AMMI Canada POSITION STATEMENT:

The Use of Early Antiretroviral Therapy in HIV-infected Persons

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**AMMI Canada POSITION STATEMENT:** In Canada, antiretroviral therapy (ART) should be initiated in all adult persons living with HIV-1 infection (PLHIV) as soon as a diagnosis of HIV infection is confirmed and regardless of the CD4 count.

**Background**

The benefits of antiretroviral therapy (ART) on AIDS and AIDS-related mortality have been clearly demonstrated in asymptomatic HIV-1 infected adults with CD4<350 cells/mm$^3$ based on randomized controlled trials (RCTs). As such, the initiation of ART at CD4< 350 cells/mm$^3$ has been uniformly recommended by international panels for many years, including the World Health Organization (WHO), the United States Department of Health and Human Services (DHHS), the International AIDS Society (IAS), the European AIDS Clinical Society (EACS), and the British HIV Association (BHIVA). (1-4,8)

The evidence of benefits of ART on AIDS-related events and AIDS-related mortality in asymptomatic adults living with HIV-1 infection with CD4>350 cells/mm$^3$ has until recently been limited to observational studies (6,7). This lack of definitive evidence accounted for a discordance in international recommendations, with IAS (8) and DHHS (3) being early adopters recommending treatment at this CD4 level (with the acknowledgement that this was based on a lower strength and quality of evidence).

Recommendations supporting early ART in asymptomatic HIV-1 patients were strengthened by publications demonstrating benefits (not limited to AIDS and AIDS-related mortality) on severe non-AIDS-related events (SNA) linked to the beneficial effects of early ART on immune activation and inflammation (9,10). Data from the Study on Management of ART (SMART) trial demonstrated an excess of opportunistic infections, as well as SNA events (e.g., cardiovascular, renal, hepatic, and non-AIDS-related malignancies) in patients who delayed treatment compared to those who initiated treatment earlier (10). The benefits of early initiation of ART were maintained in a subset of patients in the SMART trial who were treatment naïve or had stopped ART for 6 months prior to enrolment (11).

The next important development that further validated the role of early ART in asymptomatic PLHIV was the emergence of evidence of demonstrable prevention benefits. The HIV Prevention Treatment Network study (HPTN 052) was a mulitcenter RCT conducted in Africa, Brazil, and India. The primary prevention endpoint showed a reduction in HIV-1 transmission to previously HIV-1 uninfected heterosexual partners with a single linked transmission in the early ART group compared to 27 linked transmissions in the delayed ART group (Hazard Ratio(HR)=0.04; 95% CI 0.01-0.27). In addition, the primary clinical endpoint (death, WHO HIV stage 4 HIV-1 disease, pulmonary tuberculosis and severe bacterial infections) supported early initiation of ART with 40 events in the
early treatment arm compared to 65 events in the delayed ART arm, HR =0.59 (95% CI 0.44-0.80), driven primarily by a reduction in extrapulmonary tuberculosis (12).

A broader consensus across international panels recommending ART initiation for all PLHIV, regardless of CD4 count, was reached by BHIVA (“Strong recommendation with high quality evidence”), EACS (‘Recommendation’ for asymptomatic with CD4>350), DHHS (A-II for 350<CD4<500, B-II for CD4>500), and the WHO ("Strong recommendation with moderate quality evidence"), supported by two RCTs: the Strategic Timing of Antiretroviral Therapy (START) study, and the ANRS TEMPRANO study, which are discussed below. (1-4, 13,14)

The evolution of guidelines to support early ART has been supported by evidence that the benefits continue to outweigh the risks. The START trial demonstrated no increase in Grade 4 symptomatic adverse events (i.e. life-threatening reactions) in patients who started early ART compared to those who delayed treatment, reflecting the use of ART with an acceptable therapeutic index (13-14).

**Risks and Uncertainties**

Guidelines supporting early ART in PLHIV must consider the broader implications of this recommendation in a Canadian context to include: 1) a consideration of the economic impacts at an individual and health system level, 2) the need for uniformity in the provision of ART given that delivery and costs of health care in Canada are a provincial and territorial responsibility, 3) the concerns of greater cumulative toxicities acquired from lifelong ART adherence, 4) the potential for greater accumulation of antiviral drug resistance, which may limit future treatment options, 5) individual readiness and willingness to adhere to lifelong ART and the potential for treatment-related fatigue, 6) the need for further empirical studies demonstrating the public health benefits on HIV-1 transmission of early ART not limited to heterosexual serodiscordant couples (16,17), and lastly, 7) the requirement to have the necessary supports to promote adherence and retention in care. Examples of the latter include: patient health navigation, community and peer outreach, provision of culturally appropriate print media, verbal messages promoting health care utilization and retention from clinic staff, youth-focused case management and support systems and linkage for broader health care needs (18).

The purpose of this paper is to provide AMMI Canada’s position on the optimal timing of ART initiation for PLHIV in the Canadian context and to discuss the evidence base for the position. This position paper is not intended to provide recommendations on the ideal treatment regimens for HIV. Those wishing to review the latest recommended regimens for the treatment of treatment-naïve or -experienced PLHIV are referred to the most recent
DHHS guidelines (5). Finally, this paper is not intended to discuss pre or post exposure prophylaxis.

**Methods**

Following a request by the Public Health Agency of Canada (PHAC) for a statement on AMMI Canada’s position on early ART initiation, a working author group (MB, JC, GAE, SH, SDS) was established by the AMMI Canada Guidelines Committee drawing on volunteers and recommendations from a group of AMMI Canada members. The Chair of the Guidelines Committee (GAE) served as a coordinator and liaison with the working group (WG). Following an initial WG meeting, sections were assigned to the author group along with instructions for an approach to developing the evidence base for the position paper. References were obtained by reviewing the bibliographies of relevant guidelines (backward citation tracing) and electronic databases (PubMed, Google Scholar), which were searched in October 2015. Keywords included ('early HIV treatment' OR 'early antiretroviral treatment') AND ('transmission' OR 'viral load' OR 'prevention'), and 'treatment as prevention'. Studies that reported individual or population-level effects of early ART initiation were considered.

An initial draft of the paper was reviewed by a group at PHAC for their input on specific objectives for the position paper. A final draft was revised by the WG for final approval.

**Early Initiation of ART: Individual health benefits, risks, uncertainties**

Both cohort studies and randomized clinical trials (RCTs) demonstrate substantial health benefits to HIV-1 infected adults from the early initiation of ART.

**Cohort studies**

The When To Start Consortium (6) analyzed data from 21,247 HIV-1 infected adults in 18 cohorts from North America, Europe and Argentina and noted that deferring ART until a CD4 cell count of 251–350 cells/mm³ was associated with higher rates of AIDS and death compared to starting therapy in the range of 351–450 cells/mm³ (HR 1.28, 95% CI 1.04–1.57). The CASCADE study (18) evaluated 9455 HIV-1 seroconverters in Europe and found that starting ART at CD4 counts below 500 cells/mm³ was associated with reduced disease progression, but this analysis did not show a benefit in starting ART in patients with CD4 counts between 500 and 799 cells/mm³. The NA-ACCORD study (7) examined 17,517 HIV-1 infected patients under care in Canada and the United States. In an analysis of 8362 patients, 2084 (25%) initiated therapy at CD4 counts of 351 to 500 cells/mm³, and 6278
(75%) deferred therapy. There was a 69% increase in the risk of death in the deferred therapy group compared with the early therapy group. In a second analysis of 9155 patients, 2220 (24%) initiated therapy at a CD4 count above 500 cells/mm³ and 6935 (76%) deferred therapy. Among patients in the deferred therapy group, there was a 94% increased risk of death (relative risk, 1.94; 95% CI, 1.37 to 2.79; P<0.001). The HIV-CAUSAL Collaboration is a consortium of prospective cohort studies from the United States and six countries in Europe. HIV-CAUSAL examined 55,826 HIV-1 infected adults and found that patients who started ART at a CD4 threshold of 500 cells/mm³ had improved overall survival compared with starting at a CD4 count below 350 cells/mm³ (20).

In addition to benefits related to AIDS-free survival and all-cause mortality, cohort studies have also demonstrated benefits with respect to chronic hepatitis B (HBV) and hepatitis C (HCV). In the Multicenter AIDS Cohort Study (MACS), patients receiving suppressive ART had an 80% reduction in the incidence of HBV infection (21). The protective effect against HBV appears to be mediated by the use of antiviral drugs that are dually active against HIV and HBV (22). Several cohort studies have demonstrated that effective ART slows the rate of hepatic fibrosis in HIV-HCV co-infected persons (23-26) and reduces the risk of hepatic decompensation (27). While curing HCV with interferon-free therapy is the best way to prevent HCV-related morbidity and mortality, many HCV-infected patients do not meet the current restrictive criteria for publicly funded interferon-free therapy, and others are active illicit injecting drug users at high risk of HCV reinfection who are not optimal candidates for a therapy for which only a single course is funded. For these patients with HIV-HCV co-infection, effective ART is the best way to slow hepatic fibrosis until they can be successfully treated for HCV.

**Randomized Clinical Trials**

A randomized, open-label trial comparing the early initiation of ART (within 2 weeks of enrollment, CD<350 cells/mm³), to the standard timing for initiation of therapy at the time (CD4<200 cells/mm³ or onset of AIDS defining illness), was conducted in 816 HIV-infected adults in Haiti who had a CD4 cell count from 201 to 349 cells/mm³ and no history of an AIDS-defining illness (28). In this study, in which the median baseline CD4 count across both groups was ~280 cells/mm³, early initiation of ART was associated with a 75% reduction in mortality (6 deaths in the early group versus 23 deaths in the ‘standard treatment’ group) and a 50% reduction in the incidence of tuberculosis (18 cases in the early group versus 36 cases in the ‘standard treatment’ group).

HPTN 052 was conducted in 1763 heterosexual couples (54% in Africa) discordant for HIV-1 infection (12). HIV-1–infected patients with CD4 counts between 350 and 550 cells/mm³ were randomly assigned to receive ART immediately or after a decline in the CD4 count to < 250 cells/mm³ or the diagnosis of an AIDS-defining event or onset of HIV-1–related
symptoms. The primary clinical end point was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a WHO stage 4 HIV event, or death. Immediate ART was associated with a 36% relative reduction in AIDS-defining events (40 events in the early group versus 61 in the delayed group), and a 51% relative reduction in the incidence of tuberculosis (17 events in the early group versus 34 in the delayed group) (29).

The SMART trial randomized 5472 HIV-1 infected persons > 13 years of age with CD4 counts above 350 cells/mm³ to either continuous ART or a drug conservation group in whom ART was deferred until the CD4 count decreased to below 250 cells/mm³ or the onset of symptomatic AIDS-related events, at which time ART was initiated (or reinitiated) and continued until the CD4 count increased to above 350 cells/mm³ (10). The study was stopped upon the recommendation of an independent data and safety monitoring board (DSMB) when it was demonstrated that continuous ART was associated with significant reductions in death from any cause (47 events compared to 120 in the continuous treatment and drug conservation groups, respectively), serious opportunistic infections (OIs) (2 events compared to 13 events, respectively), and non-serious OIs (18 events compared to 63 events, respectively). In addition, the incidence of major cardiovascular, renal, and hepatic diseases was significantly increased in the drug conservation group compared with the continuous ART group (65 events compared to 39 events, respectively; HR 1.7; 95% CI 1.1–2.5) (10).

The START study randomized 4685 ART-naïve asymptomatic HIV-positive patients with a CD4 count above 500 cells/mm³ to immediate ART or deferring ART initiation until the CD4 count fell below 350 cells/mm³, and used the same primary endpoint as the SMART study. START enrolled patients from April 2009 through December 2013 and was stopped early (in May 2015) upon the recommendation of the independent DSMB when it was demonstrated that immediate ART was associated with significant reductions in the primary endpoint (42 events compared to 96 events in the ‘immediate’ and ‘delayed’ groups respectively; HR= 0.43; 95% CI 0.30 - 0.62), as well as serious AIDS-related events (14 events compared to 50 events, respectively; HR= 0.28; 95% CI 0.15 - 0.50), serious non-AIDS-related events (29 compared to 47 events, respectively; HR=0.61; 95% CI 0.38 - 0.97), grade 4 bacterial infections (14 compared to 36 events, respectively), tuberculosis (6 compared to 20 events, respectively – a component of the primary endpoint), lymphoma (3 compared to 10 events, respectively – a component of the primary endpoint) and Kaposi’s sarcoma (1 compared to 11 events, respectively – a component of the primary endpoint) (13).

SMART and START demonstrated that many of the benefits of early and/or continuous ART are non-AIDS-related health outcomes, including less cardiac, renal, hepatic and malignant disease.
TEMPRANO ANRS 12136 (15) was a 2 x 2 factorial RCT evaluating early ART and a 6-month course of isoniazid preventive therapy (IPT) in 2056 HIV-1 infected patients in Ivory Coast with CD4 < 800 cells/mm³ who did not meet WHO criteria for ART at the time. The median CD4 count at baseline was ~460 cells/mm³. The risk of death or severe HIV-related illness was lower with early ART (immediate initiation) than with deferred (until CD4 count of 500 cells/mm³ or other WHO ART initiation criteria reached) ART (64 events and 111 events, respectively; adjusted HR, 0.56; 95% CI, 0.41 to 0.76; adjusted HR among patients with a baseline CD4 count of ≥ 500 cells/mm³, 0.56; 95% CI, 0.33 to 0.94) and lower with IPT than with no IPT (adjusted HR, 0.65; 95% CI, 0.48 to 0.88; adjusted HR among patients with a baseline CD4 count of ≥ 500 cells/mm³, 0.61; 95% CI, 0.36 to 1.01). The primary end-point component that occurred most frequently was tuberculosis (42%), followed by invasive bacterial diseases (27%), and death from any cause (23%).

**Risks & Uncertainties**

Despite these benefits, there remain uncertainties and potential risks from the use of early ART. In HPTN 052, ART was provided alongside other important prevention interventions and care services including: the use of condoms, an uninterrupted supply of and access to ART, and regular clinical followup and counseling. This led to high medication adherence and raises some uncertainty as to whether the study findings are generalizeable to real-world settings. Although life-threatening reactions to ART drugs are relatively rare, mild, moderate and severe reactions could lead to medication interruption. The influence of non-life-threatening and severe reactions on medication adherence can be important contributions to medication adherence as well (92). Ongoing daily adherence is pivotal to realizing the clinical benefit of early initiation seen in clinical trials. Some trials like START were stopped early, not allowing the opportunity to observe other potential longer-term adverse reactions, which might have an impact on individual health or long-term adherence to therapy. In one study, early interrupted treatment was no better than delayed continuous treatment for personal health outcomes, suggesting that (at least for personal health) it may be better to delay the initiation of ART in individuals not able to adhere to their treatment regimen (60). Uncertainties about cumulative toxicities and uncommon adverse reactions due to life-long use of ART remain, and ultimately modifications in recommendations could result, especially as cohorts of patients receiving early initiation of ART are followed for longer periods of time.

**Early Initiation of ART: Population Health Benefits, Risks, Uncertainties**

Treating to prevent the spread of communicable diseases is a cornerstone activity of disease control. By treating infected cases, the pool of infected persons from whom infection can be acquired is reduced (30); this approach has long been used to control
epidemics of sexually transmitted infections (31). In the case of HIV infection and transmission, the infectivity of individuals may be controlled with appropriate therapy that reduces viral load.

Early initiation and long-term adherence to ART represents a promising tool in the control and prevention of HIV worldwide. Through HIV suppression via ART, both per-act transmission probability and the duration of the infectious state are markedly reduced (30,32-34). Early and long-term ART may ultimately change the course of the HIV epidemic.

Using ART to control the spread of HIV was first documented in the mid-1990s; a trial of zidovudine for HIV-positive pregnant women demonstrated a significant reduction in perinatal HIV transmission (35,36). Since then, biological (37,38,39), mathematical modeling (33,40,41), ecological (42,43), and epidemiological (32,44,45) studies have investigated the use of ART to prevent the sexual transmission of HIV. The biological and epidemiological studies provide empirical evidence that with sustained adherence, ART decreases HIV viral load in blood and genital secretions and reduces the sexual transmission of HIV. The ecological and mathematical modeling studies suggest that ART may positively affect various population HIV indicators, such as community viral load and HIV incidence, and subsequently prevalence. However, there are significant limitations with these types of studies based on model assumptions and therefore related outputs should be interpreted with caution. Whether the infectivity of the HIV pool can be reduced sufficiently with early initiation of ART to reduce transmission globally is, at present, uncertain.

Earlier initiation of ART also has the potential to boost current HIV prevention efforts (46). Since modern ART regimens are less toxic, more tolerable and flexible (92), higher adherence rates with therapy are more likely so that early treatment of infected individuals for the benefit of the population has become a compelling strategy for changing the course of the HIV epidemic. Several studies of early ART initiation demonstrate the benefits of ART medications at both the individual and population level (12,14,15,29). These trials provide evidence that early ART (at CD4 counts >500 cells/mm³) in comparison to deferred treatment, contributes to a reduction in HIV transmission among serodiscordant heterosexual couples as well as a reduction in AIDS and non-AIDS related events. This also translates to increased AIDS-free survival and mortality patterns similar to those of the general population (47-49). Based on this knowledge, early initiation of ART is now recommended (1-4).

While there is evidence to suggest benefits of early ART initiation, close monitoring is still necessary to understand the long-term implications both at the individual and population levels (14, 15). For example, the generalizability of current findings to other at-risk
populations (e.g., men who have sex with men (MSM) and people who inject drugs (PWID)) is unknown. While one research study suggests a positive effect of ART on the reduction of sexual transmission among MSM (PARTNER Study) (50) conclusions are limited by study design (no comparison group). Ongoing research is needed to be decisive regarding this strategy for MSM and other populations, including PWID (43,50).

While modeling studies suggest early ART to be cost-saving and cost-effective (51), most of these were conducted assuming ART initiation at lower CD4 counts (less than 350 cells/mm$^3$) (41,52-54). It is also important to consider that most of the current studies evaluating immediate ART are occurring in high-endemic, low resource settings (55-59); therefore, certain results (e.g., cost-effectiveness) may not be generalizable to the Canadian context. Local implementation and monitoring efforts are necessary to fully evaluate the potential benefits and harms of early ART.

**Risks & Uncertainties**

To derive the promising effects of early ART initiation on population health, sustained life-long high level adherence to ART is critical. Lack of ART adherence strongly influences prevention and health outcomes. The evidence supporting early ART demonstrates a reduced risk but not complete prevention of sexual transmission of HIV, highlighting the importance of ensuring that other HIV prevention strategies are used in combination with ART. Otherwise, positive outcomes seen at the individual level (e.g., prevention of HIV transmission) may not translate to similar population level outcomes. Similarly, ART does not prevent against other STIs, further highlighting the importance of combined prevention approaches. Other factors, such as HIV drug resistance could also undermine the effectiveness of ART as a prevention method. The major risk to achieving the potential population health benefits lies in maintaining sufficiently high levels of adherence to ART, which at present is uncertain.

**Discussion**

There is growing evidence regarding the benefits of early initiation of ART. With this recognition, there has been a shift globally to recommend provision of ART regardless of CD4 count. The United States DHHS (3), BHIVA (1), EACS (4) and most recently, the WHO (2) have all recommended initiation of ART for all adults living with HIV. With this position paper, AMMI Canada lends its support to the recommendation for early initiation of ART in Canada based on the individual, as well as potential public health benefits. However, there are some important considerations that require further discussion.

**Resource Implications**
Evidence supports the cost-effectiveness of ART when initiated using previously suggested criteria in North American and European settings (61,62). With revised guidelines and earlier initiation of treatment, the direct treatment costs for ART will increase. Other direct medical costs related to caring for PLHIV will also increase (e.g., outpatient care, laboratory services and non-ART medication costs). However, substantial cost savings could also be realized by decreasing the numbers of patients experiencing a delayed HIV diagnosis and who present late in their HIV disease course (63,64). These higher costs are a result of higher health care costs associated with late presentation to care including outpatient, inpatient and medication costs. Earlier diagnosis, linkage to care and initiation of treatment can prevent many of the associated co-morbidities, and resulting costs which occur with delayed HIV diagnosis. In order to fully understand the complexity in caring for PLHIV and the resource implications, policy makers need to ensure that a broad range of costs are considered when conducting economic analysis for expanded ART coverage. For instance, if patients are lost to follow-up or develop opportunistic infections or other morbidities due to factors such as poor adherence, this could adversely affect the cost effectiveness of a treat-all strategy. However, early treatment will prevent some secondary cases of HIV infection, thereby also averting future costs. It is difficult to estimate the numbers of HIV cases averted, but if they are significant, the cost savings would also be substantial.

**Implementation Considerations**

In addition to important resource considerations, there are critical implementation considerations. The most critical is ensuring long-term adherence to therapy over a person’s life time. The challenges with the latter are well known to physicians caring for PLHIV. In addition, despite the tremendous scale up of ART globally, significant gaps in treatment coverage still remain. It is estimated that at the end of 2013, a total of 12.9 million PLHIV were receiving ART (65). While this represents significant success, it is important to recognize that this is less than 40% of the total number of PLHIV in the world. In Canada, there are an estimated 75,500 PLHIV (66). Currently, it is unclear how many people are on treatment in Canada and the size of the treatment gap. However, evaluation efforts are underway (67-69). According to marketing data provided by the Canadian affiliates of two large pharmaceutical companies, about 30,000-35,000 Canadians are receiving ART (Gilead and Merck, personal communication), suggesting that there may be a large treatment gap in Canada. A clear understanding of the epidemiology and characteristics of the HIV care cascade is essential for the monitoring and evaluation of an expanded treatment policy (70, 71).

In Canada, delivery and administration of healthcare services is a provincial and territorial responsibility. This may pose an issue of non-uniform coverage for early initiation of ART.
Having said that, the availability of ART across all provinces is not currently limited by criteria-based approvals. In Ontario and some other provinces, a facilitated access system simply restricts prescribing of ART to physicians with experience in managing PLHIV. However, in order to treat all HIV-infected Canadians, it will be necessary to continue to build more capacity in health care resources for PLHIV to realize a meaningful impact on patient-specific and public health outcomes.

Many factors contribute to a treatment gap and these can occur at any point along the HIV care cascade. These points include: not testing for HIV and therefore being unaware of one’s HIV status (approximately 21% of all PLHIV in Canada); having tested positive but not linked to care; linked to care but not initiated on ART; initiated on ART but unwilling or unable to adhere to medications (72). Often the causes for delayed initiation of ART are multi-factorial (73-75) and include factors at the individual patient and provider level as well as structural factors at the health systems or population level. Fear of a diagnosis and low perception of risk are two examples of patient level barriers (76-78). At the system level, access to HIV testing and distance from HIV care play an important role (76,79). Further, broader societal and structural factors such as stigma and legal environment including policies around criminalization of non-disclosure, affect the HIV care cascade (80-82).

Earlier initiation of ART requires that individuals be diagnosed sooner in their disease course and linked to care in a timely manner. However, as a result of the factors discussed earlier, delayed diagnosis and late entry to care, has been, and continues to be, a major challenge. It is estimated that in North America and Europe, 15-55% of HIV positive individuals present late to care (83-88). Therefore, resources and efforts are required to support policies and programs to ensure the availability and accessibility of a range of testing options. Alongside this, processes to support timely linkage to HIV care for individuals testing positive are also needed. Once linked to care and started on treatment, ensuring retention in care and long-term adherence to ART is essential (89,90). While modern ART is well tolerated, there remains a possibility that unanticipated long-term toxicities will emerge. In addition, the more people on ART, the more potential cases of virological failure with treatment-emergent drug resistance can be expected. The population effect of more cases of ART-resistant HIV is uncertain.

Barriers resulting in late presentation and/or non-adherence to ART have implications at the individual, population and health system level. At the individual level, delayed presentation and non-adherence can result in persons becoming ill from associated opportunistic infections or other comorbidities, resulting in worse outcomes. At the population level, individuals who are infected and undiagnosed or diagnosed but not retained in care, are at greater risk of transmitting the virus to others. A recent surveillance study in the US, suggests that individuals who are HIV infected but undiagnosed (18.1% of
the total HIV-infected population) and individuals who are HIV diagnosed but not retained in medical care (45.2% of the population) were responsible for 91.5% of all HIV transmissions (91). And finally, at the health systems level, individuals who are ill as a result of HIV infection require additional physician visits, hospitalization and medication, resulting in a greater burden on the health care system.

Guidelines recommending early initiation of ART will only be effective when accompanied by comprehensive prevention, treatment and care programs and policies that address stigma and discrimination and ensure long-term adherence to therapy.
References


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