ClinicSearch

International Journal of Biomed Research

Rehan Haider *

Open Access

Review Article

Management of HBV/HIV Co-Infection

Rehan Haider*

Riggs pharmaceutical, Department of Pharmacy, University of Karachi, Pakistan.

***Corresponding Author:** Rehan Haider, Riggs pharmaceutical, Department of Pharmacy, University of Karachi, Pakistan.

Received date: March 15, 2023; Accepted date: March 28, 2023; Published date: April 04, 2023

Citation: Haider R., (2023), Management of HBV/HIV Co-Infection, *International Journal of Biomed Research, 2(2):* **DOI:**10.31579/2834-8087/016

Abstract

The prevalence and transmission routes of HBV co-infection in the HIV+ population vary substantially by geographic region. In the United States and Europe, the majority of HIV-positive gay men have evidence of past HBV infection, and 5–10% show persistence of HBs antigen, with or without replicative hepatitis B as defined by the presence of HBV DNA. Overall, rates of HBV/HIV co-infection are slightly lower among intravenous drug users compared to gay men and much lower among people infected through heterosexual contact. In endemic regions of Africa and Asia, the majority of HBV infections are transmitted vertically at birth or before the age of 5 through close contact within households, medical procedures, and traditional scarification. The prevalence among youth in most Asian countries has substantially decreased since the introduction of vaccination on a nationwide scale. In Europe, vaccination of children and members of risk groups is promoted and reimbursed by health care systems in most countries. The natural history of hepatitis B is altered by simultaneous infection with HIV. Immune control of HBV is negatively affected, leading to a reduction in HBs-antigen seroconversion. If HBV persists, the HBV DNA levels are generally higher in HIV-positive patients not on antiretroviral therapy. In addition, with the progression of cellular immune deficiency, reactivation of HBV replication despite previous HBs-antigen seroconversion may occur. However, after immune recovery due to antiretroviral therapy, He-antigen and HBs-antigen seroconversion occurs in a higher proportion of patients compared to HBV mono infected patients treated for chronic hepatitis B. In untreated HIV infection, faster progression to liver cirrhosis is reported for HBV/HIV-co-infected patients Moreover, hepatocellular carcinoma may develop at an earlier age and is more aggressive in this population.

Keywords: liver/hepatitis; antiretroviral therapy; antiviral therapy; pathogenesis; reverse transcriptase inhibitors

Introduction

Being HBV-coinfected results in increased mortality for HIV-positive individuals, even after the introduction of effective antiretroviral therapy (ART), as demonstrated by an analysis of the Euro SIDA Study, which shows a 3.6-fold higher risk of liver-related deaths among HBsAg-positive patients compared to HBsAg negative individuals (Konopnicki 2005, Nikolopoulos 2009) [16] (Figure 1). In the Multicenter AIDS Cohort Study (MACS), an 8-fold increased risk of liver-related mortality was seen among HBV/HIV co-infected compared to HIV-mono infected individuals, particularly among subjects with low nadir CD4+ cell counts. Even at present, despite the widespread use of tenofovir, HBV/HIV coinfection is still associated with increased morbidity (Crowell 2014) [18], and liver-related deaths in HBV/HIV-infected patients still do occur (Rosenthal 2014) [19].The beneficial impact of treatment of HBV in HBV/HIV coinfection was first demonstrated by data from a large cohort showing a reduction in mortality with lamivudine treatment compared to untreated patients (Puoti 2004, Brau 2007)This result is even more remarkable because lamivudine is the least effective HBV polymerase inhibitor due to the rapid development of drug resistance. In general, because of its limited long-term efficacy, lamivudine monotherapy cannot be considered an appropriate therapy for either mono HBV infection or HBV/HIV coinfection.

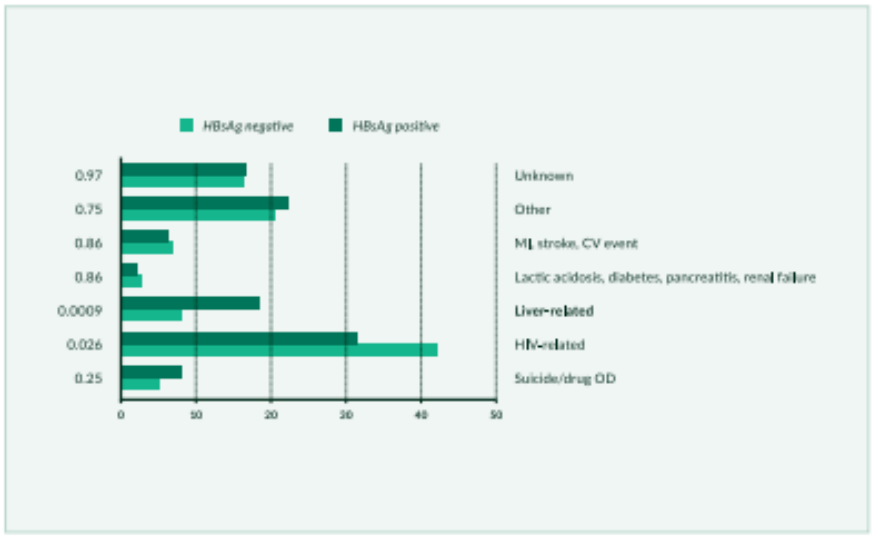

Figure 1: Association of HBV/HIV coinfection and mortality (Konopnicki 2005). More than one cause of death allowed per patient; p-values from chi-squared tests.

In addition, two large cohort studies (EuroSIDA and MACS) plus data from HBV mono-infection studies showing a reduction in morbidity and mortality established the need to treat chronic hepatitis B in HBV/HIV-co-infected patients.

Treatment of chronic hepatitis B in HBV/HIV-co-infected patients on antiretroviral therapy

In the well-known, beginning hepatitis B therapy depends on the diploma of liver fibrosis and the HBV DNA level. however, as the artwork is now encouraged for all HIV sufferers unbiased of CD4-be counted to reduce HIV-associated morbidity and mortality and to prevent HIV transmission, all HBV/HIV-co-infected patients are considered eligible for art with the aid of cutting-edge hints (e.g., every 2016). The previous complicated recommendations for a way to deal with continual hepatitis B in patients without artwork are obsolete. As antiretroviral capsules which can be additionally lively towards HBV can commonly be used, interferon-based total treatment of HBV is now not often indicated. statistics within the literature for HIV-co-infected patients on interferon therapy for HBV infection are restrained and no longer very encouraging. In addition, intensified treatment research combining pegylated interferon with adefovir or intensifying TDF therapy with pegylated interferon for 12 months confirmed no boom in HBV seroconversion quotes (Ingiliz 2008. In widespread, tenofovir is the usual care for HBV in HIV-co-infected patients, because of its strong HBV polymerase hobby and antiretroviral efficacy. Tenofovir has been a protracted-acting and effective therapy in the giant majority of dealt with HBV/HIV-co-infected patients (van Bömmel 2004, Mathews 2009, Martin-Carbonero 2011, Thibaut, its antiviral efficacy isn't impaired in HBV/HIV-coinfected as compared to HBV-mono infected sufferers. No conclusive pattern of resistance mutations has been recognized in research or cohorts (Snow-Lampart 2011). [28] These data are nonetheless legitimate at the cease of 2016. In idea, resistance might also arise in sufferers on lengthy-time period therapy, as with some other antivirals. For patients with HBV DNA <2000 IU/mL and no relevant liver fibrosis, no specific artwork routine is recommended. however, because of the favorable resistance profile, a routine along with tenofovir is the first preference. while selecting an HBV polymerase inhibitor, whole suppression of HBV DNA is critical to keep away from the development of HBV drug resistance. whilst HBV DNA is above 2000 IU/mL in HBV treatment naïve sufferers, a combination of tenofovir plus lamivudine/emtricitabine to treat each infection is commonly recommended. Even for sufferers who harbor lamivudine-, telbivudine- or adefovir-resistant HBV because of previous treatment plans this approach stands. the advice is to maintain lamivudine/ emtricitabine is primarily based on behind-schedule resistance to adefovir visible when doing so, however, the identical impact has no longer been in aggregate with tenofovir (Berg 2010, Patterson 2011)30. beginning art such as tenofovir ended in higher prices of HBe antigen loss and seroconversion as predicted from HBV-mono infected patients (Schmutz 2006, Piroth 2010, Kosi 2012). This may be due to an additional effect of immune reconstitution in HBV/HIV co-infected patients complicating the immunological control of HBV replication. For patients with advanced liver fibrosis or liver cirrhosis, a maximum active continuous HBV polymerase inhibitor therapy is important to avoid further fibrosis progression and hepatic decompensation and to reduce the risk of developing hepatocellular carcinoma. Tenofovir plus lamivudine/emtricitabine is the treatment of choice. If the results are not fully suppressive, adding entecavir should be considered. A reduction in the incidence of hepatocellular carcinoma has been shown for patients on HBV polymerase inhibitors compared to untreated patients, strengthening the anti-proliferative effects of suppressive antiviral therapy. Liver ultrasound is needed at least every six months, for early detection of hepatocellular carcinoma. In patients with advanced cirrhosis, esophagogastroscopy should be performed as screening for esophageal varies. For patients with hepatic decompensation and full treatment options for HBV and who have stable HIV infection, liver transplantation should be considered as post-transplant life expectancy seems to be the same as for HBV-mono infected patients (Coffin, 2007, Tateo. Patients with hepatocellular carcinoma may also be considered a liver transplant candidate, although according to preliminary observations from small cohorts, the outcome may be worse than for HBV-mono infected patients (Vibert, 2008). In prospective controlled studies, tenofovir was superior to adefovir for the treatment of HBe antigen-positive and HBe antigen-negative patients. The acquisition of adefovir resistance mutations and multiple lamivudine resistance mutations may impair the activity of tenofovir although even in these situations, tenofovir retains sufficient activity against HBV In lamivudine-resistant HBV, the antiviral efficacy of entecavir in HIV-co-infected patients is reduced, as it is in HBV mono-infection (Shermann 2008). Because of this and the property of tenofovir as a fully active antiretroviral, tenofovir-DF is the preferred choice in treatment-naïve HBV/HIV co-infected patients who will use ART. The use of entecavir, telbivudine, or adefovir as an add-on to tenofovir or other drugs in the case of not fully suppressive antiviral HBV therapy has not yet been studied in HBV/HIV coinfection. This decision should be made on a case-by-case basis. Based on the history of ART, combination HBV therapy of

tenofovir plus lamivudine/emtricitabine was expected to be superior to tenofovir monotherapy, in particular in patients with highly replicative HBV infection. However, this hypothesis has not as yet been supported by studies. Data are showing better viral suppression for entecavir and tenofovir-DF compared to entecavir monotherapy in highly replicative patients with HBV-mono infected, but no such study is available for comparison with tenofovir monotherapy. In the case of HIV resistance to tenofovir, it is usually important to continue using tenofovir for HBV activity when switching to other ART. Discontinuation of the HBV polymerase inhibitor without maintaining the antiviral pressure on HBV can lead to necro-inflammatory flares that can result in acute liver decompensation, particularly in patients with liver cirrhosis.In 2015, tenofovir alafenamide (TAF) was approved as antiretroviral therapy in Europe and the US. TAF is a new formulation of tenofovir with lower plasma exposure of the active drug tenofovir compared to tenofovir diproxovil fumarate (TDF). TAF has not shown superior antiviral activity against HIV or HBV compared to TDF but may offer advantages concerning long-term toxicities involving bone and kidney over TDF. TAF can substitute TDF as HBV therapy in HBV/HIV-co-infected patients. In November 2016, TAF was approved for HBV treatment in the US, followed by the approval in Europe in January 2017.

The potentially nephrotoxic effect of TDF is a concern. Although nephrotoxicity is rarely observed in HIV-negative patients treated with TDF monotherapy renal impairment has been more frequently reported in HIV-positive patients using TDF as a component in ART and may be associated in particular with the combined use of TDF and ritonavir-boosted HIV protease inhibitors (Mauss 2005, Fux 2007, Goicoechea 2008, In addition, the recently approved cytochrome P450 3A inhibitor cobicistat can also increase creatinine levels. Regular monitoring of renal function in HBV/HIV-co-infected patients, including estimated glomerular filtration rate (eGFR) and assessment of proteinuria, is necessary. In the case of a reduced eGFR, TDF should be substituted by TAF or should be dosed at a reduced frequency according to the label. In the case of significant proteinuria, TDF should also be replaced by TAF. Alternatively, in specific situations in the case of tenofovir-associated nephrotoxicity, tenofovir can also be replaced by entecavir.

Conclusion

The number of available HBV polymerase inhibitors for chronic hepatitis B has increased substantially over the last few years. In general, the choice is confined to two mostly non-cross-resistant classes, the nucleotide, and nucleoside compounds HBV/HIV co-infected patients, ART is indicated to treat both infections simultaneously. The HBV treatment of choice is tenofovir. Due to the rapid development of resistance when HBV is not fully suppressed HBV monotherapy with either lamivudine or emtricitabine should not generally be considered. A combination of tenofovir plus lamivudine or emtricitabine as a primary combination therapy has theoretical advantages over tenofovir alone, but studies supporting this concept have not been published to date. However, as tenofovir is combined with emtricitabine or lamivudine in most antiretroviral regimens today. This seems to be a more theoretical argument and not reflected by reality. In general, the treatment of HBV as a viral disease follows the same rules as HIV therapy, aiming at full suppression of the replication of the virus to avoid the development of resistance. Successful viral suppression of hepatitis B results in the inhibition of necro-inflammatory activity, reversion of fibrosis, and most importantly a decrease in the incidence of hepatic decompensation and hepatocellular carcinoma.

Acknowledgment

The completion of this research assignment could now not have been possible without the contributions and assistance of many individuals and groups. We're. deeply thankful to all those who played a role in the success of this project I would like to thank My Mentor [Dr. Naweed Imam Syed Prof branch of mobile Biology at the University of Calgary for their useful input and guidance for the duration of the research system. Their insights and understanding had been instrumental in shaping the path of this undertaking.

Authors' Contribution

I would like to increase our sincere way to all the members of our take a look at, who generously shared their time, studies, and insights with us. Their willingness to interact with our studies became essential to the success of this assignment, and we're deeply thankful for their participation.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The authors declare no conflict-of-interest.

References

1. Alter M. (2006). Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*; 44:69.
2. Konopnicki D, Mocroft A, de Wit S, et al. (2005), Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*; 19:593-601.
3. M, Puoti M, Camino N, Soriano V. (2003), Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin Infect Dis*; 37:1678-1685.
4. Modi A, Feld J. (2007), Viral hepatitis and HIV in Africa. *AIDS Rev*; 9:25-39.
5. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. (2008), Hepatitis B virus infection: epidemiology and vaccination. Epidemiol, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology*; 48:99-108.
6. Bods worth N, Donovan B, Nightingale BN. (1989), The effect of concurrent human immunodeficiency virus infection on chronic hepatitis B: a study of 150 homosexual men. *J Infect Dis*; 160:577-82.
7. Bodsworth NJ, Cooper DA, Donovan B. (1991), The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. *J Infect Dis*; 163:1138-1140.
8. Hadler SC, Judson FN, O'Malley PM, et al. (1991), The outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J Infect Dis*; 163:454-459.
9. Soriano V, Puoti M, Bonacini M. (2005), Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. *AIDS*; 19:221-240.
10. Schmutz G, Nelson M, Lutz T, et al. (2006), Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS*; 20:1951-1954.
11. Piroth L, Pol S, Lacombe K, Miailhes P, et al. (2010), Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. *J Hepatol*; 53:1006-12.

12. Kosi L, Reiberger T, Payer BA, et al. (2012), Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. *J Viral Hepat*,19(11):801-810.
13. Puoti M, Torti C, Bruno R. (2006), Natural history of chronic hepatitis B in co-infected patients. *J Hepatol*; 44:65-70.
14. Puoti M, Bruno R, Soriano V, et al. (2004), Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation, and outcome. *AIDS*; 18:2285-2293.
15. Brau N, Fox R, Xiao P, et al. (2007), Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: A US-Canadian multicenter study. *J Hepatol*; 47:527-537.
16. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. (2009), Impact of Hepatitis B virus infection on the progression of AIDS and Mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis*; 48:1763-1771.
17. Thio C, Seaberg E, Skolsky R. (2002), HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS). *Lancet*; 360:1921-1926.
18. Crowell TA, Gebo KA, Balagopal A, et al. (2014), Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. *J Acquir Immune Defic Syndr*. 65(4):429-37.
19. Rosenthal E, Roussillon C, Salmon-Céron D, et al. (2014), Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: The Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey. *HIV Med*.
20. Matthews GV, Manzini P, Hu Z, et al. (2011), Impact of lamivudine on HIV and hepatitis B virus-related outcomes in HIV/hepatitis B virus individuals in a randomized clinical trial of antiretroviral therapy in southern Africa. *AIDS*; 25:1727-1733.
21. Núñez M, Puoti M, Camino N, Soriano V. (2003), Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin Infect Dis*; 37:1678-1685.
22. Ingiliz P, Valantin MA, Thibault V, et al. (2008), Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*; 13:895-900.
23. Boyd A, Piroth L, Maylin S, et al. (2016), Intensification with pegylated interferon during treatment with tenofovir in HIV-hepatitis B virus co-infected patients. *J Viral Hepat*. 23(12):1017-1026.
24. Van Bömmel F, Wunsche T, Mauss S, et al. (2004), Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology*. 40:1421-1425.
25. Matthews GV, Seaberg E, Dore GJ, et al. (2009), Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV-coinfected individuals. *AIDS*. 23:1707-15.
26. Thibault V, Stitou H, Desire N, Valantin MA, Tubiana R, et al. (2011), Six-year follow-up of hepatitis B surface antigen concentrations in tenofovir disoproxil fumarate treated HIV-HBV-co-infected patients. *Antivir Ther*. 16:199-205.
27. Plaza Z, Aguilera A, Mena A, et al. (2013), Influence of HIV infection on response to tenofovir in patients with chronic hepatitis B. *AIDS*. 27(14):2219-2224.
28. Snow-Lampart A, Chappell B, Curtis M, et al. (2011), No resistance to tenofovir disoproxil fumarate was detected after up to 144 weeks of therapy in patients mono infected with chronic hepatitis B virus. *Hepatology*. 53:763-773.
29. Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, et al. (2007), Low resistance to adefovir combined with Lamivudine: a 3-year study of 145 Lamivudine-resistant hepatitis B patients. *Gastroenterology*. 133:1445-1451.
30. Berg T, Marcellin P, Zoulim F, et al. (2010), Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic hepatitis B virus infection. *Gastroenterology*, 139:1207-1217.
31. Ratcliffe L, Beadsworth MB, Pennell A, Phillips M, Vilar FJ. (2011), Managing hepatitis B/HIV co-infected: adding entecavir to Truvada (tenofovir disoproxil/emtricitabine) experienced patients. *AIDS*. 25:1051-1056.
32. Hosaka T, Suzuki F, Kobayashi M, et al. (2012), Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*.
33. Coffin CS, Stock PG, Dove LM, et al. (2010), Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV co-infected transplant recipients. *Am J Transplant*. 10:1268-1275.
34. Tateo M, Roque-Afonso AM, Antonini TM, et al. (2009), Long-term follow-up of liver transplanted HIV/hepatitis B virus co-infected patients: perfect control of hepatitis B virus replication and absence of mitochondrial toxicity. *AIDS*. 23:1069-1076.
35. Marcellin P, Heath Cote EJ, Buti M, et al. (2011), Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleotide analogs. *AIDS*. 25:73-79.
36. Fung SK, Andreone P, Han SH, et al. (2005), Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. *J Hepatol*. 43:937:943.
37. Berg T, Marcellin P, Zoulim F, et al. (2010), Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic hepatitis B virus infection. *Gastroenterology*. 139:1207-1217.
38. Patterson SJ, George J, Strasser SI, et al. (2011), Tenofovir disoproxil fumarate rescue therapy following the failure of both lamivudine and adefovir digitoxin in chronic hepatitis B. *Gut*. 60:247-254.
39. Petersen J, Ratziu V, Buti M, et al. (2012). Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: An international multicenter cohort study. *J Hepatol*. 56(3):520-526.
40. Schmutz G, Nelson M, Lutz T, et al. (2006), Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS*, 20:1951-1954.
41. Matthews GV, Avihingsanon A, Lewin SR, et al. (2008), A randomized trial of combination hepatitis B therapy in HIV/HBV co-infected antiretroviral naïve individuals in Thailand. *Hepatology*, 48:1062-1069.
42. Matthews GV, Seaberg E, Dore GJ, et al. (2009), Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV-coinfected individuals. *AIDS*. 23:1707-1715.
43. Price H, Dunn D, Pillay D, et al. (2013), Suppression of HBV by tenofovir in HBV/HIV co-infected patients: a systematic review and meta-analysis. *PLoS One*. 8(7): e68152.

44. Lok AS, Trinh H, Carosi G, et al. (2012), Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. *Gastroenterology*.143(3):619-628.
45. Agarwal K, Fung SK, Nguyen TT, et al. (2015), Twenty-eight-day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol*. 62(3):533-540.
46. Sax PE, Wohl D, Yin MT, et al. (2015), Tenofovir alafenamide versus tenofovir disoproxil fumarate, co-formulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomized, double-blind, phase 3, non-inferiority trials. *Lancet*. 385(9987):2606-2615.
47. Gallant J, Brunetta J, Crofoot G, et al. (2016), Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide in HIV-1/Hepatitis B-Coinfected Adults. *J Acquir Immune Defic Syndr*. 73(3):294-298.
48. Heathcote EJ, Marcellin P, Buti M, et al. (2011), Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*, 140:132-143.
49. Mauss S, Berger F, Flimann N, et al. (2011), Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. *J Hepatol*. 55:1235-1244.
50. 50Mauss S, Berger F, Schmutz G. (2005), Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS*, 19:93-95.
51. Fux CA, Simcock M, Wolbers M, et al. (2007), Swiss HIV Cohort Study. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther*, 12:1165-1173.
52. Goicoechea M, Liu S, Best B, et al. (2008), California Collaborative Treatment Group 578 Team. Greater tenofovir-associated renal function decline with protease inhibitor-based versus non-nucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 197:102-108.
53. Mocroft A, Kirk O, Reiss P, et al. (2010), Estimated glomerular filtration rate, chronic kidney disease, and antiretroviral drug use in HIV-positive patients. *AIDS*. 24(11):1667-1678.