The HIV Care Cascade: Identifying Gaps and the Role of the Pharmacist

Eleventh Annual HIV Pharmacy Education Day – December 12, 2019

Introduction

The eleventh annual HIV Pharmacy Education Day was an opportunity for Ontario pharmacists from community and hospital settings to share experience, and to learn more about emerging issues and opportunities in HIV pharmacy.

New Paradigms for Treating HIV

Two-drug vs three-drug regimens in management of HIV

Pierre Giguere, Pharmacist, The Ottawa Hospital

Although two-drug treatment combinations have been discussed for a while, there has been a limited uptake of these combinations in treatment guidelines. Why have they not become a greater focus?

History plays a role:

- early 1990s treatment options (two NRTI drugs) had very low rates of viral suppression/quick resistance
- three drug combos emerged in the mid to late 1990s (adding either a PI or a NNRTI to the existing NRTIs), they improved viral suppression with high toxicity
- a study of four drugs, found no additional benefits

Investigations then focused on three-drug combinations working to improve their tolerability and efficacy by improving the NRTI backbone and developing more powerful and tolerable third drugs. This has led to the evolution of today's most widely used combinations featuring two NRTIs and an Integrase Strand Transfer Inhibitor (INSTI), and to relatively little attention to reducing the number of drugs in the combination.

Currently reliance on a single drug is not an option. Although the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (Department of Health and Human Services, US) rely primarily on three drug options, it does list some two drug options for therapy naïve patients where ABC, TAF or TDF cannot be used or are "not optimal." [NOTE: In the most recent guidelines released December 18th 2019, the Panel has added DTG/3TC to the list of Recommended Initial Regimens for Most People with HIV.] These two drug combinations do work, but at the end of the day, reviewers have been reluctant to mess with success. Triple drug therapies are usually well tolerated, and we now have years of data, with little emergence of resistance mutations using effective triple combinations involving integrase inhibitors like DTG or BIC. Pierre did note a recent case report of a previously unreported integrase mutation in a treatment-experienced patient taking BIC/F/TAF (Andre-Garnier E et al. EACS CC3/1, 2019). This is one of the first failures noted, and it illustrates the point that with time the virus does find a way.

However, two-drug combinations might well offer:

- less short and long-term toxicity
- preserve drug class options
- potentially contain costs

There is growing evidence for the non-inferiority of a two-drug regimen:

- most notably the GEMINI studies which recently released 96-week data comparing DTG/3TC to DTG/TDF/FTC showing the durability of this therapy (Mascolini M. IAS 2019)
- cohort studies are looking at real world issues (do dual combos enable better adherence)
- few discontinuations are seen with either type of therapy

Remaining questions for two drug regimens:

- Will dual therapies prove as durable at 3, 4, 5 years as triple therapies have?
- Is there any evidence of low level (<40 copies/ml) viral replication with these therapies?
- What is the presence of archived resistances that could potentially undermine dual therapies? (Preliminary work has not yet demonstrated a problem.)
- Can dual therapies be used in rapid start approaches without added risk?
- Will the significance of drug interactions change in two drug regimens, compared to what we know about these interactions in three drug combos?
- Will dual therapies change the threshold for adherence? (What happens with 80% adherence?)

Question for Pierre: Do 3TC and FTC respond similarly in patients from a side effect perspective?

- Pierre thinks they are largely similar with perhaps a higher incidence of the relatively rare side effect of hyper-pigmentation with FTC
- a small study recently presented in Switzerland using dual therapy with DTG/FTC (instead of 3TC) and showed similar outcomes in terms of tolerance and efficacy
- several pharmacists present reported personal experiences with patients formerly on 3TC who had switched to FTC regimens reporting difficulty with GI symptoms

CARLA (Cabotegravir/Rilpivirine Long Acting)

This emerging two drug injectable regimen

- has a different resistance profile and is metabolized differently than similar drugs like DTG
- has a low risk of drug interactions
- delivered by IM injection
- Absorption is lower in females and patients with higher BMI

Initial oral induction of the drug is given followed by monthly injections. There are three key studies: LATTE-2 (Margolis et al. HIV Glasgow, 2018); ATLAS and FLAIR (48 weeks - Fernandez C et al. HIV AIDS (Auckl). 2019).

Response rate in these trials was fantastic. However, two patients had baseline mutations and developed resistance, and two others with no documented baseline resistance also experienced virological failure. These mutations did not cause resistance to DTG. Treatment is well tolerated; injection site reactions are the main challenge. This treatment is currently under-review and Canadian approval is expected mid to late 2020.

Injectable ARV: practical considerations regarding administration, tolerability, & delivery

Nancy Tremblay, Registered Nurse, The Ottawa Hospital

Nancy Tremblay is a nurse with extensive experience delivering CARLA as part of trials at the Ottawa Hospital. She focused on the benefits that she and her patients perceive with CARLA, practical experiences of use, and what needs to happen to implement these therapies as part of routine care.

The Trials

- LATTE-2 began in Ottawa in 2014. Patients were ARV naïve, and had 20 weeks of oral induction therapy priority to beginning IM injections, and then four weeks with oral therapy containing CAB. Participants were randomized to CARLA injections at 4 weeks, 8 weeks or oral drugs and offered injectables later. Current Ottawa patients have now completed week 264.
- ATLAS participants were already on successful ARV and virally suppressed. After 4 weeks oral CAB containing therapy, if viral suppression was maintained, they were randomized to stay on oral therapy or 4-week injectable CARLA. This study is not ongoing, but rolled into another trial.
- FLAIR was intended to collect more data about women. It recruited women who were ARV naïve. Women began with 20 weeks of Triumeq. If suppressed, women were randomized to continue oral treatment or have CARLA injections every 4 weeks. Ottawa patients are now at week 132.
- ATLAS 2M – Adults on successful ARV, including the original ATLAS participants (then at week 52). Participants were randomized to 4 or 8 weeks CARLA IM injections. Ottawa patients are at week 92.

In total from all studies, the Ottawa Hospital has 22 patients on CARLA IM therapies: 11 receiving injections every 4 weeks, and 11 receiving injections every 8 weeks. There have been no dropouts for dissatisfaction.

Injection of Drug

- The volume of the injections is quite high; each treatment requires two injections, one on each side of the body. Four-week injections require a 2 ml volume; eight-week injections require a 3 ml volume.
- The injections need a big muscle. The ventrogluteal site (on the side at the front of the hip) is recommended, instead of the dorsogluteal site (at the back), traditionally preferred in nursing practice. This area is further from blood vessels and major nerves (sciatic). Patients lie down for the injections.
- A longer needle is used - 1.5 inch (or 2 inch for larger patients). CAB is a thinner fluid and can use a 23-gauge needle, while the Rilpivirine is a more viscous fluid that must be refrigerated until 15 minutes before injection. It requires a 21-gauge (larger bore) needle. Two-inch versions are special orders.
- A "Z track" injection technique is used.

Risks

Most patients report pain and or discomfort for 2-3 days especially going up or down stairs. Four weeks is enough time to heal, so site rotation is not necessary. Over the series of injections, patients begin to report less pain. Tylenol and heat/cold are suggested for pain. No vigorous activity is recommended for 24-48 hours, but patients who severely limit their activities report more severe and lasting pain.

With any IM injection, there is a risk of intravenous injection or partial IV injection. Nancy has had a probable IV injection and they have been reported by others.

- The patient will feel immediately "unwell," but there seem to be no lasting ill effects.
- The concern is that these patients may not have received an adequate and sustained dose of drug.
- There is also the possibility of QT prolongation. This was a dose-related side effect noted in early phase studies and resulted in use of 25 mg daily dose moving forward vs 75-100 mg daily
- Possible protocols for suspect IV injection are not clear.

Why do we need Injectables?

- a good option for patients with poor GI absorption
- adherence easier for some (keeping an appointment easier than taking a pill)
- more freedom from stigma, avoiding questions about their medications when traveling or in public

Issues as the treatments are commercialized (likely in 2020):

- Where are these injections going to be given and by who?
- In studies, participants have optimal support. Injections were permitted one week late (or one week early.) In routine use, how are patients kept on schedule? How do we respond to missed doses?
- Who are appropriate/inappropriate patients? Consider weight, visit adherence, lifestyle.
- There are workload issues. Currently physicians and pharmacists see stable HIV patients every six months; injections happen every 4 or 8 weeks. People need to lie down, and be monitored after.

There are US studies of different settings for this treatment (hospitals, infusion centres, homecare). How will this "fit" in the Ontario system?

A slide was provided with resources offering additional perspective on injectables:

- https://www.pharmaceutical-technology.com/comment/hiv-injections-viiv-healthcare/
- https://www.nature.com/articles/d41586-019-00721-w
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6682757/
- https://viivhealthcare.com/en-gb/media/press-releases/2019/july/viiv-healthcare-announces-start-of-first-ever-study-to-identify-and-evaluate-approaches-to-implementing-its-once-monthly-injectable-hiv-treatment-in-clinical-practice/
- https://www.medpagetoday.com/meetingcoverage/idweekvideopearls/82787

Medical Cannabis – the good, the bad, the unknown

Multidisciplinary approach to harm reduction

Wiplove Lamba, Psychiatrist, Canadian Society of Addiction Medicine

Dr. Lamba is a psychiatrist who does a lot of work in addictions. Alcohol is the most common, but opioids cause the most chaos in people's lives. Initially, he had little to offer beyond methadone, but as he talked to patients, he realized the importance of harm reduction and the value of information like safe injection technique to his clients. He began to work to become "harm reduction capable." He came to recognize the value of having people with lived experience on his team, and to stress human interactions with clients.

With cannabis, he feels biased by the patient population he sees. This population has a lot of underlying medical illnesses and often feel that cannabis is the only way they can cope. His view of best practices is shaped by addictions and pain guidelines, but also by the experiences of the people in front of him.

At St. Mikes, there is a multi-disciplinary addictions team, including people with lived experience. His experience prescribing cannabis is limited, mostly for harm reduction purposes. However, he reflected on the practice of harm reduction, and the possibility that for some small portion of patients harm reduction strategies may cause harm. For cannabis, there is an associated withdrawal syndrome. About 10% of users may become addicted (lower than many drugs.) It is important to screen for problematic use.

Resources:

- Canadian Research Initiative in Substance Misuse. Lower-Risk Cannabis Use Guidelines (multiple resources), Oct 2018.
- Canadian Centre on Substance Use and Addictions. Clearing the Smoke on Cannabis. Oct 2019.

Medical cannabis as harm reduction

M-J Milloy, Research Scientist, The University of British Columbia

Dr. Milloy's work focuses on the risks and possible benefits of cannabis in the context of the opioid epidemic. Last year in Canada, there were over 5000 completely preventable opioid-related deaths. In BC, drug overdose has surpassed suicide, car accidents and homicide combined as a cause of death. This is largely due to the contamination of the drug supply. Despite recent government action, rapid access to barrier free care is an exception, not the rule, for those most affected.

Can cannabis be part of the solution? There are several papers, which link change in opioid use to the availability of medical cannabis. The first (Bachhuber MA et al. JAMA Internal Medicine 2014) observed that US states with medical cannabis laws have approximately 25% lower rates of opioid overdose deaths. Subsequent papers have continued to explore (and debate) this connection.

Two subsequent studies have approached these questions more directly:

- Boehnke KE et al. J Pain 2016 showed that medical cannabis could help chronic pain patients using prescribed opioids to reduce their opioid use
- Lucas P et al. Harm Reduction Journal 2019 surveyed 2032 medical cannabis users and found that about a third were using cannabis to substitute for opioid drugs (both prescription and non-prescription), and some were able to completely eliminate opioid use

This is interesting preliminary data, which needs more information from people directly at risk of opioid harm. In Vancouver, data from such populations is collected through three cohort studies:

- Vancouver Injection Drug Users Study – 1500 people who inject drugs
- At Risk Youth Study – 1000 street-involved youth who use drugs (other than cannabis)
- AIDS Care Cohort Evaluate Exposure to Survival Services (ACCESS) – 1100 people living with HIV who use illicit drugs – half are stabilized on methadone, others primarily using crack

Data from all three studies can be pooled. It has found the following:

1. There is a lot of cannabis use in these populations, over half used cannabis at least once in the last six months, and about half of those use daily; getting high is the most common reason for use, but three quarters report some medical use
2. Many said they were using cannabis as harm reduction to deal with their other substance use. The team has published on intentional use of cannabis to reduce crack use (Socias ME et al. Addiction Behavior 2017) associated with a decline in crack use
3. Cannabis use is beneficially associated with reducing the risk factors for overdose.
   - Daily cannabis users are less likely to start injecting drugs (Reddon H et al. Drug Alcohol Rev. 2018)
   - Those with THC in their urine are 50% less likely to have trace fentanyl (Hayashi K et al. Drug Alcohol Depend 2017)
   - Daily users are more likely to be retained in opioid treatment (Socias et al. Addiction. 2018)
   - Among those with chronic pain, daily users of cannabis were less likely to be using illicit opioids (Lake S et al. PLoS Med. 2019)
4. Virtually all cannabis used by this population is being purchased from illegal sources

There are still very clear limitations to this information. We cannot conclude cause and effect. We need more information about cannabis use patterns: doses, type etc. Only two relevant controlled trials have been done:

- Cooper ZD et al. Neuropsychopharmacology. 2018 – Combining opioids and cannabis in a double-blind study of 18 healthy volunteers increased the subject's pain threshold and tolerance
- Hurd Y et al. Neurotherapeutics, 2015 – Injections of CBD reduced the craving for heroin when experienced users were exposed to visual cues

Cannabis is not a panacea and we need better measures of potential harms. Dr Milloy's group is now beginning trials, the Generalized Experiments in Medical Marijuana and Addictions (GEMMA), which will test these benefits through controlled trials. The first study will co-dispense cannabis with opioid agonists.

Medical Cannabis as treatment

Sarah McFarland, Nurse Practitioner, The Allan Clinic, Toronto

Cannabis is not a new medication. In the early 1930s, 28 cannabis-containing medications could be prescribed. These medications (and all research) was banned in the US in 1939.

The body's endocannabinoid system affects many body processes including stress, mood and immune function. There are two major endocannabinoids endogenous to the body. Two receptors in the body respond to these substances:

- CB1 – primarily in the brain and spinal cord
- CB2 – found more broadly (guts, kidneys, etc.)

In addition to these endogenous human cannabinoids, there are over 100 plant-based cannabinoids. Two are best studied: THC and CBD. In addition, there are synthetic cannabinoids.

What are cannabinoids used to treat?

This is a polarizing topic. The same evidence has often been used to reach vastly different conclusions and there are many conflicting systematic reviews. It is not currently first line therapy for any condition, but quality evidence supports use for:

- Chronic pain
- Muscle spasticity in MS
- Epilepsy (Davet)
- Chemo-induced nausea

… and mounting evidence for other uses!

When should we use cannabis in HIV? Symptoms we know people with HIV are experiencing, where cannabis use may be relevant:

- Anxiety/depression/PTSD/stress
- Nausea/vomiting (drug related)
- Loss of appetite
- Pain

What should be considered when contemplating cannabis use in HIV treatment?

- What symptoms are you trying to manage?
- What other medications and other non-pharmacological treatments has the patient tried?
- What are the patient's thoughts/feelings about cannabis?

Contraindications

- Less than 25 years of age
- Severe mental illness
- Pregnancy and breastfeeding (absolute)

Strain selection is based on the balance of THC and CBD:

- THC – associated with the high and the psychotropic effects, induces analgesia, anti-spasmodic, reduces nausea and vomiting
- CBD – little or no psychotropic effects, analgesia and anti-inflammatory properties

How do you select strains? Sarah's clinic uses validated scoring tools, but in general, in older patients with complex comorbidities or risk of falling – CBD should be predominant.

- No DINs to help you decide
- START LOW and GO SLOW
- Monitor patient for severe side effects

Dosage

Don't titrate dose around patient's experience of a high. Aim for a dose that causes a therapeutic response, defined as at least a 30% reduction in pain or other symptoms. Most patients will respond to a gram a day or less. Tolerance does not generally develop.

Side effects

Most common: drowsy, dizziness, dry mouth (mostly caused by THC). In response, lower the dose or reduce the proportion of THC. Can discontinue, if symptoms are problematic.

Your patients are using cannabis, and will turn to you for information. They need consistent follow-up.

Medical cannabis –what pharmacists really need to know in context of the opioid crisis

Laura Murphy, Pharmacist, University Health Network

Fentanyl has had the biggest impact in terms of opioid mortality, but there are still many deaths related to prescription opioids. Fewer people are being prescribed opioids on a long-term basis, and many are stopping. This is a good thing for many patients, but some are having experiences of abandonment (Antoniou T et al. Int. Journal of Drug Policy 2019).

People are now searching for other tools to manage their pain. There is incredibly conflicting evidence in this regard. Laura was recently part of a scoping review (not yet published). About half of the papers support a role for cannabis use in reducing opioid use, the other half do not.

The Ontario College of Pharmacists has introduced an Opioid Strategy, initially approved in Sept 2017. Learn more.

The College has also developed a Cannabis strategy including mandatory education about cannabis for all pharmacists in the province. A number of courses have now been approved and more are coming. This education is to be completed by March 2020.

Pharmacists need to support clients around cannabis use (and other substances) with a shared decision-making model. With cannabis, checking drug interactions will be a key role for pharmacists.

- Very little clinical information about drug interactions is available:
  - CBD: substrate for CYP 3A4, 2C19; inhibits 2C19
  - THC: Substrate of CYP 2C9, 3A4
- ARV can interact with cannabis, but usually the ARV increases the levels of THC and CBD, rather than cannabis impacting ARV drug levels
- Have been case reports of failures of drugs to suppress transplant rejection
- May be combined CNS effects with opioids, benzodiazepines, gabapentinoids

Adverse effects

- There is a tool to screen for cannabis use disorder – CUDIT-R. As well, there is an excellent paper on the risks of marijuana use including withdrawal (Volkow ND et al. NEJM 2014)
- Euphoria is an adverse effect that we try to mitigate
- Pharmacists can be helpful in identifying Cannabinoid Hyperemesis Syndrome (severe vomiting, relief from a hot bath, hot shower)

Pharmacists have an important role in harm reduction and education around high doses of THC, storage methods that promote mold, product stability, travel and driving (yes really wait 6 hours after inhaling or 12 hours after ingesting!)

Questions:

- The source of the measure of therapeutic response (30% reduction in pain) was questioned. Most pain studies use 30% or 50% as a signal for efficacy. This is a subjective measure by the patient. Researcher have moved to focus on functional measures, this seems like a clinical practical target.
- Sarah was also asked about adverse affects of vaping cannabis. She has not personally seen any, and most of her patients use oils or capsules. This is partly about cost; vaping is expensive.
- The cost of cannabis treatment is an ongoing battle. More and more private insurers are covering, but it is not covered by public plans and this makes it difficult to encourage people to use more costly legal sources.
- There have not been any verified cases of cannabis cut with fentanyl. There are other contaminants (mold, pesticides), which are a concern with illicit product. It is also difficult to know exactly what you are taking. Illicit drug should be avoided by people with compromised immune systems, but cost wise this is impractical for many.
- Is there any data about harm reduction uses of cannabis for methamphetamine use? There are some client reports, but that is as far as it goes. There are no signals of this effect in the quanti-tative cohort data.
- Is there training happening for physicians as for pharmacists? Not really. It is also very difficult for physicians to have time to do this properly.

Improving Care for Women Living with HIV

Sharon Walmsley, Physician/Director, Immunodeficiency Clinic & HIV Clinical Research, Toronto General Hosp.

Dr. Walmsley began with a discussion of women's overall risk of HIV. In US data, overall risk is 1:200, however race/country of origin make a huge difference. Black women are far more at risk (1:48), than white or Asian women (1:800). For Canadian women, the overall risk is even lower (3.3 per 100,000). One quarter of new cases in women in Canada are over 50 (postmenopausal women have unprotected sex).

Does PrEP work for women?

Efficacy studies in women have not been as good as in men who have sex with men:

- Partner study (heterosexual serodiscordant couples) the efficacy rate was 60-70% (Baeten JM et al. NEJM 2012)
- Women-specific studies of oral PrEP, FEM-PrEP (Van Damme L et al. NEJM 2012) and VOICE (Marrazzo JM et al. NEJM 2015) were entirely ineffective
- Other delivery methods, such as the tenofovir gel (Abdool Karim Q et al. Science 2010), and dapivirine ring (Glaubius R et al. JIAS 2019) have shown some effect (the ring will be licensed)
- Topical forms may be preferred by women (and seem to thus have better adherence)
- For topical forms, it is important to consider the impact of the vaginal microbiome, as women with a gardernella-dominant microbiome can have inactivation of tenofovir

What about TAF for PrEP?
TAF concentrates in cells rather than in plasma. Are levels in the mucosa sufficient for protection? The DISCOVER study was done to ask this question, and showed that TAF was non-inferior to TDF (Hare CB et al. CROI 2019). However, there were no women in the DISCOVER trial! This issue was highlighted in a recent NEJM editorial, Where Were the Women? Gender Parity in Clinical Trials.

Bottom line, the challenges around PrEP use in women are related to adherence. We need education tailored to women if these tools are going to be useful. Different forms are needed because one type (pills, rings, gel, etc.) will not fit all. Ideally, PrEP should be combined with contraception and other STI protections.

Treating HIV in Women

When thinking about treating women:

- for younger women must consider potential pregnancy issues
- for older women must consider comorbidities (particularly at menopause)

…. and drug interactions for all (contraceptives, hormone therapy, antidepressants, lipids/anti-cholesterol and bone density drugs)!

Gender and HIV Drug Trials

There is a huge shopping list of potential drugs for naïve patients, but the key trials are all in MSM. This has not improved. In the BIC trials, 8% of participants were women.

Trials have been pushed to do sub-analysis by gender, but they are not adequately powered. While there is little or no difference in efficacy between men and women, there clearly are differences in adverse effects. **We need studies to compare drugs to determine optimal therapies in women.**

Pregnancy and HIV Treatment

The most important thing for a woman considering pregnancy is having an undetectable viral load. We have very little data about the safest drugs during pregnancy. There is a 10-15 year lag between identifying an ARV for the general HIV population and have information about pregnancy.

- Treatment drugs must be considered before pregnancy; there is a high rate of unintended pregnancy
- It is difficult in drug combinations to identify the drug causing trouble
- Vomiting in pregnancy can reduce the effective dose of drug
- Pharmacokinetics of some of the drugs (eg. cobicistat-boosted drugs) do not support adequate protection against mother-to-child transmission
- Remember the risk of postpartum depression and associated adherence challenges

For a woman diagnosed later in pregnancy, INSTIs are wonderful drugs for dropping viral load quickly:

- Viral load reduced faster in late stage pregnancy with RAL than EFV (Mirochnick et al. CROI, 2019). Viral load could be suppressed in 8 days!
- Viral load reduced faster in late stage pregnancy with DTG than EFV (Khoo S et al. CROI 2019) and the difference in much more marked in those with the highest viral loads

The concern with INSTI drugs is primarily the link to neural tube defects (NTD). The neural tube closes by 8 weeks pregnancy, so INSTI drugs can be used safely late in pregnancy.

Concern has been focused on the potentially negative outcomes of ARV on the pregnancy. This is important, but viral suppression is paramount, as vertical HIV transmission is a much greater risk:

- Comparative study of safety of ARV drugs in pregnancy showed that TDF/FTC/EFV was associated with a lower risk for adverse birth outcomes than other regimens (Zash R et al. JAMA Ped 2017)
- The Tsepamo study links NTD to pre-conception DTG-regimens (Zash R et al. NEJM 2019).

Neural Tube Defects and DTG

The Tsepamo study in Botswana was commissioned to determine if EFV was safe. It was extremely well done, including more than a quarter of all pregnancy in HIV-positive women in Botswana. Mid-study, most women began to be prescribed DTG regimens. The mechanism of NTD is not clear, but work was done to exclude other possible causes like Zika virus. There were four NTD in 426 exposures (9X the risk of the general population.) In Botswana, there is no folate supplementation (regardless of HIV status). It is possible that DTG interferes with folate metabolism, but there is not a great deal of supporting evidence. The researchers have continued to follow this cohort. At the 2019 International AIDS Conference, they reported that they had found only one additional case of NTD. This translates to three per 1000 exposures or 3X the general population rate. (Zash R et al. IAS, 2019.) There continues to be debate and controversy in Africa about this, because INSTI drugs are the most effective readily available therapies, whereas in Canada a woman and her physician have many more options. WHO is now supporting DTG treatment during pregnancy. In Brazil, a study of 382 women on DTG at conception (Fonseca FF et al. IAS 2019) showed no NTD, but Brazil does recommend folate supplements and has very low rates of NTD (study under-powered.) The AIDS Pregnancy Registry has a very low rate of NTD reported with DTG, but many physicians don't report. Ultimately, it may be optimal to avoid DTG in the first 8-12 weeks of pregnancy, but the risk of transmission is much greater that the risk of NTD.

Comorbidities in Older Women

Older women may not perceive themselves as at risk, and take fewer precautions (due to relationship power imbalances), but there is likely also a biological increase in risk due to age-related changes in the T-cells in the mucosa. A woman's symptoms may be initially dismissed as signs of aging.

Ontario study of comorbidities in HIV-positive women shows that women with HIV do have more comorbidities and that this effect is magnified as they enter menopause. (Kendall C et al. BMC Public Health, 2014). Women with HIV may have earlier menopause, and more severe symptoms, (Tariq S et al. CROI 2018) which makes the use of hormone replacement therapy (HRT) an important question to examine.

Loss of bone mineral density (BMD) and fragility is an important comorbidity in older women with HIV

- Higher loss of bone mineral density with TDF particularly in combination with a boosted PI
- Increased fracture incidence in women with HIV (Sharma A et al. JAIDS 2015)

Heart disease in women

- HIV is associated with increased rates of CVD in women (Womack JA et al. J Am Heart Assoc. 2014)
- Ischemic stroke risk increases as HIV positive women age (Chow FC et al. AIDS 2018)

In addition to questions about comorbidities for older women (heart disease, BMD, mental health) there are also outstanding questions about the pharmacokinetics of ARV therapy and the impact of menopause. Dr. Walmsley team is putting together the CHANGE HIV study to look at the impact of aging on optimal drug therapies. The study will be 20% women.

Malignancy

- No evidence of higher rates of breast cancer in HIV positive women
- The relative risk of cervical cancer is twice as high (and five-fold higher with low T cell counts)
- HPV vaccine beneficial for women even with previous HPV infection (Brophy J et al. Ped Inf Dis J 2018)

All of these issues are important to women, but as pharmacists it is also vital that you remember how isolated many women with HIV feel. You may be the only person they are able to speak to openly about their therapy.

Modern therapies and weight gain: real or imagined?

Deborah Yoong, Pharmacist, St. Michael's Hospital, Toronto

Deborah's presentation on weight gain associated with HIV focused on two populations:

- Treatment naïve people who experience weight gain in the period after treatment begins
- Treatment experienced patients who have switched to a newer therapy (often a second generation INSTI) who experience notable weight gain after this treatment switch

Globally:

- 39% of people are overweight and 13% are obese
- More women than men are affected

In 2017, WHO stated that there were 4.7 million premature deaths due to obesity, compared to 1 million for HIV/AIDS. There are many links to different kinds of mortality.

Obesity is defined by BMI

- BMI = weight in kg x height in metres^2
- BMI >25 are overweight
- BMI > 35 obese

BMI does not consider proportion of fat.

In people with HIV, all of the traditional risk factors for weight gain apply (diet, lack of exercise, age), but we also need to consider the impact of the virus and ARV treatment. AIDS is a wasting disease; weight gain is initially seen as a return to health. This is illustrated in the longstanding US Veterans Cohort (Kumar S. Samaras K et al. Frontiers in Endocrinology 2018) where weight gain is associated with reduced mortality. However, weight gain is also associated with increased risk of CVD and diabetes, and other comorbidities.

The large NA-ACCORD cohort shows the following weight patterns associated with ARV treatment from 1998-2010 (Koethe JR et al. AIDS Res Hum Retroviruses 2016):

- The pre-treatment weight of people starting ARV has been increasing, with women at higher BMI.
- After 3 years, the greatest BMI increases are in those with initially low BMI and non-white females

As the INSTI drugs have been used in a widespread way, reports have started to emerge:

- A French cohort noted a few discontinuations of DTG due to weight gain. They looked retrospectively (Menard A et al. AIDS 2017) at 462 people on DTG-containing regimens and observed an average 3 kg weight gain after a year on DTG. Twenty percent of these patients had a weight gain of greater than 10% body weight! The slope of weight gain was steeper in women, particularly with an ABC backbone.
- Another study (Norwood A et al. JAIDS 2017) of people switching from EFV (after an average of two years, not return to health gains), showed that there was really no difference when switching to a PI, but marked weight gain when switched to an INSTI (an average 5.3 kg weight gain)

Deborah started looking at this because of patients returning to clinic concerned about weight gain, a reminder to listen to our patients. Significant evidence has since emerged:

- A South African trial (60% women, 99% black) compared TDF or TAF plus /FTC/ DTG to TDF/FTC/EFZ (Venter WDF et al. NEJM 2019)
    - Efficacy of all regimens was the same
    - Weight increase was significant with regimens combining DTG and TAF. Women gained an average 6.4 kg and men 4.7 kg men at 48 weeks. Weight gain did not plateau even up to 16 kg.
    - People on all regimens gained some weight: most gain with TAF/DTG regimen, then TDF/DTG, with the EFZ regimen being the least
- Further study of the body composition of these patients (McCann K et al. EACS PS3/3 2019), found that this is primarily fat – particularly truncal fat in women
- Another trial (Bhagwat P et al. Open Forum Infect Dis. 2018) compared RAL to PI containing regimen:
    - More weight gain with RAL regimens
    - More pronounced in female and black participants
    - More advanced baseline HIV disease state was a strong predictor of larger abdominal increases

A huge pooled analysis of eight trials (Sax PE et al. Clinical Infectious Diseases 2019) has now concluded that:

- INSTI drugs associated with more weight gain than PI or NNRTI
- Of INSTI drugs, DTG and BIC associated with more weight gain than EVG/COBI
- TAF associated with more weight gain than TDF, ABC or AZT
- RIL associated with more weight gain than EFZ

Risk factors (Sax PE et al.) included low initial CD4 count, higher VL, women and black race, with no clearly established mechanism and many unanswered questions about diet, other risk factors, etc. Does it matter what are you switching from? A confusing array of studies are now looking at different switches.

How meaningful are these weight gains? A study of patients (n=110) switching from TDF to TAF without changes in the other agents (Schafer J et al. Open Forum Infectious Diseases 2019) found increases in weight, LDL, HDL, cholesterol and cardiovascular disease risk scores with the switch.

What do we do now to manage patients with these concerns?

- Look at diet, lifestyle and risk factors for comorbidities
- Consider other medications that may be associated with weight gain
- Switch INSTI? Go back to EFZ? (No published data, we do not know if this will stabilize weight)
- What is the role of DOR and its single tab formulations, which seems to have a favourable lipid profile?

Consider risk factors for weight gain before starting therapies.

Hepatitis C: is it cured already or do we still need to think about Drug Drug Interactions (DDIs)?

Alice Tseng, Pharmacist, AAHIVP, Toronto General Hospital

There have been mind-bending changes in HCV treatment and the number of drugs available. There are now two established first-line therapies (AASLD-IDSA HCV Guidance updated November 2019):

- A simplified regimen of glecaprevir (300 ml) + pibrentasvir (120 mg) for 8 weeks
- Sofosbuvir (400 mg) + velpatasvir (100 mg) for 12 weeks in those that are ineligible for the first

Even with the most commonly used drugs; there are still issues with drug transporters. There is still potential for inhibition as well as potential absorption issues.

- A study of 116 hospitalized HCV patients found that 68% had at least one DDI; 39% related to a gastric acid inhibitor (Messier L et al. Antiviral PK Workshop 2019)
- Similar outcomes in a presentation at AASLD (Curry et al. AASLD 2019 #1503)

Acid Reducing Agents

- Drug spacing needs to be considered with acid reducing drugs and several DAAs

<table>
<tr><th></th><th>Ledipasvir</th><th>Velpatasvir</th><th>Glecaprevir/pibrentasvir</th></tr>
<tr><td>H2RAs</td><td colspan="2">Administer H2RA simultaneously or 12 hours apart</td><td rowspan="3">No adjustments required</td></tr>
<tr><td>PPIs</td><td>Simultaneously</td><td>Simultaneously with food</td></tr>
<tr><td>Antacids</td><td colspan="2">Separated by 4 hours</td></tr>
</table>

Studies of real world use have found few problems (Esteban et al. AASLD 2018, #702; Verrault et al. Antiviral PK Workshop 2019, #42; Flamm S et al. Clin Gastroenterol Hepatol 2019)

Statins

Direct-acting antivirals (DAAs) can increase statin concentrations via inhibition of CYP and/or transporters. Almost all statin drugs are a concern with both of the first line regimens.

- Guidelines recommend discontinuing statins during DAA therapy, if possible.
- Excellent review article is available (Smolders EJ et al. Clinical Pharmacokinetics 2019)

DAA and HIV ARV

- About 25% of people with HIV also have HCV; management of DDI may still be a treatment barrier
- Older study (Cope et al. AIDS Patient Care STDs 2015) demonstrated that the majority of co-infected patients needed to switch their ARV treatment to begin DAA therapy: patients on boosted PI regimens had limited options for switching and 40% were unable to switch due to drug resistance
- Most first line HIV treatments are now safe to use in combination with most first line HCV treatments; the challenge is for those with established resistance to many HIV therapies
- Detail tables of DDI are available in the ***HIV/HCV therapy guide*** at https://hivclinic.ca

Managing Seizures

- This is a challenge; all anticonvulsants are contraindicated regardless of the DAAs used
- Retrospective study of HIV/HCV patients treated with DAAs, showed that DDI with anticonvulsants was the most frequent cause of treatment failure (Machado et al. AASLD 2019, #1627)
- Dutch have reported some success with altered doses of DAC (60 mg 2 or 3 times a day) in SOL/DAC combo therapy (Van Seyen et al. J Hepatol 2019), however DAC has been removed even as an alternative drug in the latest version of the AASLD-IDSA HCV Guidance
- Possible strategies (none with sufficient data!)
    - Use high dose daclatasvir (still covered by ODB)
    - Attempt double dose of other fixed-dose combination products – cost prohibitive!
    - Add ribavirin to protect against reduced DAA exposures – most likely increased DAA dose
    - Use a booster (e.g., ritonavir or cobicistat) to attempt to protect against reduced DAA

    In all of these scenarios, you would ideally want to be able to monitor drug levels.

Anti-coagulants (DOACs)

- Potential increases in all direct oral anti-coagulants (DOAC) drugs with all DAA combos; dabigatran is contraindicated with both glecaprevir/pibrentasvir and sofosbuvir/velpatasvir
- In a survey of British pharmacists re: co-prescribing DAAs and DOACs (Boyle A et al. EASL 2018) over two third prescribed rivaroxaban, a quarter apixaban, with a small number of other DOAC options; with clinical monitoring no serious bleeding reported
- Possible strategies
    1) Use DOAC plus DAA:
        - Consider apixaban or rivaroxaban which are also partially metabolized via CYP3A4
        - Use non-PI DAA regimen. Some PIs have weak CYP3A4 inhibiting effects in addition to transporter inhibition
    2) Use alternative anticoagulant plus DAA
        - Switch to warfarin and monitor INR – improvements in liver function due to HCV treatment may require dose adjustments within first couple weeks (Gov.UK Drug Safety Update 2017)
        - Switch to low molecular weight heparin (LMWH)

Evolution of HCV therapy choices has been fantastic and allowed simplification of management:

- Proton pump inhibitors have no impact on viral suppression
- Antiretrovirals most unboosted regimens are OK
- Statins are manageable although discontinuation still preferable
- Anticonvulsants and anticoagulants are still a challenge

Try to check at least two DDI resources (at least one HCV focuses) Recommend resources:

- ***Hep Drug Interactions*** (University of Liverpool) https://www.hep-druginteractions.org/checker
- ***HIV/HCV therapy guide*** (UHN) https://hivclinic.ca