HIV treatment as prevention: The key to an AIDS-free generation

Mark W. Hull, Julio S.G. Montaner*

Division of AIDS, Department of Medicine, University of British Columbia, Vancouver, Canada

Keywords:
Human immunodeficiency virus (HIV) care cascade
Linkage to care
Seek and treat
Treatment as prevention

Abstract

The presence of elevated human immunodeficiency virus (HIV) viral load within blood and genital secretions is a critical driver of transmission events. Long-term suppression of the viral load to undetectable levels through the use of antiretroviral therapy is standard practice for the clinical management of HIV. Antiretroviral therapy therefore can play a key role in curbing HIV transmission. The results of a randomized clinical trial and several observational studies have now confirmed that antiretroviral therapy markedly decreases the risk of HIV transmission. Mathematical models and population-based ecologic studies suggest that further expansion of antiretroviral coverage within current guidelines can play a major role in controlling the spread of HIV. The expansion of so-called “treatment as prevention” initiatives relies on maximal uptake of the HIV continuum-of-care cascade to allow for the successful identification of people who are not yet known to be HIV-infected, for engaging patients in appropriate care, and for subsequently achieving sustained virologic suppression in patients with the use of antiretroviral therapy. Since 2010, the joint United Nations AIDS (UNAIDS) program has called for the inclusion of antiretroviral treatment as a key pillar in the global strategy to control the spread of HIV infection. This has now been invigorated by the release of the World Health Organization’s 2013 Consolidated Antiretroviral Therapy Guidelines, which recommends offering treatment to all HIV-infected individuals with CD4 cell counts below 500/mm³, to serodiscordant couples, to individuals coinfected with tuberculosis and hepatitis B virus, to pregnant women, and to children below the age of 5 years (regardless of CD4 cell count in this group).

1. Introduction

The introduction of combination antiretroviral therapy (ART) has been associated with significant improvement in human immunodeficiency virus (HIV)-related morbidity and mortality [1,2]. Long-term virologic suppression through the use of ART is the primary goal of HIV therapy [3]. The potency of modern ART regimens has increased in association with a concomitant decrease in toxicity and simplification of the regimens with the increased availability of once-daily dosing.
and fixed-dose combinations. As a result, HIV-infected individuals who are appropriately engaged in care are expected to see an expansion of their life expectancy on the order of four decades, which approaches the overall longevity of the general population [4,5].

Despite these advances, challenges exist in the global approach to controlling the HIV epidemic, which persists with an estimated 2.5 million (range, 2.2–2.8 million) individuals who may have newly acquired HIV in 2011 [6]. Prevention strategies have focused initially on behavioral interventions and condom use. Recent alternate biomedical prevention interventions have shown mixed results with no benefit in trials involving the treatment of genital ulcerative disease (i.e., herpes simplex virus) [7]; mixed outcomes in the results of trials of vaginal microbicides [8,9] and oral pre-exposure prophylaxis [10–12]; and positive benefit in male circumcision trials [13]. Because of the incontrovertible benefit of ART to HIV-infected individuals who meet treatment requirements, attention has been focused on the potential secondary benefits that may be gained from expanding ART treatment programs with an associated decreased risk of transmission in individuals accessing successful ART. As described later, the results of a randomized clinical trial and several observational studies have now confirmed that ART markedly decreases the HIV transmission risk. Mathematical models and population-based ecologic studies suggest that further expansion of antiretroviral coverage within current guidelines can play a major role in controlling the spread of HIV. Maximizing programmatic identification of undiagnosed HIV-infected individuals and subsequent initiation of suppressive antiretroviral therapy has been the focus of so-called “seek and treat” or “treatment as prevention” initiatives.

### Table 1 – Ecologic studies of community viral load and treatment as prevention of new HIV infections [55].

<table>
<thead>
<tr>
<th>Setting</th>
<th>Period</th>
<th>Evaluation</th>
<th>Outcomes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>1984–2002</td>
<td>National HIV surveillance data</td>
<td>Transmission rate 0.391 new cases /prevalent cases pre-ART</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transmission rate estimated by an exponential model</td>
<td>Transmission rate 0.184 new cases /prevalent cases post-HAART</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall decrease 53%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cox regression model to association with HIV incidence</td>
<td>CVL associated with time to HIV seroconversion (hazard ratio 3.32 per log_{10} increase)</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV incidence</td>
<td>After median viral load decreased to &lt;20,000 copies/mL, but showed no statistical association with HIV incidence</td>
<td></td>
</tr>
<tr>
<td>San Francisco</td>
<td>2004–2008</td>
<td>HIV/AIDS public health surveillance for new diagnoses and calculated HIV incidence</td>
<td>Significant decline in mean CVL 2004–2008 (p = 0.037)</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean community viral load</td>
<td>Reduction in CVL associated with decrease in new HIV diagnoses (p = 0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson models for CVL and new HIV diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>British Columbia, Canada</td>
<td>1996–2009</td>
<td>HAART coverage from a centralized registry</td>
<td>547% increase in ART uptake</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV public health surveillance for new diagnoses</td>
<td>52% decrease in new HIV diagnoses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median CVL</td>
<td>For every 100 additional individuals on ART, new cases decreased by factor of 0.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson models for CVL, ART coverage, and new HIV diagnoses</td>
<td>For every 1 log_{10} drop in CVL, new cases decreased by factor of 0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort of 16,667 HIV uninfected individuals</td>
<td>As ART coverage within a community expands, risk of acquisition decreases: for communities with 30–40% ART penetration, risk of new infection dropped 38% compared to communities with &lt;10% ART uptake</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ART coverage and HIV prevalence within the surrounding community assessed,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rate of new seroconversions captured</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ART** = antiretroviral therapy; **CVL** = community viral load; **HAART** = highly active antiretroviral therapy; **HIV** = human immunodeficiency virus.

### 2. Biologic plausibility for “treatment as prevention”

#### 2.1. Mother-to-child transmission

Vertical transmission has long been linked to the degree of maternal viral load [14,15]. Use of suppressive combination antiretroviral therapy during pregnancy, delivery, and breastfeeding significantly reduces the risk of vertical transmission, even in the context of a resource-limited sub-Saharan setting where transmission occurred only in 1.1% of live-born infants [16]. In the developed world, vertical transmission is uncommon. The transmission rate among HIV-infected women receiving ART in the United Kingdom and Ireland was 0.7% in the setting of vaginal delivery or planned caesarean section [17].
2.2. HIV viral load and sexual transmission

In a community-based study of 15,127 individuals in Rakai, Uganda, a relationship was clearly evident between the HIV plasma viral load and the risk of transmission, and a multivariate analysis showed an increase of 2.45 in the seroconversion rate ratio [95% confidence interval (CI), 1.85–3.26] for each log increase in the viral load [18]. The study further showed no evidence of transmission for 51 individuals with plasma viral loads below 1500 copies/mL [18]. In a multivariate analysis in a study of male-to-female transmission among 493 heterosexual couples in Thailand, each log increment in the HIV viral load was associated with an odds ratio (OR) of 1.81 (95% CI, 1.33–2.48) for transmission [19]. No transmission events were documented for individuals with viral loads below 1000 copies/mL [19]. In an analysis of 3381 serodiscordant couples enrolled within the double-blind placebo-controlled randomized Partners in Prevention Herpes Simplex Virus (HSV)/HIV Transmission trial of acyclovir for HIV transmission with 5017 person-years of follow-up in South and East Africa [7], the HIV transmission risk was 2.24 per 100 person-years in a log-linear relationship to log(10) of plasma viral load. Using this data, a mathematical model predicted a 50% reduction in transmission with a 0.70 log reduction in plasma viral load [20].

2.3. Antiretroviral therapy to reduce sexual transmission of HIV

Use of sustained ART in the context of serodiscordant heterosexual relationships was associated with a reduced risk of transmission soon after the introduction of combination regimens [21,22]. Recent observational data continue to show a significant reduction in the transmission risk with the use of ART. In the serodiscordant cohort nested within the Partners in Prevention study, ART use was associated with a 92% reduction in transmission from 2.24/100 person-years (95% CI, 1.84–2.72) to 0.37/100 person-years (95% CI, 0.09–2.04) [23]. A meta-analysis evaluated 5,021 heterosexual couples and found an overall reduction in the rate of transmission among...
couples receiving ART from 5.64/100 person-years to 0.46/100 person-years (95% CI, 0.19–1.09) (a 92% reduction in risk of transmission) [24].

More recently, a randomized clinical trial, the HIV Prevention Trials Network 052 (HPTN 052)—which evaluated the effect of early versus deferred ART on the transmission risk among serodiscordant couples—has now been completed [25]. In this study, 1,763 couples (54% from Africa, 50% male HIV-infected partners) were randomized to receive immediate ART (at a CD4 cell count of 350–500 cells/mm³) or deferred therapy that was initiated after CD4 decline or at HIV symptom onset. There were 28 linked transmission events with only one event occurring in the early ART group [hazard ratio (HR), 0.04; 95% CI, 0.01–0.27], which is a 96% reduction in transmission risk [25]. Some observational studies have not demonstrated similar benefits [26]. However, the preponderance of evidence now supports a clear role for ART in reducing HIV transmission.

3. Evaluation of treatment as prevention within British Columbia, Canada

3.1. Mathematical models

Mathematical models of the potential impact of ART on the incidence of HIV have been used extensively over the past decade in various settings in the developed world and in epidemics among men who have sex with men (MSM), and have been used to assess the epidemic in sub-Saharan Africa [27]. These models are sensitive to the assumptions made for treatment uptake, adherence, resistance to ART, and transmission risk, but they serve to guide evaluation and potential interventions of treatment as prevention programs.

An early mathematical model was evaluated in British Columbia to assess the effects of the potential expansion of antiretroviral coverage among individuals who were eligible for treatment, which was defined initially as a CD4 cell count of <200 cells/µL [28]. In the semideterministic dynamic transmission model, increasing ART coverage from a baseline of 50–75% or 100% of people eligible under contemporary provincial treatment guidelines (with an unchanged level of adherence) was predicted to be associated with a decrease in the annual incidence of HIV by 37% and 62%, respectively [28]. The model was updated to account for changing treatment guidelines, and assessed the coverage for people deemed eligible for therapy on the basis of a CD4 cell count < 350 cells/µL [29]. Expanding coverage to 75% of people deemed eligible for therapy may potentially avert 47% of new infections over 5 years [29]. Other models in the setting of developed world epidemics have shown similar outcomes in some studies [30,31], but not in other studies [32,33].

3.2. Ecologic studies

The effects of ART at a community and population level have been evaluated in British Columbia and in other settings (Table 1). During the period of 1996–2007, the effect of ART on HIV incidence was assessed in a cohort of injection drug users within Vancouver’s Downtown Eastside neighborhood [34]. A community viral load (calculated as the median measure of all viral load measurements for individuals with a known HIV status) was followed longitudinally (based on a total of 12,435 measures). The impact on HIV incidence was also evaluated, while adjusting for risk behavior. The median community viral load concentration fell below 20,000 copies/mL after 1998 (i.e., after the introduction of ART). The community viral load remained independently associated with time to HIV seroconversion (HR, 3.32; 95% CI, 1.82–6.08), but this was no longer statistically significant after median viral loads declined below 20,000 copies/mL [34]. Similar decreases in the HIV incidence have been observed in the Azimilide Post-infarct Survival Evaluation (AIDS Linked to the Intravenous Experience cohort, ALIVE) cohort (Baltimore, MD, USA) in which the incidence decreased by 74% for every log decrease in the community viral load [35]. In addition, there has been no evidence of behavioral disinhibition among a cohort of injection drug users in Vancouver where the initiation of antiretroviral therapy was not associated with a subsequent increase in unprotected intercourse [adjusted odds ratio (aOR), aOR 0.87; 95% CI, 0.61–1.40] in a multivariate analysis [36]. This result is in keeping with findings from ART programs in sub-Saharan Africa [37]. However, the contrasting results showing increases in unprotected intercourse have been observed among certain MSM populations [38].

A population-based ecologic evaluation of ART expansion and decreasing new HIV diagnoses has been presented [39]. Antiretroviral therapy is provided free of charge to HIV-infected individuals within the Province of British Columbia, Canada via a central Drug Treatment Program, which maintains a population-based registry of individuals receiving ART. Between 1996 and 2012, the number of individuals receiving therapy increased by 547% from 837 individuals to approximately 7,700 individuals. During this period, the proportion of individuals with a viral load less than 500 copies/mL increased
from less than 10% to 50% (p <0.0001). Between 1996 and 2012, new diagnoses of HIV decreased overall from 702 cases to 248 cases per year (see Fig. 1). The number of HIV diagnostic tests increased during this period, and the rates of syphilis, gonorrhea, and chlamydia increased, which suggests no changes in risk behavior [39]. The overall effectiveness of current regimens has improved viral load suppression. The proportion of individuals achieving full virologic suppression (with a plasma viral load less than 50 copies/mL) increased from 64.7% (in 2000) to 87.0% (in 2008) [40]. In addition, the proportion of individuals with a resistance to more than two drug classes has fallen from 12% of individuals in 2000 to less than 2% of individuals currently enrolled in the program [41]. These findings stand in contrast to other jurisdictions in Canada where new diagnosis rates of HIV are either stable or increasing (Fig. 2) [42].

3.3. Cost effectiveness

In the British Columbia model, cost-savings accrue over time with averted infections. Expanding ART access from 50% to 75% of individuals meeting the 2008 treatment guideline criteria has been predicted to result in an eventual cost-savings of $900 million over 30 years [43]. In an updated model in South Africa, expanding coverage to individuals with CD4 cell counts of 350 cells/mm³, 500 cells/mm³, or any CD4 level would avert infections and be cost-saving; these benefits would be diminished if patient retention in care programs were diminished [44,45]. By contrast, in models that have evaluated scenarios in which treatment programs do not achieve full implementation or coverage, costs would in fact increase [46].

3.4. The continuum-of-care cascade

The HIV care cascade has been a seminal framework in which to evaluate potential gaps in HIV programs [47]. The care cascade evaluates the HIV treatment model from initial estimates of undiagnosed individuals living with HIV through the proportion of individuals who are appropriately diagnosed, who are engaged and retained in care, and who ultimately achieve sustained virologic suppression. Each aspect of this care cascade should be maximized if treatment as prevention programs are to succeed. Gardner et al [47] evaluated the care cascade for the United States (U.S.) as a whole, and based estimates on reported values for each step (Fig. 3). Of the 1.2 million HIV-infected individuals in the U.S., approximately 20% were unaware of their diagnosis, and ultimately only 19% of individuals were successfully retained and their viral load was suppressed on ART. These estimates are remarkably similar to the U.S. Centers for Disease Control and Prevention (CDC) estimates obtained by using a number of U.S. national surveillance instruments that showed 28% of all HIV-infected individuals’ viral loads were fully suppressed on ART [48]. A similar HIV care cascade has been generated for British Columbia that evaluates estimated undiagnosed cases within the province, patients engaged and retained in care, patients adherent to medications, and patients with fully suppressed viral loads [49]. In this model, virologic suppression was defined as a sustained undetectable plasma viral load (i.e., less than 50 copies/mL during the period of 1999–2009). Only 14% of individuals overall were believed to be undiagnosed in 2009, compared to 47.1% in 1996. In 2009, 32.1% (range, 26.8%–37.3%) of individuals had a fully suppressed viral load [49].

4. Conclusions

Antiretroviral therapy can reduce individual level morbidity and mortality for people affected by HIV, and it significantly reduces the transmission risk, particularly among heterosexual serodiscordant couples. At a population level, the expansion of successful ART programs translates into decreased community burden of viremic individuals and a concomitant decrease in the transmission of HIV and a decreased incidence of HIV. Potential barriers may include the impact of acute HIV infections as a cause of ongoing transmission, the efficacy of ART for prevention benefits within the MSM communities, and the risks of concomitant behavioral disinhibition. At present, the overall proportion of individuals receiving ART is low because of the high proportion of undiagnosed individuals and because of incomplete virologic suppression in people known to be HIV-infected. Strategies to improve engagement at each step of the care cascade represent critical interventions to maximize the individual and societal impact of ART and therefore deliver on the promise of HIV treatment as prevention. Since 2010, the joint United Nations AIDS (UNAIDS) program has called for the inclusion of antiretroviral treatment as a key pillar in the global strategy to control the spread of HIV infection [50]. This has now been invigorated by the release of the World Health Organization’s 2013 Consolidated Antiretroviral Therapy guidelines, which call for treatment to be offered to all HIV-infected individuals with CD4 cell counts below 500/mm³, to serodiscordant couples, to individuals coinfected with tuberculosis and hepatitis B virus, to pregnant women, and to children below the age of 5 years (regardless of CD4 cell count in this groups) [51]. The stage is therefore set for the global community to implement treatment as prevention as a highly cost-effective opportunity to achieve the dual goal of halting HIV/AIDS-related morbidity and mortality and curbing the spread of HIV.

REFERENCES


