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Updates from the HIV Drug Development Pipeline-2019

Amesika N Nyaku, MD MS, Assistant Professor,
Division of Infectious Diseases, Department of Medicine, Rutgers New Jersey Medical School
Shobha Swaminathan, MD, Associate Professor,
Division of Infectious Diseases, Department of Medicine, Rutgers New Jersey Medical School

Introduction

Heavily treatment experienced persons with multidrug resistance have limited treatment options. The prevalence of individuals with multidrug resistance has decreased over time as more patients are being treated initially with potent regimens. In a study from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, the prevalence of individuals with ≤2 active drug classes peaked at 7.5% in 2004 and decreased to 0.8% by 2017.[1] Of those who have multidrug resistance, 85% (775) were male and the median age was 51 (interquartile range 44-57) years old. It is reassuring that the population of patients with limited drug treatment options is shrinking, however, these patients are still in dire need of potent treatment options. New classes of Antiretroviral treatments (ART) are being developed to address this need as well as the ongoing need for medications with long half-lives that allow for less frequent dosing, and parenteral formulations that overcome barriers such as pill aversion and pill fatigue. Table-1 provides an overview of the medications that are currently in development.

Table-1: Novel Antiretroviral Medications in Development

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase translocation inhibitors	EFdA (MK-8591) Islatravir	Implant	Preclinical
		Oral	Phase IIb
	Tenofovir alafenamide (TAF)	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	Intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Approved in China
	Broadly neutralizing antibodies	Intravenous	Phase II/III
	Fostemsavir	Oral	Phase III
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical
Maturation inhibitors	GSK2838232	Oral	Phase II
	GSK3640254	Oral	Phase I/II

This discussion will focus on some of the medications that are in clinical development:

Fostemsavir (FTR) is a prodrug of temsavir (BMS-626529), which prevents viral entry by binding to the gp120 protein on the HIV envelope and blocking HIV attachment to the CD4 receptor.[2] All HIV-1 subtypes except subtype AE and O are

susceptible to FTR, but FTR has no activity against HIV-2 due to intrinsic resistance. There is no cross resistance with other drug classes including other fusion/entry inhibitors. The BRIGHTE study* is an ongoing phase III study of FTR plus optimized background therapy in heavily treatment-experienced people failing their current ART.[3] Eligible participants failed their current regimen with an HIV-1 RNA≥400 copies/mL with either no treatment classes or active drugs available (non-randomized, compassionate use cohort), or they had no more than 2 classes of drugs available but were unable to construct a viable regimen from the available drugs. Three hundred seventy-one participants were enrolled. Twenty two percent of participants were women, 70% were white, and the median age was 49 years old (interquartile range [IQR] 17-73). The median CD4+ T cell count was 80 (IQR 11-202) cells/mL. Two hundred seventy-two participants had some active agents and they were randomized in a 3:1 fashion to receive FTR 600mg oral twice daily with their failing regimen versus placebo with their failing regimen for 8 days. At day 9, all participants received FTR 600mg oral twice daily with an optimized background regimen (which for many included dolutegravir). Ninety-nine participants were in the non-randomized, compassionate use cohort. They received FTR 600mg oral twice daily with an optimized background regimen, which could include other investigational ART such as ibalizumab.

At week 96, in the randomized cohort, 60% (163/272) had HIV-1 RNA <40 copies/mL. In the non-randomized, compassionate use cohort, 37% (37/99) had HIV-1 RNA <40 copies/mL. Increases in CD4+ T cell counts were noted in both groups and strongly correlated with achieving HIV-1 RNA <40 copies/mL. Additionally, participants with baseline CD4+ T cell count <20 cells/mL had the largest increases in CD4+ T cell with a mean increase of 240 cells/mL. In terms of safety, serious adverse events (AEs) occurred in 48% and 34% of participants in the non-randomized and randomized cohorts, respectively. Deaths occurred in 16% and 4% of participants in the non-randomized and randomized cohorts, respectively. The majority of the deaths were attributed to complications of advanced HIV. The results from the BRIGHTE study demonstrate that FTR is an important new drug for heavily treatment experienced patients with multidrug resistant virus. FTR is available through an expanded access program offered by ViiV Healthcare and the company plans to file a new drug application with the US FDA by the end of 2019.

Islatravir (ISL) (MK-8591 or EFdA) is nucleoside reverse transcriptase translocation inhibitor (NRTTI). ISL has demonstrated significant in vitro potency and has potent activity against nucleoside reverse transcriptase inhibitor resistant HIV-1 strains.[4] ISL has a long intracellular half-life, which allows for non-daily dosing, such as once a week.

The **DRIVE2Simplify** study** is a phase IIB, randomized, double-blind, comparator-controlled, dose-ranging trial.[5,6] Participants were ART-naïve, had HIV-1 RNA≥1000 copies/ml, and CD4+ T cell count³ 200 cells/mL. Participants were ineligible if they had baseline ART resistance and/or co-infection with hepatitis B or C. One hundred twenty-one participants were enrolled and randomized. Nearly all of the participants were male (92.6%) and 76% were white and almost half (49.6%) were of Hispanic ethnicity. The median age of participants was 28 years of age (IQR 18-75). Twenty-seven (22.3%) participants had HIV-1 RNA >100,000 copies/mL. Participants were randomized in a 1:1:1:1 fashion to either receive ISL 0.25mg, 0.75mg, or 2.25mg oral once daily with doravirine (DOR) 100mg oral once daily and lamivudine (3TC) 300mg once daily or a single tablet formulation of doravirine 100mg and lamivudine 300mg and tenofovir disoproxil fumarate 300mg (DOR/3TC/TDF). After week 24, participants with HIV-1 RNA <50 copies/ml were transitioned to the second stage of the study in which 3TC was removed and participants remained on a 2 drug regimen of ISL 0.25mg, 0.75mg, or 2.25mg in combination with DOR 100mg PO daily or 3 drug DOR/3TC/TDF.

At week 24, 89.7% (26/29), 100% (30/30), 87.1% (27/31) of participants receiving 0.25mg, 075mg, 2.25mg of ISL respectively achieved HIV-1 RNA <50 copies/ml compared to 87.1% (27/31) of participants receiving DOR/3TC/TDF. No participants experienced protocol defined virologic failure by week 24. At week 48, 89.7% (26/29), 90% (27/30), 77.4% (24/31) of participants receiving 0.25mg, 075mg, 2.25mg of ISL respectively achieved HIV-1 RNA <50 copies/ml compared to 83.9% (26/31) of participants receiving DOR/3TC/TDF. Five participants (5.6%) experienced protocol defined virologic failure in the ISL group; 4 participants had virologic rebound and 1 participant had virologic non-response. One participant in the DOR/3TC/TDF had virologic rebound. In terms of drug safety, at week 24, 19.4% of participants receiving

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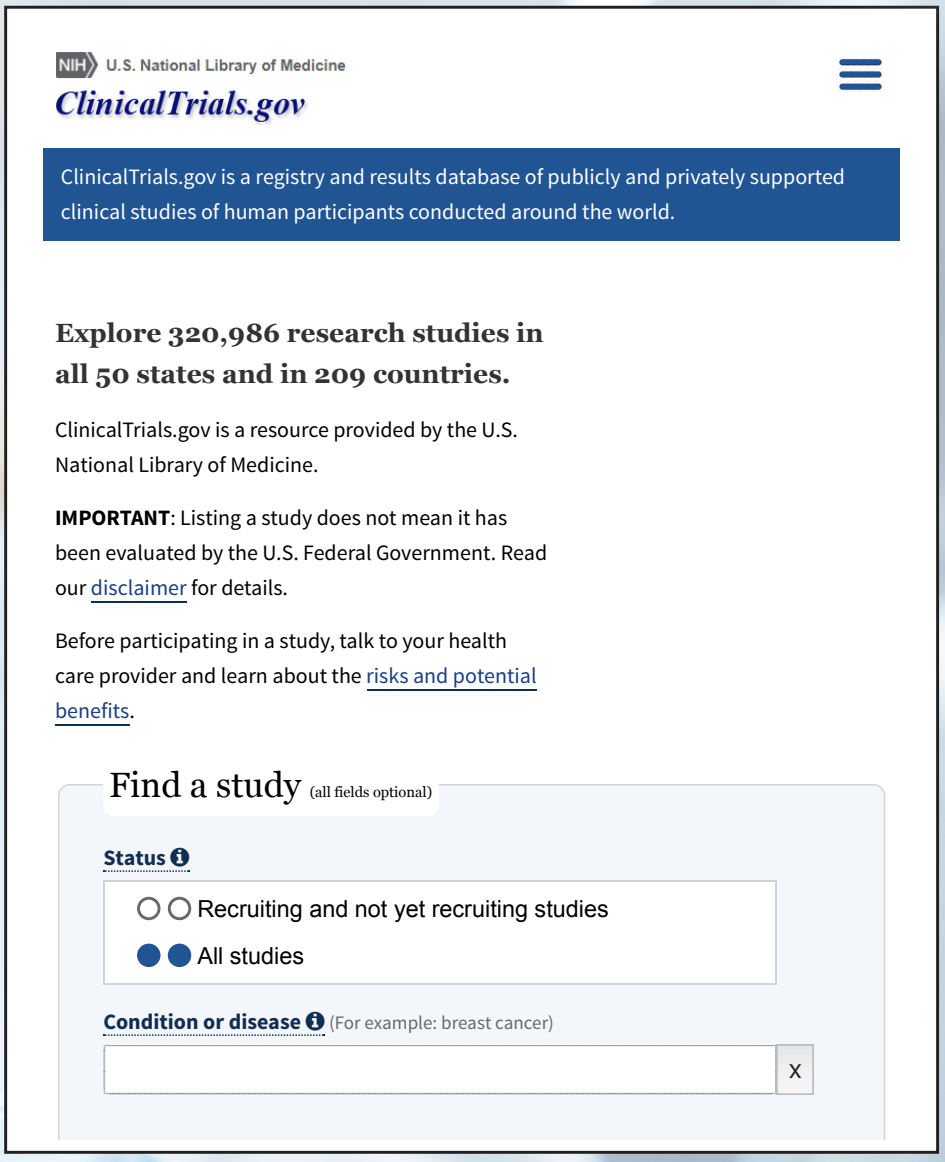
DOR/3TC/TDF experienced drug related AEs compared to 4.4% of participants receiving ISL based regimen. There were no serious drug-related AEs or discontinuations. Similarly, at week 48, 19.4% of participants receiving DOR/3TC/TDF experienced non-serious drug related AEs compared to 7.8% of participants in the 2 drug arms. Given the similar rates of virologic response across the arms and tolerability, a phase III study of ISL in combination with DOR is planned.

GSK2838232 is a second generation HIV maturation inhibitor. Maturation inhibitors target the final step in the HIV life cycle.[7] Once HIV virions have budded off of the host cell, polyproteins in the core of the virions need to be cleaved in order to form mature virions that are infectious. Maturation inhibitors bind directly to the polyproteins and prevent cleavage, which results in immature and non-infectious virions.

A phase IIa, single-arm, open label, two part dose-ranging study evaluated the antiviral activity of 4 dose levels of GSK2838232.[8] Eligible participants were ART-naïve, had HIV-1 RNA≥5000 copies/ml, and CD4+ T cell count ³ 350 cells/mL. Thirty-three participants were enrolled; 97% male and 60% white. Ten participants enrolled in part 1 received GSK2838232 100mg oral and cobicistat (COBI) 150mg oral once daily for 10 days. After an interim pharmacokinetic (PK) and safety analysis, participants were enrolled in part 2. In the second part of the study, 8 participants received 200 mg once daily, 8 participants received 50mg once daily, and 7 participants received 20mg once daily of GSK2838232, all boosted with COBI, for 10 days. GSK2838232 boosted with COBI reduced HIV-1 RNA over the 10-day study period. HIV-1 RNA levels had a mean decrease of 0.67, 1.56, 1.32, and 1.70 at 20mg, 50mg, 100mg, and 200mg doses respectively. HIV genotyping was done at baseline and at the end of receipt of study product to assess for drug resistance. Genotyping data was available for 28 of the participants. Two participants had treatment-emergent resistance with the development of A364A/V mixtures. There were no serious AEs. Five participants experienced possible drug related AEs: headache (n=2), somnolence (n=1), skin rash (n=1), abnormal dream (n=1) and pruritus (n=1). The results of this trial are encouraging because the second generation of maturation inhibitors have overcome problems of tolerability and have broader susceptibility compared to first generation maturation inhibitors.

Long Acting Parenteral Medications for HIV Treatment

Long Acting Rilpivirine (LA RPV): Rilpivirine (RPV) is an NNRTI currently approved for the treatment of HIV when used in combination with other medications. Its pharmacological properties allow for the preparation of a long acting nanosuspension that can be administered as an intramuscular injection every 4-8 weeks.[9,10] Studies have shown that



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Status

Recruiting and not yet recruiting studies

All studies

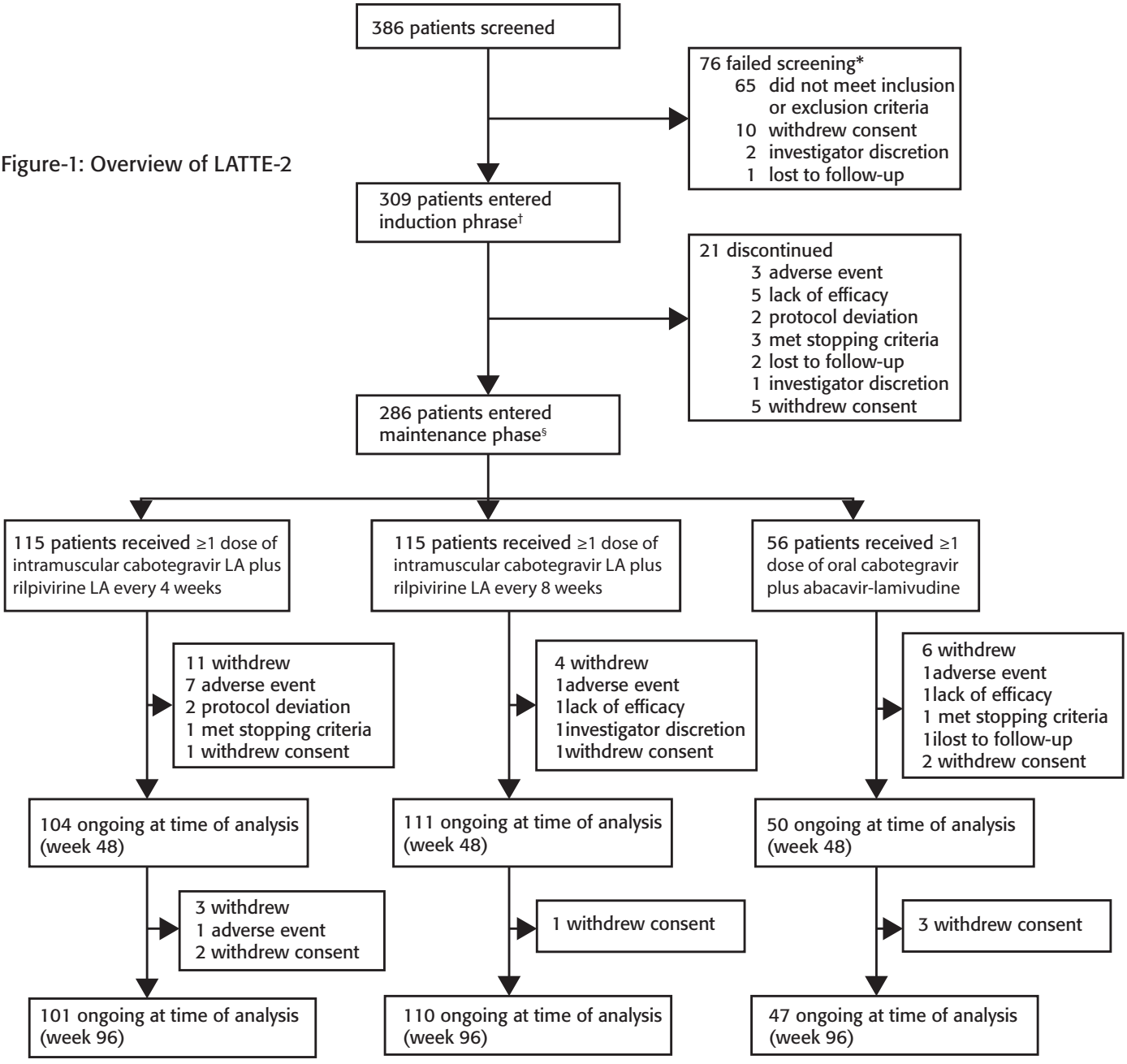
Condition or disease (For example: breast cancer)

X

LA RPV can achieve drug concentrations in the plasma similar to those given orally.[11,12] The HIV Prevention Trials Network (HPTN) 076 was a phase II prevention study that showed that RPV given as an intramuscular injection achieved protective levels when administered 8 weeks apart.[13] Further, the study also showed that the majority of the women found the injections tolerable and 61% of the women in the study strongly agreed that this was a strategy that would be acceptable for them.

Cabotegravir (CAB) is an investigational integrase stand transfer inhibitor (INSTI) that has potent activity against most HIV strains including some strains with known resistance to currently available INSTIs.[14,15] This compound is currently being developed simultaneously for HIV treatment and prevention. Early clinical studies have shown prolonged half-lives after administration of the injectable product up to 52 weeks after dosing.[16] The injection was generally well tolerated although most participants reported some injection site reactions (ISR).[16] Currently, a large phase 3 clinical study, HPTN 083, being conducted in HIV negative men who have sex with men and transgender men to establish the safety and efficacy LA CAB for HIV prevention.

Figure-1: Overview of LATTE-2



Combination Therapy of Cabotegravir and Rilpivirine: The Long-Acting Antiretrovital Treatment Enabling (LATTE)-2 was a randomized phase 2b study that enrolled 286 treatment-naïve HIV infected participants who initially received oral abacavir/lamivudine plus oral CAB 30 mg daily for 20 weeks (Figure-1). They were then randomized 2:2:1 to all injectable ART with CAB 400 mg and RPV 600 mg every 4 weeks or CAB 600 and RPV 900 mg every 8 weeks or continue oral regimen.[17]

At 96 weeks, HIV viral load was <50 copies/ml in 84-94% across the regimens. Although ISRs did occur, only 2 (<1%) of the participants discontinued the study because of ISR. Further, the degree of ISR reduced with subsequent injections, suggesting that over time most participants tolerated the study medications. Given this information, there are several ongoing phase 3 studies of a maintenance regiment with CAB LA and RPV LA.

FLAIR is a phase 3 open label study investigating whether switching to monthly CAB and RPV is non-inferior to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) among ART-naïve individuals (Figure-2).[18]

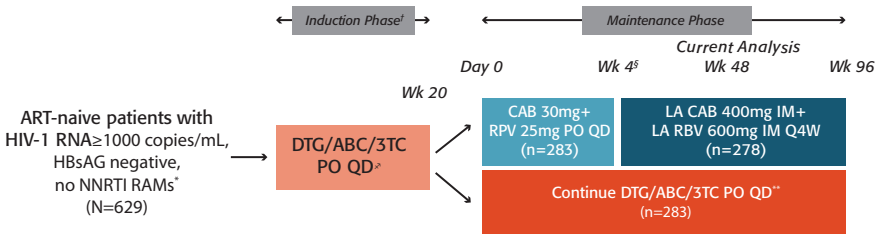


Figure-2: Overview of FLAIR

The study showed that at 48 weeks, 93% of participants in both treatment arms were virologically suppressed. Further 96 week analyses are expected soon.

The Antiretroviral Therapy as Long-Acting Suppression Study (ATLAS) is looking at participants who are virologically suppressed on their first or second ART regimen for at least 6 months and have no history of prior failure; participants were randomized to either continuing their ART or switching to monthly CB LA and RPV LA (Figure-3).[19] The study showed that at 48 weeks, there was no statistically significant differences between the two treatment arms.

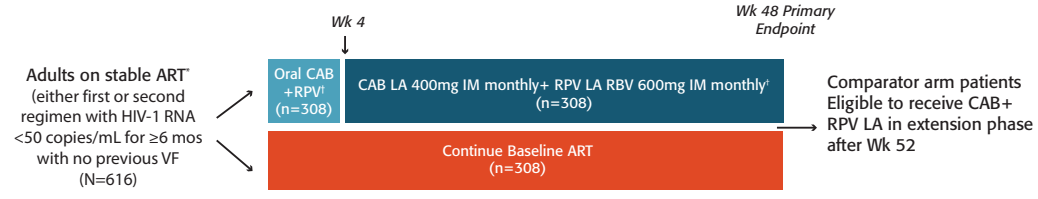


Figure-3: Overview of ATLAS

ATLAS-2M is a phase 3 randomized study evaluating the safety and efficacy of CAB LA and RPV LA every 4 versus every 8 weeks. Results of this study are expected to be announced shortly.

Based on these studies, it is anticipated CAB and RPV LA will be available as injectable agents in 2020. The exact indications, dose, and frequency will depend on Federal Drug Administration (FDA) indication for use. However, CAB and RPV LA are still exciting new options for patients who otherwise have difficulty taking medications every day and could be good strategy for many patients.

Leronlimab is a humanized monoclonal IgG4 antibody that binds to the HIV binding domain of the CCR5 receptor and prevents entry of CCR5 tropic virus into the host cell.[20] It is unique in that its binding site is distinct from maraviroc (another approved CCR5 inhibitor) thereby giving it activity against strains that may have become resistant to maraviroc.[21] It is being studied as weekly maintenance monotherapy for patients with CCR5 tropic virus and as salvage therapy for patients with multi-drug resistant CCR5 tropic strains. Recently, the FDA granted this medication orphan drug status to expedite approval for heavily treatment experienced patients.

Broadly neutralizing antibodies (bNABs) were originally isolated from long term non-progressors with HIV infection who had high levels of HIV neutralizing antibodies. Many of these antibodies are now in clinical development VRC01, VRC07, 3BNC117 and 10-1074.[22,23] Early studies have shown that bNAs are generally well tolerated and have good antiviral activity against many HIV strains. These medications are generally administered intravenously, but there is ongoing work to modify these compounds to increase their half-life to allow for longer dosing intervals.[24] New studies are being developed both for HIV treatment and prevention using a combination of bNABs and bNABs with some long acting injectable medications for persons with HIV infection.

Islatravir: This novel medication (nucleoside reverse transcriptase translocation inhibitor) is being developed as a drug eluting subdermal implant. There is early information that suggests that once implanted this medication could have serum levels suitable for HIV prevention for up to one year.[25] However, it is unclear if the same will be applicable for HIV treatment.

Tenofovir Alafenamide (TAF) implant: TAF is a medication approved for both HIV treatment and prevention. Preclinical data indicates that this medication has levels effective for HIV prevention

continued on next page

in animal models when given as an implant for over 6 months.[26]

GS-9131 is a novel nucleoside reverse transcriptase translocation inhibitor that in development for patients who may have resistance to currently available ART; invitro data showed that there was no resistance that developed with multiple cell passages.[27]

Elsulfavirine is an NNRTI that as an oral drug in a combination antiretroviral regimen showed safety and efficacy comparable to efavirenz-based regimens in clinical studies; it is approved for treatment in Russia.[28,29] A long-acting injectable formulation of elsulfavirine with the potential for monthly injection recently was reported in preclinical studies and clinical studies are planned.[30]

Challenges and Opportunities with Long-acting Medications

These novel treatment modalities offer patients alternative options to daily oral dosing to control their HIV infection and opens the door to various alternative treatment delivery strategies. Given that many of these medications are administered monthly or less frequently, it raises the possibility of directly observed therapy for patients who are not virologically suppressed. These opportunities, however, do not come without challenges. These long acting medications have very long half-lives and although many appear to be safe in clinical trials, long term data are need because clinicians will not be able to "discontinue" long-term medication in patients who develop unforeseen AEs. Further, it is likely that there may be drug levels detectable long after known half-lives, which increases the possibility of resistance should the patients be lost to care. Given the long acting half-lives of these medications, they may be challenging to use in women of childbearing age because the safety of these medications in pregnant women is unknown; it is unclear how long women will need to wait after discontinuing these medications before it would be safe for them to conceive.

Conclusion

The HIV drug development pipeline is very rich with new innovations in both novel mechanisms of action and formulations. These innovations are a much needed complement to our existing antiretroviral regimens as we aim to the end the HIV epidemic by harnessing the effectiveness of both HIV pre-exposure prophylaxis and treatment as prevention.❖

*A Multi-arm, Phase 3, Randomized, Placebo Controlled, Double Blind Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir (BMS-663068/GSK3684934) in Heavily Treatment Experienced Subjects Infected With Multi-drug Resistant HIV-1

**Islatravir (MK-8591) With Doravirine and Lamivudine in Participants Infected With Human Immunodeficiency Virus Type 1 (MK-8591-011)

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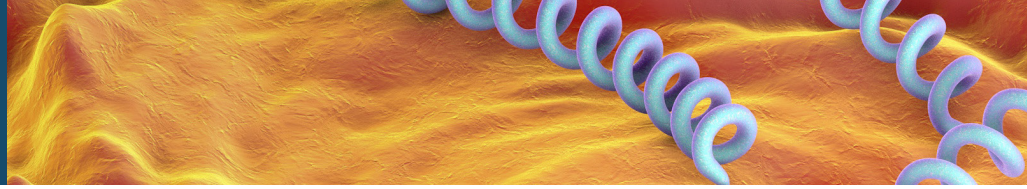


Reverse-Sequence Syphilis Testing: A Brief Overview for HIV Providers

Amelia M. Hamarman, MS.Ed., MS Coordinator-Sexually Transmitted Disease Program NJ-DOH Division of STD Services

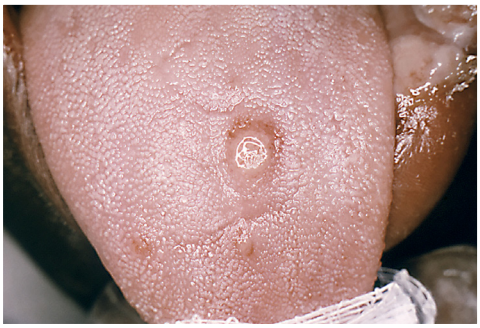
Greta Anschuetz, MPH Director-STD Services NJDOH-Division of STD Services

Diagnosing and staging a case of syphilis can prove to be challenging. Symptoms of syphilis can be elusive do to their temporary, mild, and often unspecific nature--patients may not notice painless lesions in the genital or anal areas, or providers may attribute a lesion or rash to a different cause. In addition, those who are infected can go for significant periods of time without clinical manifestations. Given this, diagnosis cannot rely on physical examination and symptoms but rather must include serologic testing with both nontreponemal and treponemal assays.

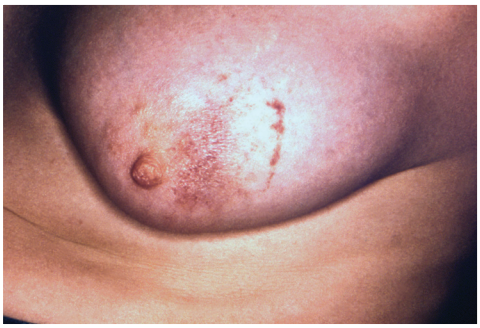
Non-treponemal tests include rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests. Both tests are highly sensitive in detecting non-specific antibodies to acute and chronic conditions, including, but not limited to, syphilis. RPR remains the most commonly used non-treponemal assay in the United States, and quantitative results (titers) often correlate with disease progression. Repeated screenings for titers are useful for monitoring infection status and treatment response.[1,2]

Treponemal tests include FTA (fluorescent treponemal antibody, T. pallidum particle agglutination (TPPA), enzyme immunoassay (EIA) and chemiluminescence immunoassay (CIA). These assays are highly specific to treponema pallidum and are therefore necessary to definitively identify a case of syphilis. However, they are qualitative and remain reactive even after adequate treatment and resolution of an infection, and therefore cannot differentiate between a current untreated infection and a historical successfully treated infection.[1]

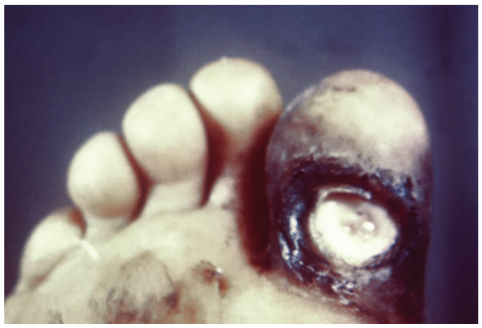
Laboratories can use one of two testing algorithms, both of which use a combination of treponemal and non-treponemal assays to detect syphilis infection. Traditional algorithms start with a nontreponemal assay (e.g. RPR) as the initial screening test, and then confirm reactive results with a treponeme-specific assay (e.g. FTA or CIA). Reverse sequence algorithms, on the other hand, use a treponeme specific test for screening followed by an RPR test which, if reactive, can then be reflexed for a quantitative titer. The increased availability of cost-effective automated treponeme-specific screens has led to more laboratories using a reverse-sequence algorithm.[3]



This image depicts a close view of the surface of an African-American female's tongue, upon which one can see a circular lesion that was diagnosed as a primary syphilitic chancre. Syphilis is caused by the bacterium, Treponema pallidum. Photo credit CDC/ Robert E. Sumpter



This image depicts a close view of a patient's left breast, highlighting a cutaneous lesion, specifically involving the area of the areola. Upon initial inspection, a differential diagnosis ruled out a hickey, caused by oral suction for an extended period, but revealed that this was actually a case of syphilis, caused by the bacterial spirochete, Treponema pallidum. Photo credit CDC/ Dr. N.J. Fiumara



This photograph depicts a view of the bottom of a patient's right foot, highlighting the region of the great toe, revealing the presence of a condition known as mal perforans. This was a chronic ulcer, which in this case, resulted from the disease, tabes dorsalis, a form of neurosyphilis, resulting from a tertiary syphilis infection, due to the bacterium, Treponema pallidum. This ulcer resulted from the destruction of the dorsal columns in the patient's spinal cord, normally responsible for one's position sense. Photo credit: CDC

The accurate diagnosis and treatment of syphilis requires that results of both types of serologic tests be considered along with patient information about recent signs or symptoms, previous syphilis diagnosis, and/or information about recent sexual activity.[1]

Considerations for Traditional Algorithm Screening

Some labs, including commercial labs Quest and LabCorp, have two different syphilis panels to choose from: a reflex to titer with confirmatory testing, and reflex to a titer only (see Table 1). The former panel is necessary for definitively diagnosing a case

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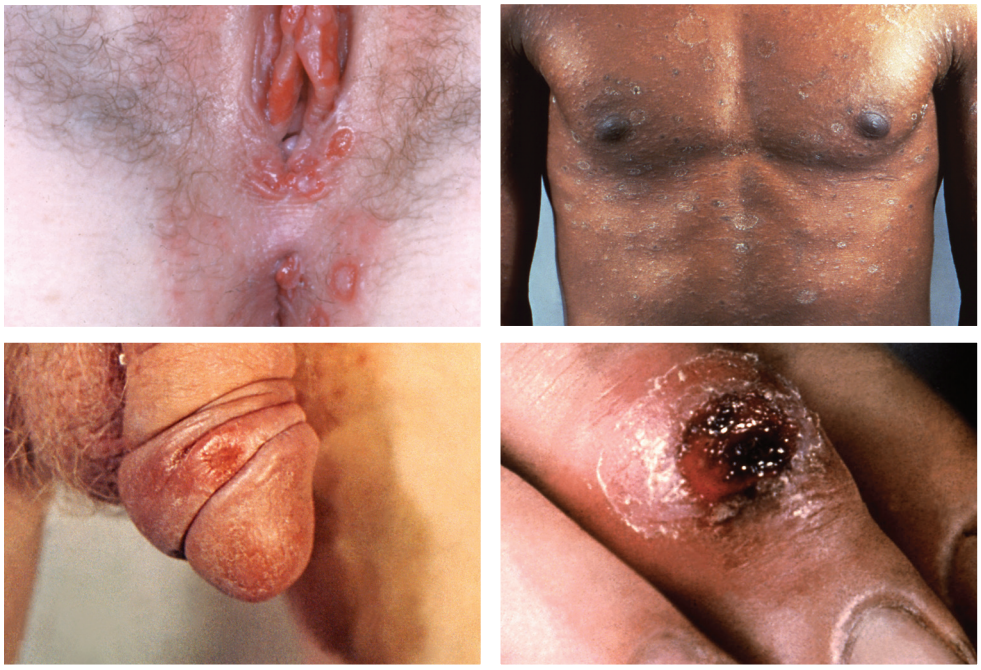

(Photo clockwise starting top left) This female patient presented with condylomata lata lesions involving the vulva and anal region, caused by the bacterium, Treponema pallidum. A patient with condylomata lata can develop lesions during secondary syphilis, which present as gray, raised papules appearing on the vulva, and near the anus, or in any other warm, intertriginous region. Photo credit CDC. (Photo top right) This photograph depicted an anterior view of a male patient's torso and upper arms, which exhibited a flattened, pigmented macular rash, that was determined to be due to a secondary syphilis infection, caused by the bacterial spirochete, Treponema pallidum. In this case, the characteristic secondary syphilitic rash, also showed signs of scaling, or flaking. (Photo lower left) This photograph depicts a close view of a patient's penis, highlighting the presence of what was determined to be a persistent primary syphilitic lesion, but which had been classified as a case of secondary syphilis, caused by the bacterial spirochete, Treponema pallidum. CDC/ Susan Lindsley. (Photo lower right) This image depicts a close dorsal view of a patient's right middle finger, revealing the presence of what turned out to be an extragenital primary syphilitic chancre. The chancre is usually firm, round, small, and painless, appearing at the spot where syphilis entered the body, and lasts 3-6 weeks, healing on its own. If adequate treatment is not administered, the infection progresses to the secondary stage. Photo credit: CDC

of syphilis. The latter panel should be used only when a patient has a well—documented history of syphilis. While electronic medical record (EMR) systems may make it challenging to determine which panel is being ordered, ensuring that the correct panel is used is essential for accurate diagnosis as well as preventing the need for additional bloodwork. In addition, the Centers for Disease Control and Prevention (CDC) requires a confirmatory test for all reported cases of syphilis so an RPR alone will not allow for the adequate capturing of the true burden of syphilis in New Jersey.

Considerations for Reverse Sequence Algorithm Screening

Historically, both nontreponemal and treponemal assays have been performed manually, making the traditional sequence preferable both in terms of time and cost effectiveness. However, the commercial availability of automated treponemal assays has led to increased consideration and use of this approach.[2,3] Thus, the question emerges as to any advantages or disadvantages in using a reverse sequence algorithm as opposed to the traditional model to accurately identify and diagnose syphilis. Below is a brief review of some of these considerations.

Better detection of very early and very late stage syphilis: RPR titers typically increase with disease progression, beginning low and increasing as the disease progresses followed by a reversal back to low or non-reactive titers in late stage syphilis even without treatment. Treponemal assays are not dependent on disease progression and therefore have the potential to detect incubating syphilis and untreated late stage syphilis when such cases may be missed by a non-treponemal initial screen with non-reactive results.[1, 3]

Increased likelihood of false positive results: Because treponemal tests remain reactive even long after an infection has been effectively treated, these tests do not differentiate between new infections and historical infections and therefore could result in the false diagnosis of active syphilis.[1] Reflexing results with an RPR titer may provide needed data to determine true positivity, however confusion may result in the case of discordant test results.

Interpretive challenges: When a patient has discordant test results, several possibilities exist: A false-positive result, very early stage syphilis, untreated latent syphilis or previously treated syphilis. Thus, a second treponeme specific test is often needed to "break the tie" between discordant results.[1,2] Additional information about a patient's syphilitic history, symptoms and recent sexual activity are also essential for determining appropriate diagnosis and treatment.[4] Table 2 provides guidance on interpreting results and treatment recommendations for various possible laboratory results of reverse sequence syphilis screening.

Implications of syphilis serologic results for patient care

Effective treatment and follow-up of a syphilis infection depend on the accurate determination of both the presence of infection as well as the stage of infection. Providers should be aware of the testing algorithms used by their selected lab and be able to interpret test results accurately. Physicians, however, should not rely solely on serologic testing to determine appropriate patient care, but should be thorough in gathering information about patient sexual history, any previous STD testing and treatment, current and historical syphilis-related signs and symptoms, information about sexual partners, physical examination findings, and disease morbidity in the

continued on next page

Reverse-Sequence Syphilis Testing

population and area in which a patient resides.[1,4] Once the provider gathers all possible information, the most appropriate course of action for patient treatment and care can be determined.

Screening, treatment and follow-up recommendations for those with HIV are largely the same as those without. Due to the high prevalence of co-morbidity of HIV and syphilis as well as the increased susceptibility for transmitting or acquiring HIV when infected with syphilis, CDC recommends annual syphilis screening for those with HIV, and an offer for HIV testing to any HIV-negative person who tests positive for syphilis.[1,4] Guidance on interpreting serologic syphilis screening results does not differ between those who have HIV and those who do not.

The New Jersey Department of Health, STD Program maintains a registry of persons who have been diagnosed with syphilis. Providers can contact the STD Program to request a record search for patients which can help provide historical patient diagnostic and treatment information to inform an appropriate course of care and treatment for patients with positive syphilis tests. Providers can call the STD Program at 609-826-4869 to request a syphilis record search.

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Table 1: Examples of Syphilis tests names available at Quest and LabCorp

	Quest	LabCorp
RPR Only Performed	RPR (Monitor) with Reflex to Titer	Rapid Plasma Reagin (RPR), Qualitative Test
RPR and Confirmatory Test Performed	RPR (Diagnosis) with Reflex to Titer and Confirmatory Testing (REFL)	Rapid Plasma Reagin (RPR) Test With Reflex to Quantitative RPR and Confirmatory *Treponema pallidum* Antibodies

Table 2: Interpretation of Serological Results Using a REVERSE SEQUENCE Syphilis Screening Algorithm

Interpretation of Serologic Results Using a REVERSE SEQUENCE Syphilis Screening_Algorithm

Step 1	Step 2	Step 3	EVALUATION AND MANAGEMENT	INTERPRETATION
Screening Treponemal Test (eg, EIA/CIA)	Nontreponemal Test (eg, RPR)	Supplemental Treponemal Test (eg, TPPA)		
Reactive	Reactive	Not performed	If no documented history of treatment: Provide stage-appropriate treatment; ensure that a quantitative RPR was obtained	• Current untreated infection
			If there is documented history of treatment[a] and adequate post-treatment serologic response: 1. If RPR titer is low and stable, history and clinical exam are negative, and patient denies any recent symptoms or known exposure to syphilis, no further action needed.	• Adequately treated syphilis with persistent (ie, serofast) serologic reactivity
			2. If sustained (> 2 weeks) ≥ 2-dilution (4-fold) increase in RPR titer, consider re-infection (especially if ongoing risk of STI) or treatment failure.	• Possible re-infection • Possible treatment failure
			3. If recent exposure or ulceration on exam consistent with primary syphilis, *see below*[b]	• Cannot rule out Incubating or early primary infection
Reactive	Nonreactive	Reactive	If no documented history of treatment: Provide stage-appropriate treatment and repeat testing to rule out early seroconversion	• Long-standing, untreated latent infection (with loss of nontreponemal reactivity)
			If there is documented history of treatment[a] and adequate post-treatment serologic response: • Likely represents serofast serology • If clinical exam is negative and no known recent symptoms or known exposure to syphilis, no further action needed	• History of syphilis with persistent post treatment serologic reactivity
			If recent exposure or ulceration on exam consistent with primary syphilis: See Below[b]	• Incubating infection • Early primary syphilis
			If signs/symptoms of possible secondary syphilis: Ask laboratory to perform quantitative RPR testing (with serial dilutions) to rule out prozone[c]	• Rule out new infection with prozone reaction[c]
Nonreactive	Nonreactive	Nonreactive	**If clinical exam is negative and no known risk for recent exposute to syphillis:** Likely represents false-positive EIA/CIA, no further action needed in low risk populations. If at increased risk for infection, consider repeating RPR and treponemal test in 2-4 weeks	• False-positive screening EIA/CIA (if patient is low risk) • Incubating infection
			If recent exposure or new onset anogenital ulceration on exam: See Below[b]	• Incubating infection • Early primary syphilis
Nonreactive	Not performed	Not performed	**If clinical exam is negative and no known recent exposure to syphilis:** No further action needed.	• No laboratory evidence of syphilis infection
			If recent exposure or new onset anogenital ulceration on exam: See Below[b]	• Incubating infection • Very early primary syphilis

Adapted from: *Use of Treponemal Immunoassays for Screening and Diagnosis of Syphilis,* California Department of Public Health Sexually Transmitted Diseases Control Branch, 2/2016 [57] Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serology Testing Silver Spring, MD 2015. [66] Sexually Transmitted Diseases Treatment Guidelines 2015. *MMWR Recomm Rep* 2015. [23] California Department of Public Health (CDPH) Sexually Transmitted Diseases (STD) Control Branch; California STD Controllers Association; California Prevention Training Center (CAPTC). Use of Treponemal Immunoassays for Screening and Diagnosis of Syphilis. Guidance for Medical Providers and Laboratories in California, February 2016.
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UseofTreponemalImmunoassays_Syphilis.pdf[57]

[a] For patients reporting a history of treatment that is not documented in the current medical record, clinical providers can contact the local/state health department to access previous testing and treatment information. All positive syphilis test results, diagnoses and treatment reported to the local or state health department are maintained in a syphilis registry for the jurisdiction.

[b] Presumptive treatment should be provided for patients who: (1) report a sexual (or needle sharing) contact in the past 90 days with a partner newly diagnosed with syphilis (See Step 7) or (2) present with a skin lesion suspicious for primary syphilis on physical examination. Lesion-based testing could also be performed if available. Even in the case of a patient presumptively treated for incubating (due to known exposure) or primary infection whose initial syphilis serology is negative, repeat serologic testing should be performed 2-4 weeks following the initial nonreactive result. Such retesting may detect early seroconversion and if reactive can confirm the syphilis diagnosis as well as establish a baseline titer useful in post-treatment follow-up.

[c] A prozone reaction can result in a false-negative RPR, in an undiluted serum specimen, when non-treponemal antibody levels are excessively high. (See Figure 7)

Abbreviations: CIA chemiluminescence immunoassay; EIA, enzyme immunoassay; RPR rapid plasma reagin.

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Using Self-Administered Rifapentine and Isonaizid 12 Dose Regimen to Treat Latent TB Infection

Patricia Woods, RN, MSN, Public Health Consultant-1, Nursing - NJDOH-TB Services

Frank Romano, MPH, Senior Public Health Advisor NJDOH-TB Services

Darcel M. Reyes, PhD, ANP-BC, Assistant Professor, Rutgers University School of Nursing

Introduction

In the United States, up to 13 million people may have latent tuberculosis (TB) infection (LTBI).[1] Without treatment, on average 1 in 10 people with LTBI will develop TB disease.[1] Rifapentine and Isoniazid, known as 3HP, is a 12 dose weekly regimen that is one of the four recommended treatments for LTBI.[2] 3HP is as effective in the treatment of LTBI as nine month daily regimens.

Recommendations for Use of 3HP

The 2011 Centers for Disease Control and Prevention (CDC) recommendations for LTBI treatment with 3HP required Directly Observed Therapy (DOT), which could be a barrier for both patients and providers.[2] At that time, people with HIV co-infected with LTBI and on antiretroviral medications could not receive 3HP.[2] In 2018, the CDC revised the recommendations to include use of 3HP as self-administered therapy (SAT) in order to reach more people with LTBI and improve treatment completion rates without the burden of DOT.[2] In addition, patient populations eligible to receive 3HP were expanded to include people with HIV or acquired immunodeficiency syndrome (AIDS) and on antiretroviral medications compatible with rifapentine.[2]

Clinical Care of Patients Taking 3HP

The clinical decision to use 3HP as DOT or SAT should take into account individual patient attributes and preferences, as well as the risk of progression to more severe TB disease.[3] If it is decided that SAT is the best option, monthly appointments are still necessary to assess adherence and monitor for adverse effects (AE). Clinicians should order baseline chemistry blood tests prior to starting SAT with 3HP, especially when treating people with HIV, patients with liver disorders including hepatitis, women in the post-partum period, and individuals who use alcohol or intravenous drugs.[3] Patients should be instructed to report any missed doses or AEs such as systemic drug reactions, loss of appetite, vomiting, liver tenderness, yellowing of the eyes, or easy bruising. Mild to moderate AEs can be treated conservatively with clinical and laboratory monitoring or the patient can be switched to DOT.[3] Severe reactions, such as hypotension, angioedema, or thrombocytopenia require immediate medical attention and discontinuation of 3HP.[3]

The CDC website contains downloadable treatment tools.

- A SAT dose tracker and AE symptom checker for patients; https://www.cdc.gov/tb/publications/pamphlets/LTBI_Medication_Tracker.pdf
- A downloadable pamphlet with information and resources for clinicians: https://www.cdc.gov/tb/topic/treatment/pdf/LTBI_Clinicians_Info.pdf

Conclusion

Once a leading cause of death in the United States, TB has had a steady decline with fewer than 10,000 cases a year.[1] Treatment of LTBI is critical for the elimination of TB disease. Shorter course regimens such as 3HP and the addition of SAT as a treatment option are key components to completion of LTBI therapy, which will result in fewer cases of TB. ❖

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Transitioning from PEP to PrEP: Another Prevention Strategy

Jihad Slim, MD, Assistant Professor of Medicine NYMC, Valhalla, N.Y.

Introduction

With current recommendations for treatment with antiretroviral therapy (ART) for all persons with HIV[1] and the availability of many different single tablet regimens (STR) that are effective and well tolerated, most people with HIV who are in care have an undetectable virus load (VL) and thus do not contribute to transmission of HIV.[2] The number of new infections reported every year to the Centers for Disease Control and Prevention (CDC) has slowly declined over the last decade, but there are still close to 40,000 new infections every year.[3] The vast majority of new infections are sexually transmitted; around 10% are related to intravenous drug use (IDU). Post exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) are effective tools to stop new transmissions. Transitioning patients from PEP to PrEP is another tool clinicians can use to curb the epidemic while we are impatiently waiting for the development of a vaccine for HIV prevention.

Case 1

A 21-year-old man, Sam M.,* presented to the clinic one Monday morning asking for PEP. Sam stated that on Sunday he had receptive anal intercourse with a man of unknown HIV serostatus and thinks that the condom broke. Sam said that he had 10 different sexual partners in the last month, all men, and always used condoms. He was currently asymptomatic and had no previous medical problems. Sam completed the series of vaccinations for Hepatitis A, Hepatitis B, and for Human Papilloma Virus (HPV). His last HIV test, one month ago was negative. We prescribed a two tablet PEP regimen of an integrase strand transfer inhibitor (INSTI) and a single tablet combination of two nucleoside reverse transcriptase inhibitors (NRTI) to start immediately and continue for 28 days.

Sam was sent to the laboratory for immediate HIV testing using a fourth generation antibody/antigen assay, Hepatitis B surface antibody titer, Hepatitis B surface antigen, Hepatitis C antibody with reflex to VL, rapid plasma reagin (RPR), Fluorescent Treponemal Antibody Absorption Test (FTA-ABS), Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), urinalysis. We also included urine, throat, and rectum nucleic acid amplification testing (NAAT) for gonorrhea and chlamydia. We told Sam that we would call with the results and gave him an appointment in 4 weeks.

His results showed a normal CBC, CMP, and urinalysis; Sam was negative for HIV, Hepatitis C (HCV), Hepatitis B surface antigen, RPR and FTA-ABS. His Hepatitis B surface antibody was reactive, and the NAAT was only positive for rectal gonorrhea. Sam returned for an intramuscular (IM) dose of 250 milligrams of Ceftriaxone with 1 gram of oral Azithromycin. He was not able to trace his contacts but was still asymptomatic and tolerating his PEP regimen well.

On the third visit, again Sam had no complaints and finished 28 days of PEP therapy. In the previous month, he had four different male partners with consistent condom use. When asked specifically about chemsex (chemsex refers to the use of drugs or "chems," e.g., Crystal Meth, to enhance the sexual experience), Sam acknowledged intermittent use. He agreed to start daily PrEP and was sent to the laboratory for an HIV VL, FTA-ABS, CMP, urinalysis and urine, throat, rectal NAAT for gonorrhea and chlamydia. Sam was told he would be notified about the results and should return to clinic in 12 weeks. His VL was undetectable and the FTA-ABS was negative. Sam's renal and liver function tests were normal; the NAAT results were negative for urine, throat, and rectum.

On the fourth visit, 12 weeks later, Sam had no complaints, reported using condoms intermittently, was 90% adherent to his PrEP regimen, occasionally drank alcohol, and had multiple anonymous sexual partners. Sam was counseled about risk-reduction behavior, and his PrEP regimen was renewed for another 3 months. Laboratory results indicated that his fourth generation HIV testing was negative, negative NAAT at 3 sites, a normal CMP, and 1+ proteinuria, however, the FTA-ABS was now positive with an RPR titer of 1:32. One dose of Benzathine penicillin G 2.4 million IU was given IM, with a follow up scheduled visit in 12 weeks.

Case 2

A 32-year-old woman, Sabrina F.,* presented to our clinic for the first time. Sabrina was brought to the Emergency Department (ED) by EMS the previous day for treatment of a heroin overdose. Sabrina said that it was the first time she shared needles with a male friend who was known to have HIV and HCV. Her last HIV test, six months earlier, was negative. She received emergency PEP in the ED and was asked to follow up with the infectious disease service.

Sabrina said that she had some nausea but was otherwise feeling fine; her physical examination was normal. Sabrina's sexual history revealed that she occasionally had sex for money, used condoms most of the time, and had a remote history of syphilis treated 10 years ago when she was pregnant. A review of her laboratory

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results from the ED revealed a negative fourth generation antigen/antibody HIV test, normal renal and liver function tests, negative HCV antibody, and Hepatitis B surface antigen with reactive Hepatitis B surface antibody and Hepatitis B core antibody IgG. We encouraged her to continue her PEP regimen, which consisted of an INSTI twice a day and two NRTIs in a single tablet once a day. We requested an RPR and vaginal swab NAAT for gonorrhea and chlamydia. We counseled Sabrina about safer sex and referred her to our mental health department for substance dependence counseling. A return visit was scheduled for four weeks. Her RPR was positive with 1:1 dilution, the reflexed FTA-ABS was reactive, and the NAAT was negative.

At the week 4 visit, Sabrina said she took all her PEP doses and her nausea had subsided after a couple of days and she had no symptoms. Sabrina was able to get her records from her obstetrician, which indicated she was treated for syphilis. The RPR titers were 1:256 at the time of treatment; down to 1:2 at the last follow up almost 18 months later. Her current male partner had a negative RPR, his HIV VL was less than 20 copies/ml and he was getting ready to get his HCV treated.

We explained the reasons she was a candidate for PrEP; Sabrina agreed and the CMP, HCV VL, and HIV antibody/antigen tests were repeated. A follow up appointment was scheduled for 12 weeks if all tests were normal. The HIV test was negative, she had mild increase in her AST and ALT with an HCV VL of 4,200,000 IU/ml. Sabrina agreed to repeat blood tests prior to her next PrEP visit and decided on HCV management at that time.

Discussion:

Of the estimated 1.1 million people with HIV in the US, it is believed that close to 400,000 do not have an undetectable VL because they are not aware of their infection, they are not taking ART, taking ART less often than recommended, or not taking the right treatment.[4] These individuals are transmitting HIV in the community at a rate of 40,000 new infection every year. Until all people with HIV have an undetectable VL, or a preventive HIV vaccine is available, the best tools to stop the spread of the epidemic are PEP and PrEP.

PEP should be offered to any person who is evaluated within 72 hours after a potential exposure to HIV.[5] The earlier PEP is started, the more likely it is to abort HIV infection, thus it should be given before the results of HIV testing of the individual or the source are available. PEP can later be discontinued if the patient is found to have HIV infection or the source is confirmed as HIV negative.

All persons offered PEP should be prescribed a 28-day course of a 3-drug ART regimen. The preferred regimen for otherwise healthy adults and adolescents is tenofovir disoproxil fumarate (TDF) (300 mg) with emtricitabine (FTC) (200 mg) once daily plus raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily. Alternative regimen could be TDF (300 mg) with (FTC) (200 mg) once daily plus darunavir (DRV) (800 mg) and ritonavir (RTV) (100 mg) once daily.

All persons who report behaviors or situations that place them at risk for recurring HIV exposure (e.g., IDU, or receptive anal intercourse without condoms) or who report receipt of more than one course of PEP in the past year should be provided with risk-reduction counseling and intervention services, including consideration of PrEP. Daily oral PrEP with the fixed-dose combination of TDF 300 mg and FTC 200 mg is recommended as one prevention option for sexually active adults and those who inject drugs and are at substantial risk of HIV acquisition.[6]

This regimen has proven efficacy and safety through multiple clinical trials. Its efficacy is dependent on adherence to therapy and the prevalence of resistant virus in the community to TDF and or FTC is rare.[7] Acute and chronic HIV infection must be excluded before starting therapy. The most common side effect is nausea and the most serious side effect is renal toxicity. HIV infection along with other sexually transmitted diseases should be assessed every 3 months while patients are taking PrEP. Renal function should be assessed at baseline and monitored at least every 6 months; TDF should be stopped as soon as any deterioration of renal function is detected. ❖

* The patients in these case studies are composites representative of patients who may need PEP or PrEP; the names used in this article are pseudonyms and do not represent any particular patient.

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HIV and Nutrition: Is the Mediterranean Diet Good for People with HIV?

Josephine DiLena, RDN
Nutritionist, François-Xavier Bagnoud Center, Rutgers School of Nursing

Introduction

With the advent of the Antiretroviral Therapy (ART) era, HIV infection is now a treatable chronic condition, there are fewer AIDS-related deaths, and the lifespan of people with HIV is similar to the population without HIV infection.[1] Along with these beneficial effects of ART, there has been a higher prevalence of co-morbidities such as cardiovascular disease (CVD), metabolic syndrome, and obesity among people with HIV. These co-morbidities may be a complication of ART, linked to HIV infection, or the result of a diet high in saturated fats and refined sugars.[1,2] Adoption of the Mediterranean diet may be one way to reduce the prevalence of these co-morbidities among the HIV population.[2]

Benefits of the Mediterranean Diet

Studies show a lower incidence of CVD, reduced oxidative stress and inflammation, and improved insulin sensitivity among the general population with adherence to the Mediterranean diet.[3] This begs the question: because current dietary recommendations are the same for people with HIV as the non-HIV population, is the Mediterranean diet as good for people with HIV as it is for the general public?[4] Only a few recent studies have examined this question.[1-4] These studies found a lower incidence of cardiovascular events and lower insulin resistance in the HIV population when participants consistently adhered to the Mediterranean diet.[3,4] Although additional studies are needed, based on these findings, some researchers recommend People with HIV follow a Mediterranean diet.[2,3,4]

In 2019, the US News and World Report voted the Mediterranean diet the best and easiest diet to follow.[5] The diet, traditionally followed in countries of the Mediterranean, can be tailored to accommodate anyone's budget. The Mediterranean diet is characterized by an increased intake of fruits, vegetables, nuts, beans, seeds, and whole grains. Low fat dairy and fish is recommended; red meats and processed meats are limited. Healthy fats, particularly extra virgin olive oil and avocados, are recommended.[4]

Components of the Mediterranean Diet

Clinicians can help patients follow the Mediterranean diet by suggesting the following foods.

Nuts and Seeds: Walnuts, almonds, sunflower seeds, and hemp seeds can be added to yogurt, oatmeal, and salads. Peanuts, a lower cost choice, have higher protein content compared to all other nuts (7.9gm per ounce).

Fruits: Encourage patients to eat four servings of fresh or dried fruits daily by including a fruit with each meal and as a snack.

Vegetables: Five servings a day of vegetables (1 serving equals 1 cup raw or ½ cup cooked) are recommended. This includes salads and vegetable-based soups or the addition of vegetables to pasta and rice dishes.

Whole Grains: Whole grains contain fiber, protein, and nutrients. Traditional Mediterranean grains include farro, barley, buckwheat, couscous, bulgur, and rice. Tell patients that they can prepare a grain dish ahead, and keep it in the refrigerator until ready to use as a side dish or addition to a salad.

Dairy: Suggest Greek or plain yogurt, feta cheese, and small amounts of a flavorful cheese such as parmesan.

Seafood: Recommend that patients eat fish at least twice a week, especially fish rich in omega-3 fatty acids such as salmon, tuna, sardines, and herring. Patients may want to limit the intake of albacore tuna due to its higher mercury content and choose chunk light tuna instead.

Healthy Fats: These include extra virgin olive oil, avocado, and nut butters such as peanut butter. Small amounts of olive oil may be used for sautéing and as a salad dressing; avocado slices can be added to sandwiches. Nut butter can be used as a spread on toast.

Meats: Tell patients to avoid processed meats such as cold cuts, hot dogs, and sausages. Suggest that patients use meat as a side dish or garnish and limit the portion to 3 ounces as a main entrée. As an alternative, suggest a plant-based protein such as beans, nuts, or quinoa for a meatless meal.[6]

For recipes and additional information on the Mediterranean diet, visit *https://oldwayspt.org*

Conclusion

Several studies have demonstrated that the Mediterranean diet is beneficial for People with HIV.[1-4] Adherence to the Mediterranean diet is associated with lower incidences of CVD, metabolic syndrome, and obesity among People with HIV.[1,2,4] Recommendations for incorporating the Mediterranean diet into a healthy lifestyle include eating more fruits, vegetables, and grains while limiting the intake of red meats. ❖

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Jackie: There is Still Life

Michelle M. Thompson, Program Manager, François-Xavier Bagnoud Center, School of Nursing, Rutgers, The State University of New Jersey,
Jacqueline Dover, Program Development Specialist, François-Xavier Bagnoud Center, School of Nursing, Rutgers, The State University of New Jersey

Jackie is a 64-year old African American female with 3 adult children, who was diagnosed with HIV in 1996. She struggled with drug use but has been clean for over 18 years. Jackie discusses her history and relationship with her children. Throughout the years and during some rough times in her life, she has had the unwavering support system of her family members.

Jackie started to work and build a work history after she went into recovery. Although clean, she found life very stressful and overwhelming and as a result, suffered a mental health crisis.

Today Jackie is very happily employed at a Community Based Organization (CBO). She has spoken on HIV and Women, shared her personal many times and remains an HIV advocate.

How have HIV medications progressed over the last 20 years?

Years ago, I used to take a lot of pills and some of them were very large. Today, I'm taking one pill a day and it makes life less stressful.

Have you received the recommended screenings for older patients?

Yes, but I still don't know if some of my conditions are from HIV and the medications or if the ailments are natural to aging.

In addition to the one pill a day ARV, Jackie is being treated and/or monitored for a heart condition, arthritis, hypertension, diabetes and chronic back pain. She takes 10 different medications per day.

How do you deal with the chronic pain?

Over the counter pain medicine and resting as much as I can.

What do you think of the state's expanded Medical Marijuana Program which includes some chronic pain conditions?

I am all for it if it will help someone. Some people can't afford to add more pills and neither can their liver. I know I can't keep taking these over the counter pain relievers myself.

Have you ever participated in a clinical trial?

No. There was never one that fit me. I was on medication and it worked. Also, no one ever asked me. I did ask a a couple of times during a doctor visit, but they told me there was nothing at the time.

Recently there has been studies related to the Mediterranean Diet which may have health benefits for people with HIV and co-conditions including cardio vascular disease. Are you familiar with this?

No, I never heard of it.

The Mediterranean Diet includes eating more vegetables, fruit and grains while limiting red meats.

I had a nutritionist who worked with me on healthy eating. We discussed heart healthy food and what foods to avoid for high blood pressure. Fresh vegetables are not cheap. The price of a head of lettuce can rise from one week to the next. Healthy eating is not always affordable eating. You have to do the best you can with what you have. I know I probably could not afford to keep up with that diet.

What are your thoughts on the stigma and ageism surrounding sexual health?

(Jackie smiles, then laughs) I'm hopeful. I want intimacy and a sexual relationship. I also enjoy companionship. I'm very honest and upfront about my status.

Many years ago, I met a gentleman in the medical field who was also HIV positive. I started having a serious relationship with him and unprotected sex with him because I thought that was ok because we both had been diagnosed. As I became more educated, I was upset to find out that having unprotected sex with another HIV positive person was just as dangerous and could lead to other health complications or re-infection. I didn't know that at the time. I ended the relationship, because I felt this was something he should have known but didn't discuss with me. It is important and could possibly be life-saving that we educate ourselves on this illness.

What is your message to providers?

Getting back to basics. I like my doctors, but I would like for all doctors to try to know more about a person they are treating instead of just prescribing medication. Look a person in the eye. Listen! I understand that you may only have 20 minutes, but please listen to what I'm saying. I know my body. Do not become complacent in long-term doctor and patient relationships or ignore my concerns. There may be something going on. Don't

look at older adults and assume they are not in a sexual relationship. Ask questions, take a sexual history. Seniors are still part of a newly infected population.

What do you want people to know about you?

I want people to look at me and see there is still life. Go for what you want. Let people know how you feel and don't let them assume anything about you. I love helping people. I want to lead by example. When I see someone struggling, it brings out the humility in me. I know that joining together in the fight against HIV/AIDS, we can bring this epidemic to an end.

"Each one, teach one, will reach one"

RED

The love of one's heart preparing
to get married…
Red is the hot sun on s summer day…
The anger of a bull during a fight…
A dozen roses given to your
Mom on Mother's Day…
A juicy red apple on a spring day…

Red is like a fire truck's siren
rushing to an emergency…
A cherry tree in the beginning of Spring…
The blush of one's cheek of
being embarrassed…

Red is the stripes of pride on
the American flag…
The soreness of your feet
after running in gym…
Red is the alert for you to stop…
Red is the glowing nose of
Rudolph on Christmas…

Red is the color of the ribbon we wear to remind us to continue to fight for the cause

RED is RED

Christina, Daughter

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Rutgers, The State University of New Jersey
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FXB Center Executive Director
Andrea Norberg, DNP, MS, RN

Editor of NJ HIVLinks
Darcel M. Reyes, PhD, ANP-BC

FXB Center NJ HIVLinks Editorial Team
Michelle Thompson
Priya Sandanapitchai, MA

FXB Center Graphic Designer
Karen A. Forgash, BA

NJ HIVLinks Medical Advisor
Shobha Swaminathan, MD

FXB Center
65 Bergen Street, Stanley S. Bergen Building,
8th Floor, Newark, NJ 07101-1709
Tel: (973) 972-5644 ▪ Fax: (973) 972-0397
FXBCenter@sn.rutgers.edu

Division of HIV, STD and TV Services
Christopher Menschner
Assistant Commissioner

New Jersey HIV Links Planning Committee

Division of HIV, STD, and TB Services

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- Darcel M. Reyes, PhD, ANP-BC
- Michelle Thompson, Program Manager

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US National Institutes of Health: a registry and results database of publicly and privately supported clinical studies conducted around the world. http://clinicaltrials.gov

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