Letters to the Editor

Considerations for Implementing Cabotegravir (Apretude) as PrEP for HIV Infection

To the Editor: Drs. El-Haddad and Erlich review an important new option for preventing HIV infection.[1] Intramuscular cabotegravir (Apretude) is much more effective than daily oral tenofovir disoproxil fumarate/emtricitabine (Truvada) at preventing HIV infection.[2] As family physicians and HIV specialists, we are excited about this option but remain wary of its potential risks. One of the more serious risks is long-acting early viral inhibition syndrome, which can occur in people who acquire HIV infection despite appropriate use of intramuscular cabotegravir.[3]

Long-acting early viral inhibition syndrome presents with minimal symptoms, conflicting serology results that can revert to negative, and low or suppressed viral loads. These mild symptoms and ambiguous laboratory findings can culminate in months-long delays in diagnosis and development of resistance to integrase strand transfer inhibitor medications.[3] This is concerning because the integrase strand transfer inhibitor drug class is a first-line treatment of HIV infection.[4] Most concerning is that long-acting early viral inhibition syndrome can be found in people receiving on-time injections with adequate serum concentration levels of cabotegravir. Prescribers must be aware of this potential risk and adhere to the monitoring recommendations.

Awareness of long-acting early viral inhibition syndrome is vital to understanding the importance of the Centers for Disease Control and Prevention recommendation to monitor patients receiving intramuscular cabotegravir for pre-exposure prophylaxis (PrEP) for HIV every 2 months (i.e., with each administration) using an antigen-antibody assay and the more sensitive HIV-1 RNA assay.[5] The sensitivity of the RNA assay allows for earlier detection of infection. It is also important to counsel patients on the cabotegravir "tail," which is the long and highly variable time when cabotegravir is detectable after discontinuation but below the level of protection. For 12 months after discontinuation, patients should continue RNA testing for HIV every 3 months. If patients have an ongoing indication for PrEP, oral cabotegravir PrEP with tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine (Descovy) should be recommended to decrease the risk of acquiring HIV infection.[5]

The Clinician Consultation Center PrEPline (855-488-7737) is available on weekdays to help with ambiguous test results and provide recommendations for people who may have acquired HIV infection while taking PrEP. We recommend obtaining integrase strand transfer inhibitor genotype resistance testing for patients confirmed to have acquired HIV infection while taking cabotegravir; if antiretroviral therapy is initiated before receiving the results of resistance testing, the regimen should include darunavir (Prezista; a protease inhibitor) boosted with ritonavir or cobicistat.[5]

Hannah Zimmerman, MD, AAHIVS
Pittsburgh, Penn.
hannahrzimm@gmail.com

Allison Vogl, MD, AAHIVS
McKeesport, Penn.

Author disclosure: No relevant financial relationships.

References

1. El-Haddad A, Erlich D. Cabotegravir (Apretude) for pre-exposure prophylaxis for HIV type 1 infection. *Am Fam Physician*. 2023;107(5):545-546.
2. Landovitz RJ, Donnell D, Clement ME, et al.; HPTN 083 Study Team. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med*. 2021;385(7):595-608.
3. HIV Prevention Trials Network. Eshleman S. HIV infections in the setting of long-acting early viral inhibition: the LEVI syndrome. June 7, 2022. Accessed December 10, 2023. https://www.hptn.org/sites/default/files/inline-files/TUES_14_Susan%20Eshleman_Lab%20Plenary.pdf
4. Clinical Info HIV.gov. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Updated December 6, 2023. Accessed December 10, 2023. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv
5. Centers for Disease Control and Prevention. US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 update. Accessed December 10, 2023. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

Editor's Note: This letter was sent to the authors of "Cabotegravir (Apretude) for Pre-exposure Prophylaxis for HIV Type 1 Infection," who declined to reply.

Longer Menstrual Cycle and Infertility Evaluation

To the Editor: In the article written by Dr. Phillips and colleagues, they describe a suggested workup for women suspected of having anovulation.[1] The article recommends that clinicians obtain a day-21 progesterone level, and for levels less than 3 ng per mL (9.54 nmol per L), conclude that ovulation has not occurred. This method leaves out a group of people with a longer menstrual cycle. If a woman has a 35-day menstrual cycle, she may not ovulate until day 21 or 22; ▶

Email letter submissions to afplet@aafp.org. Letters should be fewer than 400 words and limited to six references, one table or figure, and three authors. Letters submitted for publication in *AFP* must not be submitted to any other publication. Letters may be edited to meet style and space requirements.

This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

therefore, a day-21 progesterone level would be falsely low. The algorithm should recommend a midluteal progesterone level that would allow clinicians to discuss cycle specifics with their patients and determine which day would be the most accurate time to obtain a progesterone level. The American Society for Reproductive Medicine states, "Given the range of normal variation in ovulatory cycles, a serum progesterone measurement generally should be obtained approximately 1 week before the expected onset of the next menses, rather than on any one specific cycle day (e.g., cycle-day 21)."[2]

The article also states that the American College of Obstetricians and Gynecologists no longer recommends the examination of cervical mucus in infertility evaluation. Upon review of the cited reference, I could not find any such recommendation.[3] On the contrary, the American Society for Reproductive Medicine states that cervical fluid tracking is an inexpensive method with moderate-quality evidence for increasing the likelihood of achieving pregnancy: "A retrospective cohort study involving 1,681 cycles observed that pregnancy rates were highest (approximately 38%) when intercourse occurred on the day of peak mucus (day 0) and appreciably lower (approximately 15% to 20%) on the day before or after the peak."[4]

During a time when many patients feel a loss of control and lack of understanding, we can tailor infertility care and empower patients to understand more about their bodies.

Anne Keenan, MD
Minneapolis, Minn.
hors0097@umn.edu

Author disclosure: No relevant financial relationships.

References

1. Phillips K, Olanrewaju RA, Omole F. Infertility: evaluation and management. *Am Fam Physician*. 2023;107(6):623-630.
2. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril*. 2015;103(6):e44-e50.
3. ACOG Committee Opinion 762: Prepregnancy counseling. *Obstet Gynecol*. 2019;133(1):e78-e89.
4. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility: a committee opinion. *Fertil Steril*. 2022;117(1):53-63.

In Reply: This article was intended to serve only as a framework for the infertility workup. We agree that a patient with a longer menstrual cycle may have spuriously low progesterone levels at day 21. There are always patient-specific characteristics for which few algorithms can adequately account. We advise that the recommendations be adjusted as needed to address specific situations.

The sentence, "However, evaluation of cervical mucus is no longer routinely used in infertility evaluation" is from information provided in reference 10 and not 11, as incorrectly cited in the article. The article has been corrected online. We did not intend to suggest that cervical mucus screening cannot be used for certain patients; however, *routine* postcoital cervical mucus testing is not recommended by the American Society for Reproductive Medicine in the initial workup of infertility.[1]

Kiwita Phillips, MD, FACOG
Atlanta, Ga.
kphillips@msm.edu

Raimot Olanrewaju, MD, FACOG
Atlanta, Ga.

Folashade Omole, MBChB, FAAFP
Atlanta, Ga.

Author disclosure: No relevant financial relationships.

Reference

1. Practice Committee of the American Society for Reproductive Medicine. Fertility evaluation of infertile women: a committee opinion. *Fertil Steril*. 2021;116(5):1255-1265.

Airflow Reversibility in Patients With Asthma

To the Editor: The article by Zeller and colleagues discusses how to distinguish asthma from chronic obstructive pulmonary disease (COPD).[1] This distinction is important because the treatments for the two diseases differ. The authors state, "Asthma is diagnosed if airway obstruction on spirometry is reversible (greater than 12% and greater than 200 mL improvement in FEV_1 [forced expiratory volume in 1 second]) with administration of bronchodilators.… COPD is diagnosed if airway obstruction … on spirometry is not reversible with bronchodilators."

However, studies have shown reversibility in a significant proportion of patients with COPD. In the UPLIFT trial of patients with COPD, 54% of patients had bronchodilator reversibility based on the American Thoracic Society criteria of FEV_1 improvement of 12% or greater and 200 mL or greater, and 73% of patients had reversibility when using the sole criteria of 12% or greater improvement in FEV_1.[2] A comprehensive review of COPD reversibility in multiple studies concluded that "… many patients with COPD do indeed exhibit bronchodilator reversibility and that reversibility testing is not a reliable measure to differentiate between asthma and COPD."[3]

The European Respiratory Society/American Thoracic Society definition of reversibility was recently revised to greater than 10% of the predicted value in FEV_1 or forced vital capacity.[4] Using this updated definition would lead

to a greater proportion of people with COPD being classified as having bronchodilator reversibility compared with the previous American Thoracic Society criteria of 12% or greater.

The 2023 GOLD report states, "… assessing the degree of reversibility of airflow obstruction … to inform therapeutic decisions is no longer recommended … and has not been shown to differentiate the diagnosis [of COPD] from asthma, or to predict the response to long-term treatment with bronchodilators or corticosteroids."[5]

The critical difference between COPD and asthma is that COPD is characterized by airflow limitation that is not fully reversible, whereas for most people with asthma, airflow is variable and reverses to near normal.[5,6]

Neil Skolnik, MD
Jenkintown, Pa.
nskolnik@yahoo.com

Donald A. Mahler, MD
Hanover, N.H.

Barbara P. Yawn, MD, MSc, FAAFP
Minneapolis, Minn.

Author disclosures: Dr. Skolnik reports serving as a speaker, consultant, or advisory board member for Abbot, AstraZeneca, Bayer, Boehringer Ingelheim, Boehringer Ingelheim/Lilly, Genentech, GSK, Heartland, Idorsia, Lilly, Merck, Novartis, Novo Nordisk, Sanofi, Sanofi Pasteur, and Teva, and reports receiving research support from AstraZeneca, Bayer, GSK, Novo Nordisk, and Sanofi.

Dr. Mahler reports serving as a speaker, consultant, or advisory board member for AstraZeneca, Boehringer Ingelheim, GSK, Theravance Biopharma, Verona Pharma, and Viatris, and receives royalties from Johns Hopkins University Press.

Dr. Yawn reports serving as a speaker, consultant, or advisory board member for AstraZeneca, Boehringer Ingelheim, GSK, Sunovion, and Teva.

References

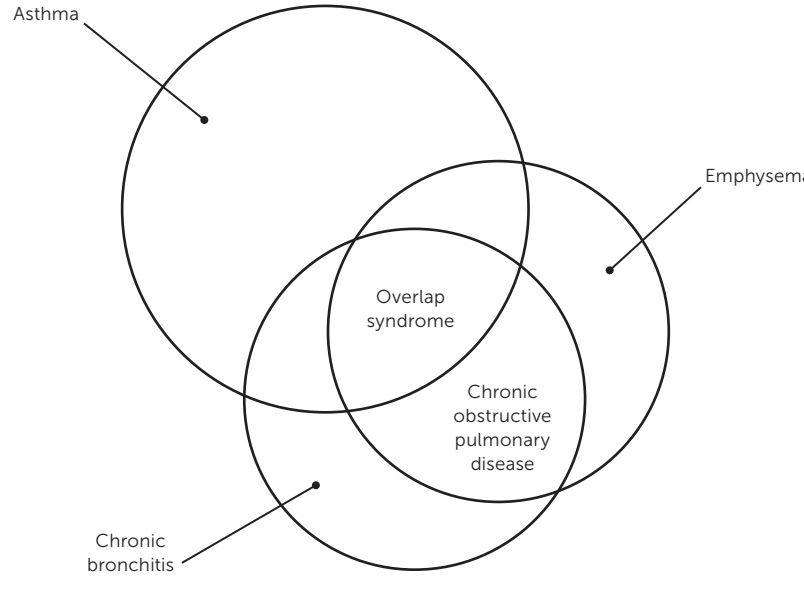
1. Zeller TA, Beben K, Walker S. Distinguishing asthma and COPD in primary care: a case-based approach. *Am Fam Physician*. 2023;107(3):247-252.
2. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J*. 2008;31(4):742-750.
3. Hanania NA, Celli BR, Donohue JF, et al. Bronchodilator reversibility in COPD. *Chest*. 2011;140(4):1055-1063.
4. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1):2101499.
5. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report). Accessed April 11, 2023. https://goldcopd.org/wp-content/uploads/2023/03/GOLD-2023-ver-1.3-17Feb2023_WMV.pdf
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2022. Accessed April 16, 2023. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf

In Reply: We appreciate the opportunity to respond to this letter. Our article does not address therapy for asthma and COPD, but rather the diagnosis of the two disease entities and distinguishing between them.

We agree that the critical difference between COPD and asthma is that COPD is characterized by airflow limitation that is not fully reversible with bronchodilators. In contrast, asthma is characterized by airflow limitation that is variable and reversible to near normal with bronchodilators.

As briefly discussed in our article, robust literature has developed around the clinical reality of coexisting asthma and COPD.[1-4] The natural history of asthma is to progress to fixed obstruction over time.[5] Some have labeled the coexistence of the two disease entities "asthma-COPD overlap syndrome," and for a time, it appeared that this might become a separate diagnosis. However, it is now standard clinical practice to diagnose

FIGURE 1



Obstructive Lung Disease Venn Diagram

Adapted with permission from Soriano JB, Davis KJ, Coleman B, et al. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest. *2003;124(2):475.*

both asthma and COPD if the patient meets spirometry criteria for both conditions. Distinguishing between asthma and COPD is not strictly an either/or, but sometimes a both/and situation. A Venn diagram has been useful as a visual aid *(Figure 1)*.[6] We hope this response helps readers in their clinical practice, and we encourage physicians to follow widely available guidelines for treating asthma and COPD.

T. Aaron Zeller, MD
Greenville, S.C.
tazelle@clemson.edu

Kati Beben, MD
Greenville, S.C.

Stephanie Walker, MD
Greenville, S.C.

References

1. Orie NGM, Sluiter HJ, de Vries K, et al. The host factor in bronchitis. *Bronchitis*. 1961:43-59.
2. Postma DS, Kerstjens HAM, Timens W. Introduction: obstructive lung diseases from conception to old age. *Proc Am Thorac Soc*. 2009;6(8):637.
3. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax*. 2009;64(8):728–735.
4. Postma DS, Rabe KF. The asthma–COPD overlap syndrome. *N Engl J Med*. 2015;373(13):1241-1249.
5. de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One*. 2013;8(5):e62985.
6. Soriano JB, Davis KJ, Coleman B, et al. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest*. 2003;124(2):474-481. ■