Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***HIV Treatment***
-July 2019-

Background:

In July 2019, the IHS National Pharmacy and Therapeutics Committee reviewed antiretroviral therapy for the treatment of Human Immunodeficiency Virus (HIV) infection and **added** two treatment options to the National Core Formulary (NCF), including **(1) bictegravir/emtricitabine/tenofovir alafenamide** and **(2) dolutegravir/abacavir/lamivudine** (*with HLA 5701 testing required prior to initiation*).

The NPTC also voted to **modify criteria for use language** to current NCF agents emtricitabine/tenofovir disoproxil fumarate plus raltegravir to include **"for treatment of HIV infection among patients with contraindications to first-line agents,"** in addition to the current indication of HIV post-exposure prophylaxis.

Discussion:

Approximately 3600 American Indian/Alaska Native (AI/AN) people are living with HIV/AIDS (PLWHA).[1] An estimated 20% of PLWHA have not yet been diagnosed. These PLWHA are served broadly throughout the service population. A review of IHS data has identified that nearly every IHS Service Unit has made an HIV diagnosis in recent years.

=HIV Epidemiology=

The main routes of transmission of HIV include men who have sex with men (MSM), injection drug use and heterosexual sex. Each community may differ in risk behaviors and HIV epidemiology. While anyone with risk factors should be tested, patients often do not know they are at risk or do not disclose risk factors. HIV screening, in addition to risk-based testing, are both essential for early diagnosis and viral suppression to improve patient prognosis and block ongoing disease transmission. HIV screening is a national GPRA measure, with approximately 43% of current patients age 13-64 screened, although some Service Units have screened over 70% of active patients. Anyone at risk should be tested and also offered HIV Pre-Exposure Prophylaxis (PrEP). Universal availability of HIV treatment throughout the IHS is a critical step toward ending the health disparity and stigma associated with HIV infection in Indian Country.

Disparities in outcomes among AI/AN PLWHA are both significant and preventable. Nationally, AI/AN PLWHA are twice as likely to develop AIDS or advanced infection.[2] Seventy-eight percent of AI/AN PLWHA report experiencing stigma[3]. AI/AN women are twice as likely as to die from HIV, compared to Whites.[2]

Continuum/cascade of care was a concept first published in 2009.[1] It measures the sequential steps of successful HIV care across a spectrum, from diagnosis through linkage to care to receiving a prescription and ultimately achieving virologic suppression. The concept of the care continuum has quickly taken hold as a method for identifying gaps in care. Since that time, attention to case management has greatly improved upon the 10% virologic suppression noted in the 2009 report. However, a 2015 estimate of the continuum of care among AI/AN PLWHA found only a 43% rate of suppression.[3]

While IHS sites that provide antiretroviral HIV treatment are achieving suppression rates upwards of 90%, a national effort is required to achieve virologic suppression and ultimately elimination of HIV in Indian Country. Recent evidence shows that virologic suppression not only effectively gives PLWHA a full life expectancy, but it also prevents transmission. The concept of "Undetectable = Untransmittable" (or U=U), previously known as "treatment as prevention," became the official CDC position in July 2018 after results confirmed that condom-less sex between sero-different partners did not transmit HIV when effective HIV therapy was used for the HIV-positive partner.[4] Thereafter, U=U became a pillar of elimination. Furthermore, U=U is also a potent weapon against stigma. As more treated patients and their communities view HIV-infection as un-transmittable, the weight from fear of transmission is lifted.

Treatment of HIV has been sufficiently simplified that uncomplicated patients can and should be treated in primary care settings. For the last 20 years, HIV treatment has been relegated to a select group of specialty providers adept at managing drug interactions and side effects for their dedicated patients. Today, highly effective regimens are available in single tablet preparations with minimal side effects and interactions.

=Antiretroviral therapy=

The NPTC has added two complete single-tablet HIV treatment regimens to the NCF and has broadened the indication for a third regimen that was previously added for Post Exposure Prophylaxis (PEP), in an effort to meet the needs of most newly-diagnosed PLWHA. These agents are intended to provide an option for first-line therapy, an alternative, and also a back-up treatment option for reproductive-aged females. These formulary additions make rapid virologic suppression available at all IHS locations. It is not the intent that all PLWHA in IHS be switched to these formulary regimens if patients are controlled on a different regimen. Patients currently well-controlled should only be switched if these agents offer improved treatment options and if patients are comfortable with switching.

Bictegravir/emtricitabine/tenofovir is intended to be the first-line treatment for the majority of patients and is available as a complete single-tablet regimen taken once daily, with or without food. It is well-tolerated with the side effects of nausea, headache, and insomnia being typically brief and self-limited. Serious side effects are rare. This combination is safe to use in CKD, with a GFR threshold down to 30 ml/min. Discontinuation due to side effects is rare. Long-term side effects, although rare, may include osteoporosis and/or renal disease. There is inadequate experience with this agent in pregnancy. As such, it is not recommended in pregnant patients or females unable or unwilling to use reliable contraception due to a concern for potential neural tube defects. Pregnancy testing is recommended prior to initiating this agent in women with reproductive potential. The combination carries the risk of interactions with metformin as well as some anti-epileptic and anti-tuberculosis medications. Divalent cations including calcium, iron, and magnesium can interfere with absorption. Patients should be counseled about co-administration with food.

Dolutegravir/abacavir/lamivudine was selected to serve as the second-line treatment, as it requires HLA B5701 testing prior to initiation. It is intended to provide an alternative to bictegravir/emtricitabine/tenofovir when the latter combination is not tolerated. It is also preferred among patients with osteoporosis or pre-existing CKD. This complete single-tablet regimen taken once daily with or without food has a similar side effect profile, with the exception of a rare but serious adverse reaction known as abacavir hypersensitivity, which can fatal. Risk of this sensitivity is accurately predicted through HLA B5701 allele testing, which is a readily-available commercial blood test. HLA B5701 testing should be done prior to initiating the regimen and use of this agent is strictly contraindicated in HLA B5701-positive patients. It has interactions with metformin and various seizure medications. Dolutegravir/abacavir/lamivudine should be avoided in patients with significant cardiovascular disease and those co-infected with hepatitis B. As above, divalent cations such as calcium, iron, and magnesium interfere with absorption and relevant patient counseling is advised.

The combination treatment approach of emtricitabine/tenofovir disoproxil fumarate plus raltegravir has been named on the NCF since 2011 for the indication of post-exposure HIV prophylaxis. This regimen is recommended as HIV treatment for women of reproductive potential and is safe for use during the first trimester of pregnancy. It is also least fraught with drug interactions so patients with concurrent seizure disorders or complicated behavioral health pharmacotherapy have this regimen available as an option. As it is a combination of two separate medications and the raltegravir component is given twice, adherence can be an issue. Administration of emtricitabine/tenofovir disoproxil fumarate is one tablet daily with raltegravir 400 mg tablet BID. Both can be administered with or without food. Again, foods containing calcium, iron, or magnesium may interfere with its absorption.

=HIV Clinical Education and Clinical Decision Support tools=

Laboratory assessment during evaluation of a newly diagnosed PLWHA is outlined in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.[5] If clinicians are considering the dolutegravir/abacavir/lamivudine regimen, HLA B5701 testing must be completed prior to initiation. This table (Table 3) from the aforementioned guidelines may be helpful in guiding HIV-specific lab monitoring. A more in-depth, self-guided educational experience for HIV Continuing Medical Education (CME) is

available through the National HIV Curriculum and supported by the University of Washington. The modules are straight forward, thoughtful, and CME credit is also offered.

Another resource available to IHS clinicians is the HIV ECHO program, a monthly telehealth service where providers new to HIV treatment and/or those with complex cases can submit items for discussion among experts and participants.

Finally, individual case consultation is available Monday through Friday for HIV management and can provide support for complicated cases through the national clinical consultation service at the HIV Warmline. Nationally recognized experts consult to assist care teams dealing with complicated issues and the experts are able to provide concrete recommendations.

Findings:

IHS served approximately 3600 patients living with HIV at the end of 2016. Nearly every Service Unit recorded a diagnostic code of HIV infection in 2018. Infection with HIV is unfortunately common throughout the IHS. The clinical decision support resources necessary to treat uncomplicated HIV are readily available and several are identified in this document. With HIV treatment medications now specified and available on the NCF alongside robust guidelines, IHS clinicians can ensure all patients in the service population have access to rapid virologic suppression.

The 4 key strategies of HIV Elimination (Diagnose, Treat, Prevent and Respond)[6] are well-established and ready for implementation. With continued screening and risk-based testing, rapid delivery of therapy to those with infection, widespread use of prevention tools including PrEP, and a rapid response to clusters of new infection, HIV elimination by 2030 is attainable.

The dedicated providers of IHS are known for their expert ability to provide high quality care often in an environment of scarcity. The addition of frontline HIV therapy to the NCF signals a commitment to the resources necessary to directly impact the health disparities and stigma associated with HIV infection among American Indians and Alaska Natives.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

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