years (33% CI)

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  - Men: 14.2 (13.6-14.8)
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### Life expectancy (years; adjusted)

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### Life expectancy and mortality are unexplained as important population health indicators. As such, several studies have explored the impact of ART on life expectancy at a population level. However, the effect of ART on life expectancy is limited understanding due to the relative novelty of this intervention. The objective of this analysis was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy (ART) within high-income countries over the period 2000-2006.

### Methods

Participants

The Antiretroviral Therapy Cohort Collaboration (ARTCC) is a multinational cohort study of adults with HIV infection in high-income countries.

**References**

Hogg et al., 2008, Lancet.
Life Expectancy

Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies

The Antiretroviral Therapy Cohort Collaboration

Summary

Background: Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population level the effect on life expectancy is not well understood. Our objective was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy (cART) vs. those not on therapy.

Methods: We performed a collaborative meta-analysis of 14 cohort studies including high-income countries. We compared mortality and life expectancy among individuals with and without cART. We also estimated the impact of cART on life expectancy for subgroups defined by CD4 cell counts, transmission risk factors, and viral load. We estimated the impact of cART on life expectancy for subgroups defined by CD4 cell counts, transmission risk factors, and viral load. We also estimated the impact of cART on life expectancy for subgroups defined by CD4 cell counts, transmission risk factors, and viral load.

Results: Mortality rates per 1000 person-years were lower among patients on cART than those not on therapy. The estimated impact of cART on life expectancy was greatest for patients with high CD4 cell counts, low viral load, and low transmission risk. The estimated impact of cART on life expectancy was greatest for patients with high CD4 cell counts, low viral load, and low transmission risk.

Conclusion: Combination antiretroviral therapy leads to significant increases in life expectancy among HIV-positive individuals, with the largest impact on life expectancy for patients with high CD4 cell counts, low viral load, and low transmission risk.

Hogg et al., 2008, Lancet

IDUs live significantly less than non-IDUs

Hogg et al., 2008, Lancet
HAART survival in IDUs

Highly Active Antiretroviral Therapy and Survival in HIV-Infected Injection Drug Users

Evan Wood, MD, PhD
Robert S. Hogg, PhD
Viviane Dias Lima, PhD
Thomas Kerr, PhD
Benita Yip, RSE (Pharm)
Brandon D. L. Marshall, MSc
Julio S. G. Montaner, MD, FRCP(C)

Context Highly active antiretroviral therapy (HAART) is often withheld from injection drug users (IDUs) infected with the human immunodeficiency virus (HIV) based on the belief that their unstable lifestyles may preclude a markedly inferior outcome with HAART. However, long-term evaluations of HIV treatment outcomes among IDUs in comparison with other risk groups are not available.

Objective To compare survival rates among HIV-infected patients initiating HAART with and without a history of injection drug use.

Design, Setting, and Patients Population-based, prospective cohort study (HAART Observational Medical Evaluation and Research [HOMER]) of 3116 antiretroviral-naive HIV-infected patients in a province-wide HIV/AIDS treatment program in British Columbia, Canada. Of the 3116 patients, 915 were IDUs (29.4%), 579 were female (18.6%), and the median age was 39.4 years (interquartile range, 33.2-46.4 years). Treatment with HAART was initiated between August 1, 1996, and June 30, 2006. The median duration of follow-up was 5.3 years (interquartile range, 2.8-8.3 years) for IDUs and 4.3 years (interquartile range, 2.0-7.6 years) for non-IDUs. Patients were followed up until June 30, 2007. Data were analyzed between November 1, 2007, and May 30, 2008.

Main Outcome Measure All-cause mortality.

Results Overall, 622 individuals died (20.0%) during the study period (223 IDUs and 399 non-IDUs), for a crude mortality rate of 20.0% (95% confidence interval [CI], 18.4%-21.5%). At 48 months after the initiation of HAART, the product limit estimate of the cumulative all-cause mortality rate was similar between the 915 IDUs (26.5%; 95% CI, 23.2%-29.8%) and 2201 non-IDUs (21.6%; 95% CI, 16.9%-26.2%; Wilcoxon P = .47). In multivariate time-updated Cox regression, the hazard ratio of mortality was similar between IDUs and non-IDUs (1.10; 95% CI, 0.92-1.29).

Conclusion In this study population, injection drug use was not associated with decreased survival among HIV-infected patients initiating HAART.
HAART survival in IDUs

No difference in survival between IDUs and non-IDUs

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Main Outcome Measure All-cause mortality.

Results Overall, 622 individuals died (20.0%) during the study period (222 IDUs and 390 non-IDUs), for a crude mortality rate of 20.0% (95% confidence interval [CI], 18.4%-21.5%). At 84 months after the initiation of HAART, the product limit estimate of the cumulative all-cause mortality rate was similar between the 915 IDUs (26.5%; 95% CI, 23.2%-29.8%) and 2 201 non-IDUs (24.6%; 95% CI, 21.6%-26.2%) (Wilcoxon P=.47). In multivariate time-updated Cox regression, the hazard ratio of mortality was similar between IDUs and non-IDUs (1.08; 95% CI, 0.92-1.29).

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JAMA. 2008;300(5):553-554.
Potential explanations

- Population-based
- HAART available free of charge
- Few barriers (financial or other) to care
- Complete reporting of deaths (thru linkages to Vital Statistics and reporting by physicians)
- Better adherence support
Adherence and survival
Intermittent use of HAART

Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up

Robert S. Hogg\textsuperscript{a,b}, Katherine Heath\textsuperscript{a,b}, David Bangsberg\textsuperscript{c}, Benita Yip\textsuperscript{a}, Natasha Press\textsuperscript{a}, Michael V. O’Shaughnessy\textsuperscript{a,d} and Julio S.G. Montaner\textsuperscript{a,e}

Table 3. Univariate and multivariate analysis of the baseline factors associated with survival among 1282 persons first prescribed any triple-combination antiretroviral therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Age (years) (continuous)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
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<td>Sex (male versus female)</td>
<td>1.17 (0.66–2.10)</td>
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<td>Protease inhibitor use (yes versus no)</td>
<td>2.12 (1.16–3.88)</td>
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<td>Injecting drug use (yes versus no)</td>
<td>0.99 (0.63–1.54)</td>
</tr>
<tr>
<td>Physician experience (per 100 patients per physician)</td>
<td>0.77 (0.59–0.99)</td>
</tr>
<tr>
<td>AIDS diagnosis (yes versus no)</td>
<td>2.15 (1.38–3.34)</td>
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<tr>
<td>CD4 cell count (per 100 × 10\textsuperscript{4} cells/l decrease)</td>
<td>1.36 (1.21–1.53)</td>
</tr>
<tr>
<td>Plasma viral load (per log\textsubscript{10} copies/ml increase)</td>
<td>1.79 (1.28–2.52)</td>
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<td>Intermittent antiretroviral use (&lt;75% of the time in the first year)</td>
<td>2.35 (1.60–3.46)</td>
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\textsuperscript{a}Including all prognostic variables that were statistically significant in the univariate analysis. CI, Confidence interval.

Objective: To characterize the impact of intermittent use of triple drug antiretroviral therapy on survival.

Design, setting and participants: Population-based analysis of 1282 antiretroviral therapy naive HIV-positive individuals aged 18 years and older in British Columbia who started triple-combination therapy between August 1996 and December 1999. Therapy use was estimated by dividing the number of months of medications dispensed by the number of months of follow-up. Intermittent therapy was defined as the participant having obtained less than 75% of their medication in the first 12 months.

Main outcome measure: Cumulative all-cause mortality rates from the start of triple drug antiretroviral therapy to 30 September 2000.

Results: As of 30 September 2000, 106 subjects had died. Cumulative mortality was 3.9% (±0.5%) at 12 months. In a multivariate model, after controlling for other variables that were significant in the univariate analyses each 100 cell decrement in baseline CD4 cell count and the intermittent use of antiretroviral drugs were associated with increased mortality with risk ratios of 1.31 (95% confidence interval (CI), 1.16–1.49; P < 0.001) and 2.90 (95% CI, 1.93–4.36; P < 0.001), respectively. In order to control for downward drift, intermittent use of therapy was measured over the first year whereas other factors were measured at the end of year 1. After adjusting for
Intermittent use of HAART

Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up

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Adherence and initial CD4

Wood et al., AIDS, 2003
Adherence and initial CD4

33 fold increase in mortality with poor adherence and low CD4s at time to start

Wood et al., AIDS, 2003
Baseline RNA and adherence

- Is poor prognosis for patients with high HIV RNA confounded by poor adherence?

- Adjusting for adherence, HIV RNA >100,000 associated with HIV-related mortality (ARH 1.81, 95% CI 1.15-2.84)

Conclusion

- Even when controlling for adherence, VL >100,000 confers a worse prognosis

Wood E, et al. 10th CROI, Boston 2003, #182
Adherence and depression

6 fold increase in mortality

Lima et al., AIDS 2006
Barriers to adherence
Barriers to adherence

- Misinformation about HAART
- Drug dependency
- Mental illness, Hep C & other co-infections
- Poor access to medical care
- Criminal enforcement
- Unstable housing
Note: Based on 1,436 HIV-related deaths from 1997 to 2005 in BC

Source: Joy et al., JAIDS, 2008
Case study: drug dependency and mental health

- Towards Aboriginal Health and Healing (TAHAH) program stabilizes all psycho-social, legal and economic crises and immediate primary health issues. For instance,
- 25 year old woman, homeless, FASD, IVDU, HCV+, PTSD, Paranoid Delusions. HIV+ at age 17; CD4 Nadir 230; pVL over 100,000; recurring opportunistic infections.
- Referred to TAHAH 2007: immediate survival needs addressed, then gradual initiation of antipsychotic meds.
- 2008: PWD application (line by line), started depo-provera, stabilized housing
- 2009: initiation of methadone, then HAART
- Dec 2009 = CD4 390, VL = 188
- Client had over 20 contacts with staff per month
Adherence and hepatitis C

Braitstein et al., CMAJ, 2005
Adherence and hepatitis C

Increased mortality related to non-adherence

Braitstein et al., CMAJ, 2005
Migration and adherence

- People on HAART who migrated at least 3 times were 1.8 times more likely to be non-adherent than those who did not.
Prison and HAART response

- Among IDUs, alcohol use and incarceration prior to start of HAART were negatively associated with viral load suppression.

Palepu et al., Urban Health, 2006
Homelessness in Vancouver

- Up 171% (since 2002), 52% on street, 48% in shelters
- 30% of homeless are Aboriginal
- 48% report addiction (39% in 2002)
- 33% have co-morbidity of addiction and mental illness
- 40% reported a health condition, 35% reported two or more.
- 30% welfare, 11% disability, 23% no income, 14% employed, 5% dumpster diving or binning, 5% illegal income
- Reasons for homelessness: 44% low $$, 25% health/addictions, 22% housing cost, 16% abuse/conflict, 13% evicted, 8% moving/ stranded

From City of Vancouver, GVRD & SPARC reports
Conclusions

• IDUs have similar survival rates as non-IDU, at least in BC
• Adherence is an important determinant of HAART survival
• Numerous barriers to HAART adherence exist, especially among IDUs
Acknowledgements

Thank you

• Julio Montaner
• Evan Wood/ Thomas Kerr
• Viviane Lima/ Benita Yip
• David Tu
• ART-CC
• NA-ACCORD
• CIHR/ NIDA/ NIH/ MRC
• Sidney Crosby

The Economist, Sept 2003