MANAGEMENT OF HIV POSITIVE PREGNANCIES IN ONTARIO: CURRENT STATUS

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ABSTRACT

Background
AIDS is one of the biggest health crises we face today. With nearly 20 million women infected with the virus that causes it, HIV, maternal transmission of HIV is increasingly becoming a serious concern and hindrance in stemming the proliferation of the disease. While an ever increasing number of pregnant women are being administered anti-retrovirals to mitigate the vertical transmission of the virus, little is known about the changing trends in the type of agents used and the duration of therapy.

Objectives
This paper attempts to identify any changes in the pattern of HIV management in pregnant women for the period of time spanning 1998 to 2005.

Methods
Data from the charts of 183 patients were reviewed. A retrospective, longitudinal and cross-sectional patient chart review was employed to obtain data. Parameters such as therapeutic management of HIV, class of drugs used and duration of treatment were assessed to identify any evolving patterns over the course of the study.

Results
It was seen that over time, the number of women receiving adequate therapeutic interventions has steadily increased. We also identified evolving trends in terms of the classes of anti-retrovirals employed and the duration of prophylaxis.

Conclusion
The strategies employed in the management of HIV positive pregnancies in Ontario, while evolving over time, were found to be in line with the guidelines in place. The information delivered by this study might enable the medical community to assess the progress in dealing with this challenge thus far and further fine tune the current strategy.

Key Words: *MTCT, HIV, pregnancy, anti-retroviral therapy*

World wide, there are approximately 20 million women of childbearing age infected with HIV. Women currently represent the fastest growing group of people with HIV in every region of the world, including Canada. An estimated 11,800 women are living with HIV/AIDS in Canada, a number that represents approximately 20% of the national total of HIV infected individuals and is 23% higher than 2002 values.[1] In Ontario, women now account for 28.1% of all HIV infections, with the Greater Toronto Area (GTA) containing the highest concentration of cases.[2] With an increasing number of these HIV sero-positive women becoming pregnant, the

pharmacotherapeutic approach adopted by physicians and health care providers is paramount to the simultaneous prevention of disease progression and mother-to-child transmission (MTCT).

The major factors governing vertical transmission of the HIV virus from mother to child can be broadly classified as maternal, obstetrical and neonatal. The single most important marker that can predict chances of MTCT is maternal viral load. The rates of perinatal viral transmission are proportional to the maternal plasma HIV RNA level.[3-5] In addition to viral RNA levels, low counts of CD4 cells have been associated with higher incidence of MTCT.[5] A Highly Active Antiretroviral Therapy (HAART) regimen during gestation offers further protection to MTCT, even in cases of low viral loads. HAART entails a minimum of three agents from at least two different antiretroviral drug classes and is the mainstay of most anti-HIV drug regimens. In terms of obstetrical considerations, pre-mature delivery (before 35 weeks), ruptured membranes and chorioamnionitis have all been found to contribute to a greater propensity for the virus to infect the child. Lastly, neonatal factors such as pre-term delivery and low birth weight are associated with *in utero* MTCT. Breast-feeding has also been implicated in viral transmission; although, this is more of a problem in resource-limited settings rather than in Western countries where formula feeding is a viable alternative. Preventing vertical transmission of the virus is a vital target that must be achieved if we are to successfully combat the threat that the HIV/AIDS epidemic poses. Health and regulatory bodies have recognized this goal across the globe and this is reflected in the guidelines issued by these agencies.

The guidelines utilized by physicians and health care professionals within Canada vary to some extent but the majority adhere to the Canadian consensus guidelines for the management of pregnant HIV-positive women and their offspring.[6] Established by the Canadian HIV Trials Network Working Group on Vertical HIV Transmission, these guidelines provide detailed recommendations for preconception counselling as well as antenatal, intrapartum and postpartum care. Briefly, according to the guidelines, preconception counselling should consist of ensuring HIV-positive women of childbearing age are properly educated on the prevention of unwanted pregnancy. Additionally, antiretroviral agents with potential teratogenic effects should be avoided when possible. Antenatal care should involve an individualized therapeutic regimen. It is recommended that HIV-positive pregnant women who have not previously received HAART should initiate a regimen consisting of two nucleoside analogues (e.g., zidovudine/AZT and lamivudine/3TC) in combination with either a protease inhibitor like nelfinavir or a non-nucleoside reverse transcriptase inhibitor such as nevirapine.[6] Treatment should be initiated 14 weeks into gestation if viral loads are sufficiently low and CD4 counts are in an acceptable range. For women already on HAART, it is recommended that their regimens be evaluated for teratogenic potential and adjusted accordingly. It is recommended that this latter group of women stay on their regimen for the entire duration of their pregnancy. Intrapartum care should consist of regular confirmation of viral load suppression. Patients should be informed of evidence to suggest that MTCT is reduced by approximately 50% when birth is via caesarean section as opposed to vaginal birth.[7] However, as studies comparing transmission rates seldom include women on HAART, it is recommended that caesarean section only be encouraged when viral loads are unsuccessfully managed.[6] Postpartum care recommendations for the mother include continuation of HAART once possible and contraception counseling.[6] Postpartum care recommendations for the infant include an absolute avoidance of breast-feeding and the initiation of zidovudine within 6 to 12 hours of birth (maintained for up to 6 weeks).[6] Immediate initiation of zidovudine/AZT and nevirapine therapy is recommended in the event that no therapy was prescribed to the mother during the antenatal or intrapartum periods. It is worth noting that U.S. guidelines formulated by the Perinatal HIV Guidelines Working Group in the United States are consistent with those of Canada.[8]

The primary objective of this study was to examine the patterns employed in the management of HIV positive pregnancies in Ontario. In particular, we were interested in

identifying the changing patterns in therapeutic strategies and duration of treatment as well as comparing our observations to issued guidelines.

METHODS

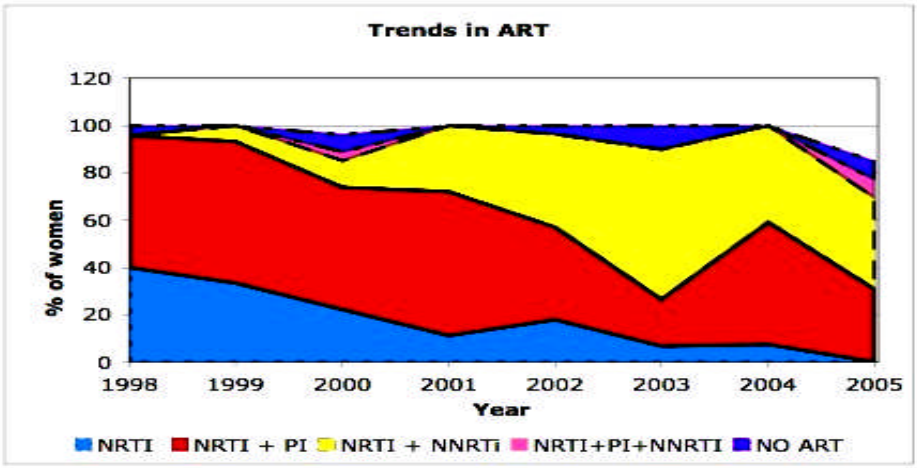
This study examined patterns in therapeutic management of HIV sero-positive pregnant women in Ontario. Patient data was obtained from a database maintained by Motherisk (Sick Kids Hospital, Toronto, ON), a program with a mandate to provide counselling to both patients and practitioners on pregnancy-related topics ranging from drug safety and usage to disease risk. The University of Toronto Research Ethics Board approved the study. A retrospective, longitudinal and cross-sectional patient chart review was carried out to collect data. The data included information from HIV sero-positive pregnant women who were involved with the program from 1998-2005.

A detailed questionnaire was prepared to extract data from the patient charts. All patient identifiers were removed before the data were collected and analysed. The following data were collected: disease progression in mother at the time of pregnancy, incidences of infections and/or hospitalization during gestation, the details of therapeutic intervention including the class of drugs and duration of therapy, the mode of delivery, IV AZT administration during labour, gestational age at birth, weight of infant at birth and any complications post partum as well as newborn HIV status. All data were transcribed by the authors onto the questionnaire. While all available patient files for a particular year were examined, charts with missing data on drug usage, type of delivery and use of prophylactics during labour were excluded from the study. To assess the trends in drug use and period of prophylaxis, we performed a linear regression test on the data using GraphPad Prism (GraphPad Software, San Diego, CA.). Statistical analysis was done in consultation with Dr. Thomas Einarson (Leslie Dan Faculty of Pharmacy, University of Toronto).

RESULTS

Patient files from 183 pregnant women were reviewed for the purpose of this study. The large majority of women were aware of their HIV status at the time of conception. The parameters were analyzed on a year-to-year basis to enable identification of evolving patterns over the course of the study. With regards to ART (Antiretroviral Therapy) during the course of gestation, some clear changes were observed over the duration of the study (Fig. 1).

FIG. 1 The evolving trend over the course of study in the classes of drug employed to manage HIV during pregnancy. The percentage of women in a particular class of drug is plotted against the various combinations available for treatment.

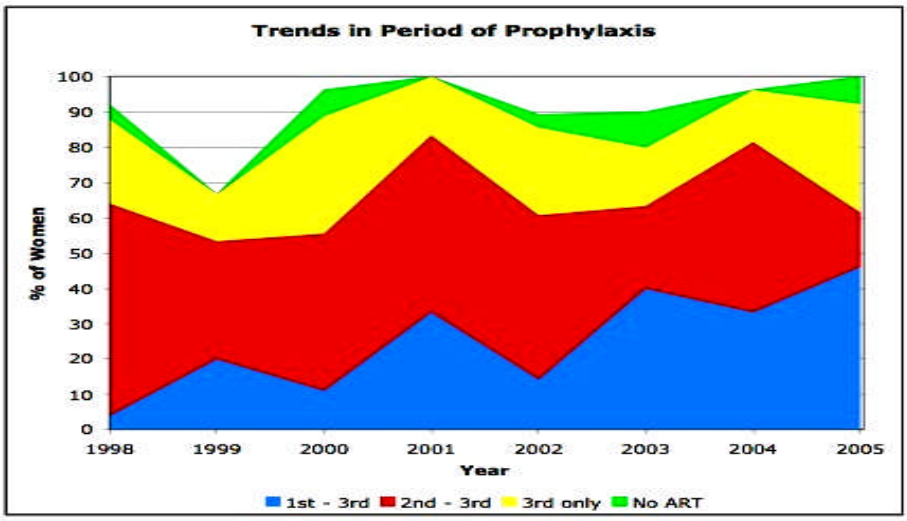


NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; PI: Protease Inhibitors; NO ART: Absence of antiretroviral therapy

While highly prevalent in 1998, the use of NRTIs monotherapy has seen a steady and steep decline with a decrease from 40% in 1998 to a complete absence in 2005. This trend was found to be highly significant ($r2 = 0.896$, $p<0.001$). Indeed the use of more than one class of antiretroviral drugs (i.e., HAART), has gained ground. The use of NRTI + PI, the traditionally favoured HAART cocktail, has also seen some changes. There appeared to be a downward trend in the use of this combination, especially from 2001 onwards; although the trend did not reach statistical significance ($p>0.05$). In the year 2001, this approach was employed to treat 61% of all analyzed cases while this number slipped down to 31% in 2005. The ground lost by the NRTI and NRTI + PI combinations was captured by NNRTI + NRTI combinations and accounted for approximately 38% of all ART in 2005. The trend towards the increasing use of NNRTI + NRTI was statistically significant ($p<0.05$; $r2= 0.69$).

The period of ART during pregnancy was also examined (Fig. 2). There was a clear trend towards extending treatment duration with almost half of the patients receiving antiretroviral therapy throughout the course of pregnancy in 2005. This changing pattern reached levels of statistical significance and had a good correlation ($r2= 0.69$). The use of ARVs during the other sections of gestation was virtually unchanged.

FIG. 2 The pattern of initiation and duration of ART in pregnant HIV women. The period of treatment is divided in terms of trimesters.



The administration of IV AZT during delivery and the mode of delivery were also tracked (Fig. 3). In recent years (from 2001 onwards), the strategy has had a very consistent with a high compliance rate (close to 80%). Additionally, the mode of delivery was tracked over the years (Fig. 4). The proportion of patients who delivered vaginally remained relatively steady from 1999-2005 (approximately 50%) while approximately one third elected to deliver by caesarean section.

FIG. 3 The use of IV infusion of AZT during parturition from 1998 to 2005

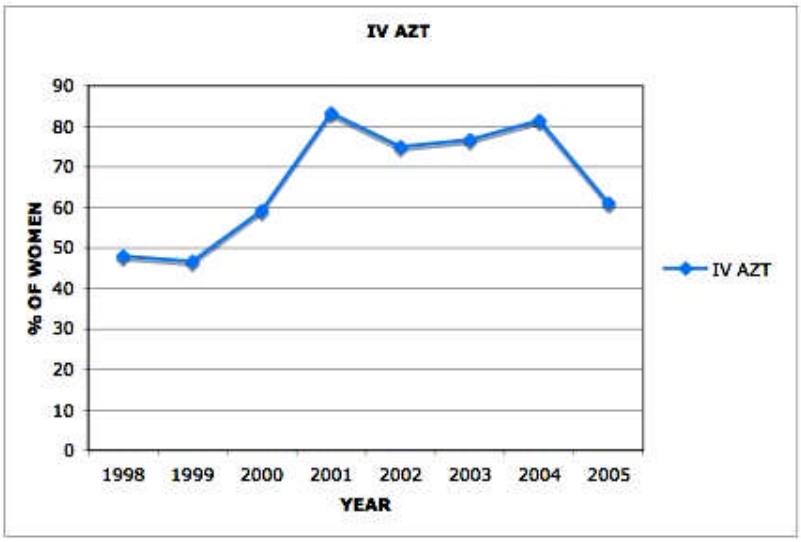
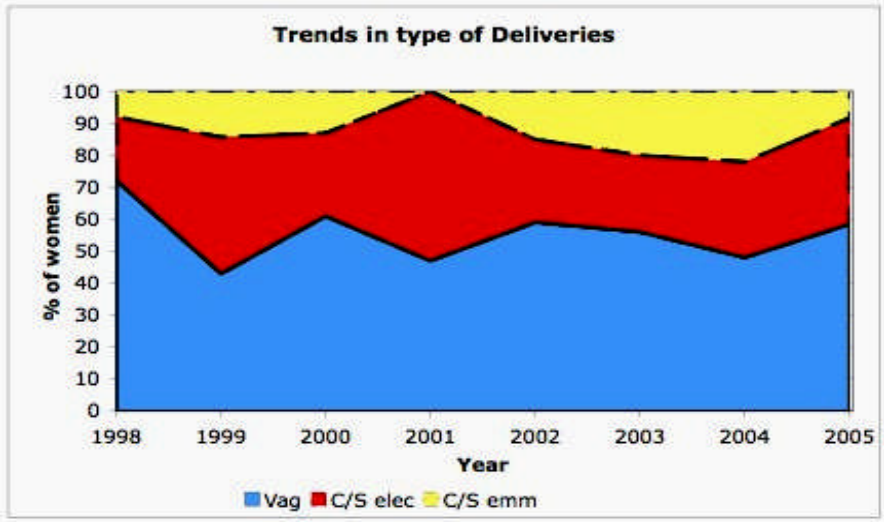


FIG. 4 The mode of delivery over the course of the study. No significant shift was observed, with vaginal mode of delivery being chosen by the majority of women.

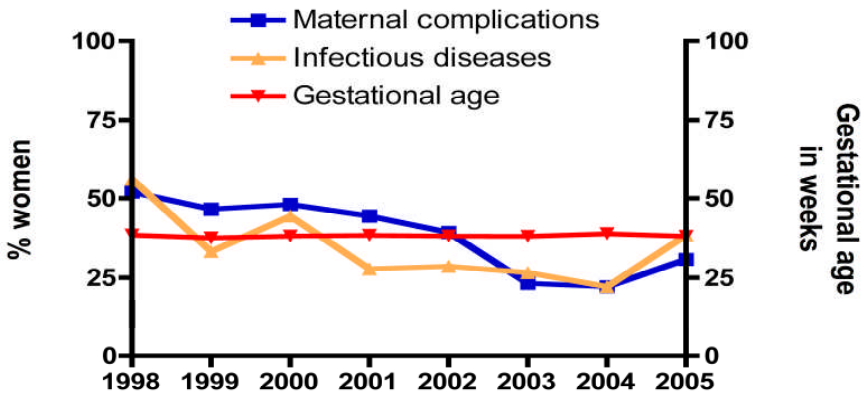


Vag: vaginal; C/S elec: elective cesarean; C/M emm: emergency cesarean

Data on the HIV status of the newborn was not well documented. While postnatal HIV testing was performed, data was not available to make accurate estimates about the extent of MTCT for the sample set. Of all the patient files available, only one case of vertical transmission was observed. However, due to the majority of the cases having incomplete HIV test result data, an accurate estimation of the success of this strategy could not be made.

There was no change over the years in the gestational age of the newborn. However, there was a clear and statistically significant downward trend in the incidence of maternal complication during the course of gestation. The incidence of infections in the mother during pregnancy also went down, but failed to reach levels of statistical significance (Fig 5).

FIG. 5 Maternal complications and gestational age



The incidences if maternal complications, infections and the average gestational age in weeks (right Y axis)

DISCUSSION

To examine if the therapeutic choices being made in the clinic are reflective of the dynamic changes in treatment guidelines, it is essential to retrospectively look at the strategies employed in managing HIV during pregnancy. In order to evaluate trends and current strategies in place, we examined the classes of drugs being used, the period of prophylaxis, the mode of delivery and use of IV infusion during labour.

MTCT is of growing concern globally as an increasing number of HIV sero-positive women are choosing to bear children. According to the latest estimates, more than 2 million HIV sero-positive women become pregnant globally. With vertical transmission rates varying between 2% and 40%, there are more than 500,000 new child infections being reported each year.[9] Current guidelines call for the use of HAART to effectively counter the HIV. This entails a drug regimen consisting of a minimum of three antiretroviral agents from at least two different classes of drugs. This strategy has been found to be the most effective in suppressing viral loads, which are directly correlated with rates of MTCT. In 1998, the most popular combination prescribed was that of two NRTIs along with one PI. This was in line with that recommended within Canadian and international guidelines at that time. For approximately 4 years, until 2001, this cocktail enjoyed the confidence of prescribers as it was steadily employed in about 60% of all women on ART. However, from 2001 onwards there was a decline in the prescription of PIs in combination with NRTI. Instead, the combination of NRTI and NNRTI seemed to find favour. In fact, this particular combination saw a rapid surge in usage from 1998 to about 2003 when it was the most widely used combination. The reasons for this shifting preference for NNRTI over the traditionally established PIs are not entirely clear to the authors. However, as some recent reports indicate, NNRTIs have been found to offer several advantages over PI boosted regimens. The primary advantages include better CNS penetration and more “patient-friendly” dosage regimens. Additionally, NNRTI agents have been found to be better tolerated in patients than the PIs. It is also important to note that while more

than 40% of treated women were not under the HAART umbrella in 1998 (many were receiving only NRTIs; this number fell rapidly from 1999 onwards. However, as recent as 2003, there were well over 10% of women receiving an ART regimen that did not meet the HAART requirements. Reasons for women still receiving suboptimal care need to be further explored and are a cause for great concern. Such high rates of inadequate treatment could possibly be explained by factors such as inability of the patient to tolerate HAART cocktails and/or non-compliance on the part of the patient rather than physicians failing to comply with established guidelines.

TABLE 1 HAART Umbrella

Year	Patient files available	% Women outside the HAART umbrella
1998	25	44
1999	15	33
2000	27	30
2001	18	11
2002	28	21
2003	30	17
2004	27	7.4
2005	13	8
Total	183	

Patient files contributing to the results of this study according to year along with teh corresponding percentage that fell outside of the HAART umbrella. The mean number of patient files available for each year was approximately 23. In 1998, 44% of patients fell outside the HAART umbrella. This value dropped signficantly to 8% in 2005.

Another important aim of this study was to examine the period of treatment during the course of gestation. The duration of prophylaxis and the point of initiation of ART during pregnancy are vital for both the efficacy of treatment and foetal safety. Keeping in mind that the agents being administered to HIV patients are highly toxic moieties, disrupting the normal cell machine,[10-18] these agents pose a very real risk to the developing foetus, especially during the early organogenesis phase (during the first trimester). The issue is complicated by the acute shortage of data on the safety of these agents during pregnancy. Only a handful of trials have been conducted for the 16 or so ARVs commonly employed.

The fact that the maternal-foetal interface is extremely permeable during early pregnancy, as the placenta is not fully developed, is also something that physicians have to consider during the management of an HIV sero-positive pregnancy. However, this is one of the rare medical conditions where the cost of erring on the side of caution carries an enormous price, both for the mother and the unborn child. The maintenance of the health of the mother should be of paramount importance while making decisions about initiation or discontinuation of therapy.

Upon examining the data pertaining to the period of ART treatment during gestation, we can identify some clear temporal trends. The most prominent trend observed over the course of the study was the steady increase in the percentage of women receiving therapy throughout the course of gestation. In the year 2005, approximately 46% of all women receiving treatment were treated throughout the gestational period and this was up from a mere 20% in 1999. This change in treatment pattern may be due to a number of factors. Firstly, it is possible that a large number of women were already on ART at the time of conception. Secondly, as per the guidelines, any woman whose viral load is not satisfactorily managed will stay on HAART, irrespective of the stage of pregnancy. Thirdly, the use of ARVs throughout the course of pregnancy could be a

sign of growing confidence in the safety of these agents during gestation.

With regards to the mode of delivery, there are two factors to be kept in mind while considering this. Firstly, there have been published studies showing a lack of any benefit of an elective caesarean against MTCT in patients already on prophylactic ART, and a number of studies espousing its benefits in minimizing risk of vertical transmission.[19-23] Secondly, since it is an opt-in procedure, the majority of patients will understandably be reluctant to undergo surgery. Together, the two factors can explain the low percentage of women opting to deliver via caesarean section when most of them have been on ART for a significant portion of the pregnancy. Thus, it is not surprising that over 60% of all women delivered vaginally and this has been the case throughout the study. Less than one third of all the cases examined deliver via elective caesarean section. The remaining women delivered via emergency caesarean section due to unforeseen complications. These figures remained more or less consistent across the study period.

Of all the cases available, only one confirmed case of vertical transmission to the neonate was observed; encouraging as this is, it must be noted that a majority of the case files had incomplete or no data at all about the serological test done to test the newborn for the virus. Thus, this study is not able to fully address the efficacy of the changing patterns of drug therapy in terms of minimizing MTCT. However, it did show that the overall health of the mother during the course of pregnancy was better, as indicated by lower complications and infections.

The HIV/AIDS epidemic is uniquely characterized by a grave socio-economic impact in addition to tangible health effects on both the affected individual and the community as a whole. This has resulted historically in varied reactions from society, regulatory bodies and health professionals. Over the last few years, the face of AIDS has begun to change dramatically. What was initially believed to be a condition affecting only homosexual males has now spread to include a much greater proportion of the heterosexual populace. Furthermore, there has been a distinct and worrisome trend with the disease infecting an increasingly larger number of women as a percentage of all HIV sero-positive patients. In addition, an increasing number of HIV sero-positive patients are choosing to bear children despite awareness of their HIV status. This may be explained by growing confidence in the efficacy of HAART in curtailing MTCT.

This new scenario has forced health and regulatory bodies to have a strategy specifically designed to address MTCT. As outlined, the guidelines call for rigorous ART with more than one class of drug during the course of pregnancy along with some other recommendations such as IV AZT during delivery, elective caesarean section when necessary and the like. While HAART has proven to be a potent strategy to counter the virus, there remain some unanswered questions regarding these potent medications. For example, there is limited foetal safety data for these agents. Agents such as AZT and 3TC have been known to cause toxicities in mice foetuses following prolonged exposure during gestation.[24-26] No such data on human foetal safety is available. Until this knowledge gap is bridged, the utilization of HAART to its maximal potential cannot be attained without some degree of risk.

In conclusion, the most effective weapon in our arsenal to counter MTCT is the judicious use of HAART. It is important to use the right combination of antiretroviral agents at the right dosage at the most appropriate time. In observing Ontario patients, we identified clearly evolving trends over time with respect to both the class of antiretroviral agents utilized and the period of prophylaxis. In addition to drugs, the mode of delivery can also play a role in determining the rates of vertical transmission of the virus for women with poorly controlled HIV. That being said, vaginal delivery seems to be the historically preferred mode and the trend we observed suggests that it will remain so in the future. It may be concluded that the management of HIV sero-positive pregnancies in Ontario, while dynamic, is in line with the issued guidelines.

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