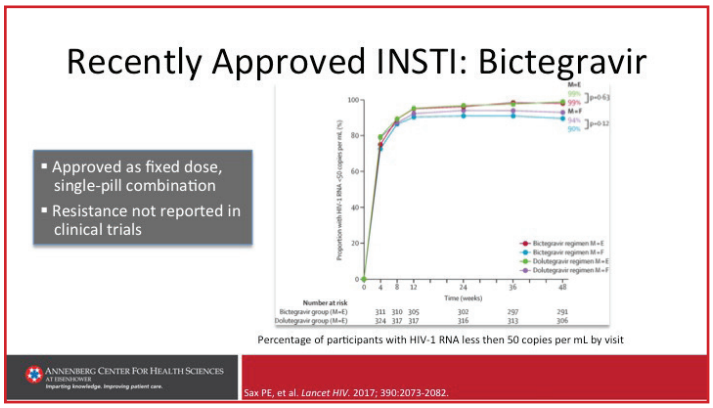
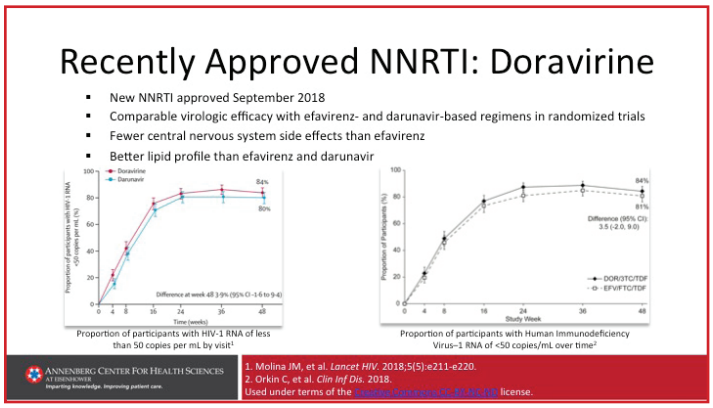
GUIDELINE RECOMMENDATIONS AND CURRENT REGIMENS

Several recent clinical trials have presented or published data on novel therapeutic regimens in the initial treatment of women who are HIV-positive.



Bictegravir (BIC) is a novel, once-daily integrase strand transfer inhibitor (INSTI) with antiviral potency and a long half-life. Results from a multinational study showed that a triple combination of BIC with coformulated tenofovir alafenamide (TAF) and emtricitabine (FTC) demonstrated similar efficacy to dolutegravir (DTG) with TAF/FTC in suppressing viral load. At 48 weeks, 97% of BIC-treated patients had HIV-1 RNA below 50 copies/ml vs 91% of DTG-treated patients.1 Safety and tolerability were similar in both groups. BIC/TAF/FTC is approved as a fixed dose, single-pill combination for treatment-naïve patients and virologically suppressed patients considering a switch from another combination.

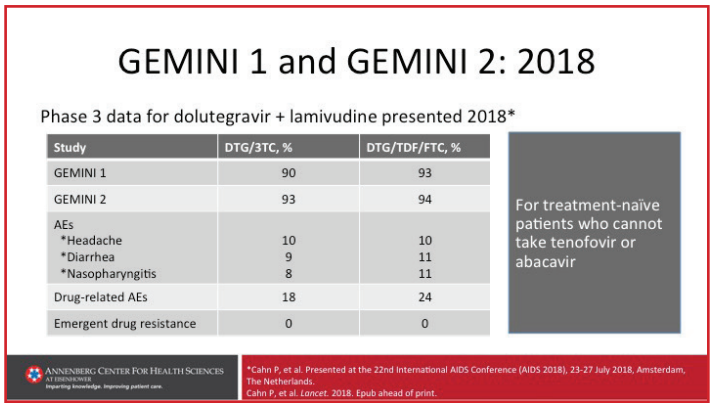
1. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390:2073-2082.



Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI), approved in September of 2018 for use in treatment-naïve patients, and is available alone or in combination with tenofovir disoproxil fumarate-lamivudine. NNRTIs such as efavirenz (EFA) and rilpivirine (RIL) can be used as a third agent in combination with 2 nucleoside reverse transcriptase inhibitors (NRTI). Results from the DRIVE-AHEAD and DRIVE-FORWARD trials showed that virologic efficacy with doravirine was noninferior to efavirenz- and darunavir-based regimens and was associated with fewer central nervous system (CNS) adverse events than with efavirenz- and darunavir-based regimens.[1,2] Like efavirenz, doravirine was associated with neurologic and psychiatric side effects (eg, dizziness and sleep disturbances) but demonstrated better lipid profiles than both efavirenz and darunavir. As yet, there are few data for using doravirine in pregnancy; however, data for other NNRTI agents such as efavirenz suggest a potential role for this agent in the treatment of HIV-infected women of childbearing potential.

1. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: Week 48 results of the DRIVE-AHEAD trial. *Clin Infect Dis*. 2019;68(4):535-544.

2. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(5):e211-e220.



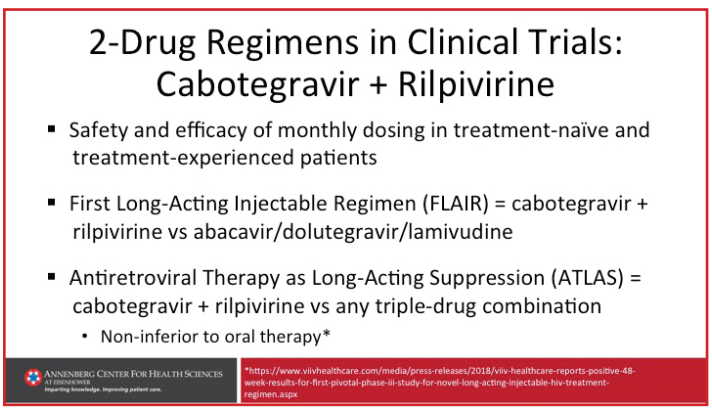
Data are emerging on the potential for 2-drug combination regimens for initial therapy. In 2018, 2 identical GEMINI 1 and GEMINI 2 studies compared a 2-drug regimen of dolutegravir/lamivudine (DTG + 3TC) vs a 3-drug regimen of dolutegravir/tenofovir/emtriciabine (DTG plus TDF/FTC).[1] These multicenter

studies enrolled 1441 treatment-naïve patients and showed virologic response rates of 91% in the 2-drug group and 93% in the 3-drug group.

Results were broadly consistent for virus suppression across individuals with higher viral load (more than 100,000 copies of viral RNA per milliliter of blood plasma [>100,000 c/mL]) and lower viral load (<=100,000 c/mL) HIV-1 plasma RNA. Virologic failure rates were ≤1% across all arms of the study and no patient who experienced virologic failure in either treatment arm developed treatment-emergent resistance. Rates of suppression were significantly lower in patients with a baseline CD4 count <200 cell/mm^3 (8-9% of the total study population). The most common (≥5%) adverse events across the studies were headache, diarrhea and nasopharyngitis in both arms (DTG + 3TC arm: 10%, 9%, and 8%, respectively, DTG + TDF/FTC: 10%, 11%, and 11%, respectively).

DHHS guidelines now list dolutegravir/lamivudine as an important option for treatment-naïve patients who cannot take tenofovir or abacavir. The studies excluded patients with viral loads >500,000 copies/mL, and the performance in those with CD4 counts <200 remains uncertain. Additional 96- and 144-week data analyses are planned to assess durability and experience in real-world patients to further clarify the risks for resistance. Drug-sparing regimens with favorable toxicity profiles, such as dolutegravir/lamivudine, represent an important advancement on antiretroviral therapy.[2] A small pilot study of dolutegravir/lamivudine (ASPIRE) showed that patients who are switched from a triple therapy regimen to dolutegravir/lamivudine maintained virologic suppression.[3] A larger study is currently ongoing (TANGO) from which data are anticipated later in 2019.

1. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet*. 2019;393(10167):143-155.
2. Kroidl A, Eberle J. A two-drug regimen for antiretroviral therapy. *Lancet*. 2019;393(10167):106-108.
3. Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. *Clin Infect Dis*. 2018;66(11):1794-1797.



Cabotegravir and rilpivirine is a 2-drug regimen being investigated for treatment-experienced patients who are virologically suppressed.[1] Recent phase 2b data presented at HIV Glasgow in October 2018 showed that this once or twice monthly injection of 2 different antivirals was noninferior to continued oral therapy.[2] At 160 weeks, 90% (104/115) and 83% (95/115) of patients treated with the long-acting regimen every 8 and 4 weeks remained virally suppressed, compared with patients treated with oral cabotegravir and abacavir/lamivudine. Approximately one quarter of patients (n=34) switched to the injectable regimen at 96 weeks, 97% and 100% of whom remained virally suppressed with injectable treatment every 8 and 4 weeks. Most patients reported mild (14%) or moderate (85%) injection-site reactions through 160 weeks, a majority of which self-resolved. Other common adverse events included nasopharyngitis (38%), diarrhea (22%), and headache (22%). Although cabotegravir and rilpivirine is potentially practice-changing, further data on HIV-infected women are awaited from phase 3 studies that are evaluating efficacy and safety of cabotegravir and rilpivirine in people living with HIV who are virally suppressed on 3-drug regimens (ATLAS, ATLAS-2M, FLAIR).[3-5]

1. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499-1510.
2. Margolis DA, et al. Safety, Efficacy and durability of long-acting CAB and RPV as two drug IM maintenance therapy for HIV-1 infection: LATTE-2 week 160 results. Presented at HIV Glasgow, 28-31 October, 2018.
3. FLAIR: Study to evaluate the efficacy, safety and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an integrase inhibitor in HIV-1 infected therapy naïve participants. https://clinicaltrials.gov/ct2/show/NCT02938520?term=FLAIR&cond=HIV&rank=2
4. ATLAS: Study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current antiretroviral regimen in virologically suppressed HIV-1-infected adults https://clinicaltrials.gov/ct2/show/NCT02951052?term=ATLAS&cond=HIV&rank=3
5. ATLAS-2M: Efficacy, safety and tolerability study of long-acting cabotegravir plus long-acting rilpivirine (CAB LA + RPV LA) in human-immunodeficiency virus-1 (HIV-1) infected adults https://clinicaltrials.gov/ct2/show/NCT03299049?term=ATLAS-2M&rank=1