JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eHIV Review

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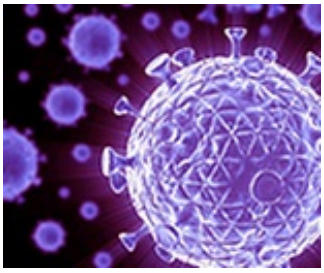

New and Emerging ART

In this Issue...

Although antiviral treatment has become very effective, many challenges remain. HIV positive individuals continue to have higher rates of noninfectious comorbidities such as chronic kidney disease. To mitigate the excess risk, it is essential that clinicians better understand the risk factors for CKD in HIV positive patients. In addition, the HIV treatment landscape continues to evolve. Currently the standard of care is a two- nucleoside reverse transcriptase inhibitor backbone with a third agent, typically an integrase strand transfer inhibitor. Novel antiretroviral agents, new long acting formulations, and novel therapy combinations are emerging that have the potential to improve the safety and acceptability of ART.

In this issue, we review …

- a clinical tool to estimate the risk of CKD in patients with HIV
- studies elucidating the risks and benefits of switching patients from their current tenofovir disoproxil fumarate (TDF)-containing regimens to similar regimens containing tenofovir alafenamide (TAF)
- the effects of regimen simplification in treatment-experienced patients
- experimental maintenance treatment with a long acting intramuscular ART regimen of cabotegravir and rilpivirine

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LEARNING OBJECTIVES

- Discuss the risks, benefits and outcomes of switching from an antiretroviral regimen that includes tenofovir disoproxil fumarate (TDF) to a regimen that includes tenofovir alafenamide (TAF).
- Describe the risk factors for chronic kidney disease in patients with HIV.
- Identify selected new therapies and combinations of therapies for treating HIV in individuals with suppressed viral load.

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GUEST AUTHOR OF THE MONTH

Commentary & Reviews

Guest Faculty Disclosure

Dr. Simmons has disclosed that she has received honoraria from the American Board of Internal Medicine, BMJ, and DynaMed and her immediate family has stock options with Eli Lilly and Company.

Unlabeled/Unapproved uses

Dr. Simmons has indicated that there will be no references to the unlabeled/unapproved uses of

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any drugs or products.

IN THIS ISSUE

COMMENTARY

With the advent of well tolerated and potent medications, HIV infection has become a treatable, chronic condition. Nonetheless, individuals with HIV have higher rates of comorbid conditions, including kidney disease, than the general population.[1,2]

Using the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, Mocroft and colleagues (reviewed in this issue) developed a clinical risk tool to estimate the risk of chronic kidney disease (CKD) over five years in patients with HIV. In addition to traditional risk factors, HIV risk exposure, nadir CD4 count, hepatitis C coinfection, treatment with TDF, atazanavir/ritonavir, atazanavir, lopinavir/ritonavir, and other boosted protease inhibitors were also associated with increased incidence of CKD in HIV positive patients. This study could not comment on the known association of race with the progression of renal disease, as race was unknown in a significant proportion of individuals studied.[3,4] The database also contained no information about proteinuria.

Individuals with higher risk of CKD may benefit from closer monitoring.[5] Kidney function also has implications for choice of ART. Current guidelines recommend avoiding TDF[5,6] in patients with CKD and considering avoiding atazanavir,[5] as it has been associated with CKD in some observational studies.

TDF is a widely used, generally well-tolerated, first-line backbone nucleoside reverse transcriptase inhibitor (NRTI). However, it has been associated with serious (though uncommon) renal complications, as well as reductions in bone mineral density. TDF is a prodrug of the active form of tenofovir. Tenofovir alafenamide (TAF) is a new prodrug of tenofovir that has an approximately 90% lower plasma concentration.[7,8] The lower plasma level is thought to lead to fewer renal and bone complications than TDF. ART is lifelong, so limiting even uncommon events is beneficial.

TAF's safety and efficacy have been compared to TDF in both treatment-naïve and

treatment-experienced, virologically suppressed patients. Mills and colleagues (reviewed in this issue) evaluated switching from regimens with a TDF-containing backbone to a single tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in an open-label, noninferiority trial. Gallant and colleagues (reviewed herein) investigated switching TDF to TAF in a combination tablet with emtricitabine while continuing the third agent.

In both studies, participants taking TAF-containing regimens achieved high virological efficacy similar to that of TDF (97% vs 93% in Mills et al and 93% vs 95% in Gallant et al). Compared to baseline, individuals on TAF had significantly higher bone mineral density, higher estimated glomerular filtration rate (eGFR), and lower levels of proteinuria. No cases of proximal tubulopathy occurred in either study.

The results in Mills et al and Gallant et al mirror those in head-to-head comparisons of TDF and TAF in treatment naïve patients.[9-11] Taken together, these studies indicate that TAF has similar efficacy to tenofovir disoproxil fumarate and an improved safety profile, with better renal and bone parameters. Clinical endpoints such as osteoporotic fractures and CKD are rare events, so longitudinal observational studies will be important to evaluate these outcomes.

With less bone and renal toxicity, the 2016 International Antiviral Society–USA HIV treatment guidelines now favor TAF over TDF for initial treatment in patients with HIV.[12] The 2017 guidelines from the Department of Health and Human Services lists both TDF and TAF as first-line elements of combination ART.[5]

Treatment experienced patients with drug resistance are often treated with complex regimens containing several tablets taken multiple times per day. Huhn et al (reviewed in this issue) evaluated simplifying HIV treatment in well-controlled patients with multiclass resistance without darunavir or integrase mutations. Participants were switched to a fixed dose combination tablet with elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine plus darunavir (two pills, once daily regimen). During follow-up, the simplification group had the same or better rates of virological suppression and significantly improved patient satisfaction. Lower pill burden and lower regimen complexity was also associated with fewer missed doses; given that HIV requires lifelong therapy, increased adherence is a key factor to successful treatment.

Another treatment strategy under investigation is long acting medications. Cabotegravir is a novel integrase inhibitor and rilpivirine is a nonnucleotide reverse transcriptase inhibitor. Margolis and colleagues (reviewed) conducted a trial of intramuscular injections of long acting cabotegravir and rilpivirine every four or eight weeks for HIV maintenance therapy compared to continuing oral cabotegravir/abacavir/lamivudine. The long-acting regimen at both dosing frequencies had similar rates of virological success at 48 weeks (95 % for q8 week regimen, 94% for q4 week regimen, 91% for oral regimen) and 96 weeks (94% for q8 week regimen, 84% for q4 week regimen, 84% for oral regimen) and was well tolerated and associated with high levels of satisfaction.

In summary: ART has had a dramatic impact on life expectancy for HIV, although excess risk for comorbid conditions like kidney disease remains. It is crucial to understand risk factors for CKD in HIV to optimize long-term renal function. Available treatments for HIV are continuing to evolve. While current antiretroviral therapy is highly efficacious and generally well tolerated, newer agents such as tenofovir alafenamide have improved safety profiles. Practitioners should evaluate if their patients on TDF are eligible to substitute TAF. Novel treatments such as long-acting formulations and various dual therapy regimens[13,14] are under investigation and may become part of the treatment landscape soon. The FDA has just approved the first dual combination tablet (dolutegravir and rilpivirine) for treating HIV.[15] Providing continuing provider education and exploring patient preferences are critical to selecting optimal therapy for HIV.

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TAF vs TDF in Patients with Well-Controlled HIV

Mills A, Arribas JR, Andrade-Villanueva J, et al; ;GS-US-292-0109 team. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis.* 2016;16(1):43-52.

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Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV.* 2016;3(4):e158-165.

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Tenofovir disoproxil fumarate (TDF) is a widely used, first-line nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of HIV. Tenofovir alafenamide (TAF) is the latest tenofovir prodrug and has a significantly lower plasma levels than TDF.[1,2] These two recent studies evaluated switching from a TDF containing regimen to a TAF- containing regimen.

In a multicenter, open-label, noninferiority trial, Mills and colleagues randomized patients with well-controlled HIV to switch to a single tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (TAF group) or to continue their current regimen (TDF group). The 1443 participants were recruited from Gilead trials of TDF-containing regimens. Participants had an estimated glomerular filtration rate (eGFR) of more than 50 mL/min and HIV viral loads of less than 50 copies/mL, and had been on their current ART for at least 96 weeks prior to randomization. The four regimens containing TDF were elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; efavirenz/emtricitabine/tenofovir disoproxil fumarate; cobicistat-boosted atazanavir plus emtricitabine/tenofovir disoproxil fumarate; or ritonavir-boosted atazanavir plus emtricitabine/tenofovir disoproxil fumarate. The primary outcome was rate of virological control with a HIV RNA of less than 50 copies/mL at 48 weeks.

Among the 959 participants who were switched to elvitegravir, cobisistat, emtricitabine, and tenofovir alafenamide, 97% achieved a viral load of less than 50 copies/mL at week 48 compared to 93% in the TDF group (adjusted percentage difference was 4.1%; 95% CI 1.6–6.7). These results indicate the TAF regimen was noninferior to the TDF-containing regimen. Both groups had virological failure rates of 1%, with ten and six patients from the TAF and TDF groups failing their regimens, respectively. One patient in the TAF group developed a resistance mutation (reverse transcriptase mutation M184I/M) related to the regimen.

The mean bone density of the spine and hip increased from baseline in the TAF group, while bone density decreased or stayed the same in the TDF group ($P < .0001$). In participants on baseline regimens that contained a booster, eGFR in the TAF group increased by an average of 1.2 mL/min, while in the TDF group the eGFR decreased by an average of -3.7 mL/min ($P < .0001$). Proteinuria was also significantly less in the TAF group ($P < .001$). Lipid levels increased significantly in the TAF group ($P < .001$) compared to the TDF group with similar proportion of patient starting lipid-lowering therapy in each group. The TAF regimen was well tolerated. No fragility fractures or cases of proximal tubulopathy were reported.

In a second open-label switch study, Gallant and colleagues evaluated substituting TAF for TDF while maintaining the rest of the HIV treatment regimen in patients who were doing well on their current ART.

In this multicenter, double blind, noninferiority trial, 668 participants were randomized to continue TDF or switch to TAF while remaining on the remainder of their regimen. The participants had a HIV RNA of less than 50 copies/mL for at least six months prior to entering the trial and had an eGFR of greater than 50 mL/min.

At 48 weeks, the TAF group had virological success rates similar to those of the TDF group, with 94% and 93% achieving HIV RNA less than 50 copies/mL (respectively adjusted

difference in percentage 1.3%; 95% CI -2.5-5.1). Five patients in the TAF group and one participant in the TDF group had virological failure. Among the three individuals with virological failure (viral load ≥ 50 copies/mL) who underwent resistance testing, one participant developed an M184V reverse transcriptase mutation in the TAF group; however, this was thought to be due to nonadherence.

Regarding bone health, bone mineral density increased from baseline in the TAF switch group and decreased or remained constant in the TDF group ($P < .001$ for both spine and hip bone mineral density). The participants in the TAF group had a small but statistically significant improvement in GFR from baseline compared to the TDF group, (8.4 mL/min minute vs 2.8 mL/min, $P < .0001$). The TAF group had a decrease in the amount proteinuria compared to TDF group, which had an increase in the amount of proteinuria ($P < .0001$ for change in proteinuria and albuminuria).

Both drugs were generally well tolerated. The rates of adverse events were similar, with no serious drug related adverse events in the TAF group and one serious drug related adverse event in the TDF group. No cases of proximal tubulopathy occurred during the study, and one patient with other risk factors for kidney disease discontinued TDF because of an elevated serum creatinine. No fragility fractures occurred. Total cholesterol in the TAF group increased from baseline compared to no change in the TDF group, and both groups had similar rates of initiating lipid-lowering medication (4%).

Longer-term follow up to 96 weeks also showed that the TAF regimen was noninferior to the TDF regimen (88.6% vs 89.1% achieving virological suppression, adjusted difference -0.5%; 95% CI -5.3 - 4.4%).[3]

Taken together, these studies highlight that TAF and TDF are similarly efficacious and switching does not compromise the high level of virological control achieved with TDF. Like the studies in ART-naïve patients,[4-6] TAF was well tolerated and associated with improvements in renal and bone biomarkers, which may lead to less tenofovir-related bone and kidney toxicity over time.

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New Calculator for CKD Risk in HIV

Mocroft A, Lundgren JD, Ross M, et al; Royal Free Hospital Clinic Cohort; INSIGHT study group; SMART study group; ESPRIT study group. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. *PLoS Med.* 2015;12(3):e1001809

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People living with HIV have increased risk of developing chronic kidney disease (CKD). Using a large, observational, longitudinal cohort study of HIV-positive persons, Mocroft and colleagues developed a risk calculator for the development of CKD in patients with HIV.

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is a prospective study of HIV positive people in Europe, the United States, and Australia. Among the over 49,000 individuals followed in the D:A:D study, the risk calculator was developed by analyzing 17,954 people with more than three GFR measurements, normal renal function at enrollment (eGFR > 60 mL/min), and no history of tenofovir disoproxil fumarate, atazanavir, or any boosted protease inhibitor treatment prior to enrollment. Seventy-three percent of the people studied were men; 46% identified as white, 7% as black, 2% as other, with race unknown for 44%. Chronic kidney disease was defined as eGFR < 60 mL/min confirmed on two measurements more than three months apart. During 103,185 person-years of follow-up (median follow-up 6.1 years per person), 641 (3.6%) developed chronic kidney disease.

The following characteristics (non-HIV and HIV-related) were found to be significant predictors of developing CKD: older age, female gender, hepatitis C coinfection, prior cardiovascular disease, lower eGFR at baseline, hypertension, diabetes, intravenous drug use compared to other HIV exposure groups, and lower nadir CD4 count. Using the risk sore model, patients were determined to have low (risk score < 0), medium (risk score 0-4) and high risk (risk score ≥ 5) of developing CKD. These risk factors are consistent with prior studies of CKD in HIV.[1-3] The probability of developing CKD over the next five years was 0.18%, 1.5%, and 14.68% in the low, medium, and high risk groups, respectively. The chance of developing CKD over the next five years went up based on risk group, with 1:393 in the low risk group and 1:47 and 1:6 in the high risk group, respectively. The risk score was externally validated in two other independent cohorts.

The investigators then analyzed the effect of starting different antiretroviral agents in the different risk groups. Starting tenofovir disoproxil fumarate, atazanavir/ritonavir, or any other boosted protease inhibitor aside from lopinavir/ritonavir was equivalent to increasing the risk score by two points and starting unboosted atazanvir or lopinavir/ritonavir was equivalent to increasing the risk score by 1. The number needed to harm or the number needed to be treated with the antiretroviral medication for one additional person to get CKD over five years varied by agent and risk group. For example, the number needed to harm was 739, 88, and 9 when starting tenofovir disoproxil fumarate, atazanavir/ritonavir, or another boosted PI (except lopinavir/ritonavir) in the low, medium, and high-risk groups, respectively.

Mocroft and colleagues have designed and validated a risk score for developing CKD over five years in patients with HIV. This study characterizes the impact on future kidney function in individuals starting potentially nephrotoxic antiretroviral agents. A separate analysis of individuals in the D:A:D cohort with normal baseline renal function (eGFR > 90 mL/min) showed a cumulative risk of risk of CKD with tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir.[4] The risk score is easy to use by clinicians and can help identify patients who are at higher risk of developing CKD who may warrant closer monitoring of renal function.[1] The tool is available at https://www.chip.dk/Tools-Standards/Clinical-risk-scores (tick the box labeled Full Chronic Kidney Disease Risk Score in Kidney column on the right and then click “Build Form”)

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Simplifying ART in Treatment-Experienced People

Huhn GD, Tebas P, Gallant J, et al. A Randomized, Open-Label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Plus Darunavir in Treatment-Experienced HIV-1-Infected Adults. *J Acquir Immune Defic Syndr.* 2017;74(2):193-200

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Treatment of HIV-positive people with multi-class resistance often includes multiple tablets and multiple doses per day, leading to lower quality of life and potential adherence issues. Huhn and colleagues conducted an open-label, multicenter, randomized, noninferiority trial of switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir (E/C/F/TAF plus DRV) vs continuing current ART in well-controlled, treatment-experienced people with HIV.

The participants were virologically suppressed (HIV RNA < 50 copies/mL) for at least four months on a darunavir-containing regimen and had previously failed at least two regimens with resistance to two or more classes of antiretrovirals. On prior genotypes, K65R mutation and up to three thymidine-analog mutations were permitted; integrase strand transfer inhibitor resistance, Q151M mutation, T69 insertion mutation, or any darunavir-associated mutations were not permitted.

Eighty-nine participants were randomized E/C/F/TAF plus DRV and 46 continued their current regimen. The study population included 75% men; half of the participants were white and 45% were black. At baseline, the median number of tablets per day was five, and the most common mutations were M184V/I and K103N/S. A pharmacokinetic study confirmed adequate boosting of both elvitegravir and darunavir by cobicistat.

At 24 weeks, 96.6% had a viral load < 50 copies/mL in the E/C/F/TAF plus DRV group vs 91.3% in the continuation group (difference 5.3%; 95% CI: -3.4% to 17.4%, $P = .23$); therefore, E/C/F/TAF plus DRV was noninferior to continuing current ART. At week 48, E/C/F/TAF plus DRV again met predetermined criteria for noninferiority and for superiority with 94% and 76% (difference 18.3%; 95.001% CI: 3.5% to 33.0%, $P = .004$) achieving virological success in the switch group vs continuation group. In the switch group, no individual developed confirmed viral rebound or had to discontinue therapy because of adverse events.

The change in eGFR during the study was similar in both groups; however, the switch group had significant decline in the level of proteinuria (median percentage change of -27 vs 5, $P = .005$) compared to the continuation group. The switch group had significantly higher improvements in mean patient satisfaction ($P < .001$) and fewer missed medication doses.

This study demonstrated that simplification of complex regimens to a newer fixed dose combination tablet plus a protease inhibitor is safe and effective in certain individuals who are well controlled on salvage HIV regimens. The participants also had improvements in proteinuria and quality of life indicators, which could lead to better long-term clinical outcomes. This study highlights both the efficacy of current antiretroviral therapy as well as the potential to reduce pill burden and improve adherence and satisfaction, even in treatment-experienced people.

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Cabotegravir and Rilpivirine: Two Novel, Long-Acting Antiretrovirals

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.

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In this multicenter, open-label, noninferiority trial, Margolis and colleagues investigated the efficacy and safety of maintenance HIV treatment with two novel, long- acting antiretrovirals, cabotegravir and rilpivirine. Cabotegravir is an integrase strand transfer inhibitor and is an analog of dolutegravir; rilpivirine is an NNRTI.

Treatment-naïve adults with CD4 counts greater than 200 cells/mm^3 were treated with oral abacavir/lamivudine and cabotegravir for 20 weeks; oral rilpivirine was then added at week 16 prior to randomization. If the induction oral regimen was tolerated and virological control was achieved (HIV RNA < 50 copies/mL), participants were randomized to have intramuscular injections every four or eight weeks of long- acting cabotegravir and long acting rilpivirine, or to continue oral cabotegravir and abacavir/lamivudine daily.

The study population consisted of 92% men, 8% women (79% white, 15% black, 6% other), with a mean age of 39. The average baseline viral load was 4.39 log copies/mL and 18% had HIV RNA levels exceeding 100,000 copies per mL. Two hundred thirty participants were randomized to intramuscular (IM) cabotegravir/rilpivirine every four weeks or every eight weeks, and 56 were randomized to the cabotegravir and abacavir/lamivudine group. Fourteen withdrew (eight due to adverse events, none to lack of efficacy) from the long acting IM ART dosed every four weeks; five withdrew (one adverse event, one lack of efficacy) from the long-acting IM ART dosed every eight weeks; and nine withdrew (one adverse event, one lack of efficacy) from the oral ART group.

The proportion of patients with a HIV RNA < 50 copies/mL at 32 weeks (primary endpoint) was 94% in the four-week group, 95% in the eight-week group, and 91% in the oral treatment group. There was no significant difference in virological control between the long acting regimens and the oral regimen. At 96 weeks of follow up, 87% in the four-week group, 94% in the eight-week group, and 84% of the oral treatment group had sustained virological control. Two participants in the eight-week group and one participant in the oral treatment group met criteria for virological failure. HIV resistance mutations developed in one person in the oral treatment group (integrase mutation R269R/G without decreased susceptibility to cabotegravir) and in one person in the eight-week group (reverse transcriptase mutations K103N, E138G, and K238T and integrase mutations Q148R).

Injection site reactions were reported in almost all people in the four-week group (97%) and eight-week group (96%), but the majority of reactions were mild. No serious adverse events related to the drugs were reported. Possible drug related liver injury occurred in two participants being treated with oral therapy. All three treatment groups reported a high degree of satisfaction with their treatment regimens. At 96 weeks, more than 99% of participants in both long-acting regimen groups and 78% in the oral therapy group indicated they would be highly satisfied to continue their current regimen.

This intriguing phase 2b study raises the possibility of a long-acting dual medication regimen for HIV maintenance therapy. This trial was conducted in treatment-naïve, predominantly male people with CD4 counts above 200. It remains to be seen how this combination performs in other populations and when switching from other regimens. Injectable cabotegravir and rilpivirine could offer an alternative to indefinite daily oral combination regimens that have been the standard of care to date for HIV. These formulations are not yet FDA approved, and additional treatment studies are ongoing, including a phase 3 trial of long-acting cabotegravir and long-acting rilpivirine for treatment-naïve subjects (FLAIR NCT02938520) and a phase 3 trial of switching to long-acting cabotegravir and long-acting rilpivirine from a variety of standard 3 drug regimens (ATLAS

NCT02951052).

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KEY TAKEAWAYS

- Risk factors for CKD in HIV include the typical risk factors for CKD, as well as HIV risk exposure, nadir CD4 count, hepatitis C coinfection, and treatment with potentially nephrotoxic ART.
- Tenofovir alafenamide (TAF) is as effective as tenofovir disoproxil fumarate (TDF) and has a better safety profile.
- Cabotegravir and rilpivirine are being studied as long-acting injectable maintenance ART.

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