

HIV with Hepatitis B Co-Infection: Optimizing Treatment in Resource-Limited Settings

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Abstract

Hepatitis B infection is a major cause of morbidity and mortality in HIV-infected patients. While the majority of persons infected with hepatitis B are found in the developing world and were infected at birth or in early childhood, most studies in HIV and HBV co-infection have been conducted in developed countries, where the main modes of transmission are either intravenous drug use or sexual transmission. The few studies that have been conducted in resource-limited settings have very few patients, and the laboratory parameters for proper evaluation of these studies are frequently incomplete. The applicability of United States and European guidelines for HBV-co-infected HIV patients in resource-limited settings (RLS) is therefore uncertain, and may be constrained by financial issues especially with regard to appropriate initiation of antiretroviral treatment. This review discusses the few studies conducted in RLS, and proposes guidelines for treatment based on the best available evidence from these studies. In addition, the effect of co-infection on disease progression, including the role of HBV genotypes and HIV subtypes and the use of hepatitis B vaccination in HIV infection is reviewed.

Keywords: HIV; Hepatitis B; Resource-limited settings; Antiretrovirals

Introduction

Hepatitis B virus (HBV) co-infection is a major contributor to morbidity and mortality in HIV-infected patients, especially in countries highly endemic for both. The treatment of HBV in HIV-co-infection in recent years has become standard as a consequence of earlier initiation of combination antiretroviral (ARV) treatment containing lamivudine, emtricitabine and/or tenofovir. Optimal treatment is partly a matter of economics since ARV recommendations for developed countries typically include a tenofovir plus lamivudine or emtricitabine backbone, while tenofovir in resource-poor countries may not be part of first-line ARV therapy due to significantly higher costs. Substantial evidence-based gaps remain, especially since most studies involving treatment of HBV/HIV co-infected patients have been conducted in resource-rich countries [1]. HBV genotypes, prevalence rates and methods of transmission of HBV are very different in resource-limited settings (RLS). HBV population prevalence rates in the resource-limited countries are much higher than developed countries and are likely to be of different genotypes in each region [2]. While the bulk of HBV in developed countries is acquired in adolescence and adulthood through sexual contact and injection drug use, most HBV infection in the developing world is through maternal and child infection [3,4]. HIV with HBV co-infection is associated with poorer outcomes beyond that from either disease alone. Rates of progression to chronic hepatitis, levels of HBV viremia, and development of cirrhosis and hepatocellular carcinoma (HCC) are all higher in HIV co-infected HBV patients [1]. In addition, occult HBV viremia with loss of hepatitis B surface antigen (HBsAg) can occur more frequently with increasing immunosuppression and thus serve as a possible reservoir for continued transmission of infection [5].

The purpose of this review is to highlight major issues in the treatment of HBV in HIV-co-infected patients in RLS, especially the applicability of current treatment recommendations, evidence for which is mostly based on studies in developed countries. We review in detail

the few studies done in RLS, and compare these with recently published studies. In addition, the effect of co-infection on disease progression of both HIV and HBV infection, as well as the effect of HBV genotypes on HBV disease manifestations and the use of HBV vaccination in HIV infection are discussed. While significant heterogeneity does exist between Asian and African HIV/HBV co-infection, the impact of cost-constraints for optimal treatment is a major limiting factor in the control of both epidemics, and needs to be fully explored and considered.

HIV/HBV Treatment Studies in ARV-Naive in RLS

Four studies in HBV/HIV co-infected patients in RLS are reviewed here and summarized in Table 1.

Matthews and her colleagues [6] performed a randomized, controlled trial in Thailand in HIV treatment-naive patients initiating ARVs. These were divided into three groups based on the HBV-active component of their regimen: lamivudine only, tenofovir only, and tenofovir plus lamivudine. There were 36 HBsAg reactive patients enrolled overall, with 22 (61%) being hepatitis B early antigen (HBeAg) positive. Follow-up time was 48 weeks. Two patients in the lamivudine arm were lost to follow-up and there was one death in the tenofovir plus lamivudine arm, but all enrolled patients were included in an

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Study/ Country	HBV definition/ genotype	Study type, N, arms	HIV treatment status	Followup	Outcomes	Remarks
Matthews et al., 2008 [6] Thailand	HBsAg + (61% HBeAg +) B 14% C 81% G 3%	RCT N=36 Arms: 3TC - 13 TDF- 12 TDF+3TC - 11	Naive	48 weeks	<p>median time weighted reduction in HBV viral load 3TC - 4.07 log₁₀ copies/mL TDF - 4.57 log₁₀ copies/mL TDF+3TC - 4.73 log log₁₀ copies/mL no difference among all regimens (p=0.70)</p> <p>undetectable HBV viral load (<170 copies/mL) - 3TC - 6/13 (46%) TDF - 9/12 (75%) TDF+3TC - 7/11 (64%) no difference among all regimens (p=0.65)</p> <p>HBV<1000 copies/mL 3TC - 6/13 (46%) TDF - 11/12 (92%) TDF+3TC - 10/11 (91%) tenofovir and tenofovir plus lamivudine equivalent, both better than lamivudine alone (p=0.013)</p> <p>HBeAg loss (overall) - 7/22 (33%) no significant difference between groups</p> <p>HBsAg loss(overall) - 3/36 (8%)</p> <p>Resistance mutations detected: L180M/M204V - 3TC arm (1) M204V - 3TC arm (1) Other treatment failures showed wild type (2), and viral load too low for sequencing (2)</p> <p>Hepatic flares (overall) - 9/36 (25%)</p>	Landmark RCT in treatment naive patients showed tenofovir containing-regimens are superior, but only at an adjusted higher HBV level (<1000 copies/mL vs. undetectable)
Avihingsanon et al., 2010 [7] Thailand	HBsAg+ (69% HBeAg +) B - 6% C - 94%	RCT N=16 Arms: FTC/ZDV/ EFV - 6 FTC/TDF/EFV - 10	Naive	48 weeks	<p>median time weighted area under the curve (TWAUC) reduction in HBV viral load FTC/ZDV/EFV - 3.25. log₁₀ copies/mL FTC/TDF/EFV - 5.32 log₁₀ copies/mL Greater reduction in TWAUC for FTC/TDF/EFV (p=0.03)</p> <p>undetectable HBV viral load (<170 copies/mL) - FTC/ZDV/EFV - 33% FTC/TDF/EFV - 90% FTC/TDF/EFV superior to FTC/ZDV/EFV (p=0.036)</p> <p>HBeAg loss (overall) - 4/11 (36%) no difference among either regimen</p> <p>HBsAg loss (overall) - 1/16 (6%), FTC/ZDV/EFV arm</p> <p>No resistance data available</p> <p>Hepatic flares (overall) - 3/16 (19%)</p>	<p>Showed FTC/TDF superior to FTC alone as HBV-active agent</p> <p>Suggested that FTC with synergistic activity to TDF compared to 3TC, hence the difference in findings compared to Matthews et al. 2008 finding</p>
Kamdoung et al., 2014 [8] Thailand	HBsAg+ (63% HBeAg +) B 17% C 83%	Prospective cohort 3TC as only active agent N=30 HBeAg+ - 19 HBeAg- - 11		12 months up to 5 years	<p>undetectable HBV viral load (<2.18 log₁₀ IU/mL, 840 copies/mL)* 12 months Overall 20/30 (67%) HBeAg+ - 9/19 (47%) HBeAg- - 11/11 (100%) Higher suppression in HBeAg- (p=0.004)</p> <p>5 years Overall 9/30 (30%) HBeAg+ - 2/19 (11%) HBeAg- - 7/11 (64%)</p> <p>HBeAg loss (overall) - 37% 5 years (7/19 total; 7/8 virally suppressed with samples at 5 years)</p> <p>HBsAg loss (overall) - 14% at 5 years (4/29 total; 4/17 virally suppressed with samples at 5 years)</p> <p>5-year cumulative resistance: 6/30 (20%), all HBeAg+</p> <p>Resistance mutations detected: M204I (1) L180M/V173L/M204V(1) L180M/M204V (2) L180M/M204I (1) L180M/V173L/M204I (1) *some samples diluted by 10 due to insufficient quantity</p>	Showed good long-term response for 3TC alone especially in HBeAg- patients, with complete suppression in these at 12 months. Long-term suppression (5 years) was 30%

Kim et al., 2011 [9] Kenya	HBsAg+ (11% HBeAg +) A1 - 100%	Prospective cohort 3TC as only active agent N=27 HBeAg+ - 3 HBeAg- - 24	Naive	18 months	undetectable HBV viral load (<100 IU/mL, 560 copies/mL) Overall 89% (17/19 evaluable patients, with 5 deaths prior to 18 months, cause of deaths not reported)HBeAg loss - not reported HBsAg loss - not reported Resistance mutations detected: M204I (1) A200V/M204I (1)	Showed good long-term response for 3TC alone with complete suppression in 89% at 18 months, no long term follow-up
Matthews et al., 2013 [10] Thailand 28.5% Australia 40.6% USA 30.9%	HBsAg+ (49% HBeAg +) A 47 (50%) C 33 (35%) All other types 13 (14%) Not tested 57	Prospective cohort N=165 Thailand n=47 Australia n=67 USA n=51 TDF+FTC/3TC - 94 FTC or 3TC - 32 TDF - 21 No HBV drug - 18	HAART-experienced, 89% on HBV-active regimen	2.8 years	undetectable HBV viral load (<357 IU/mL, 2000 copies/mL) at study visit Overall 79.2% of study visits TDF+FTC/3TC - 86% FTC or 3TC - 61% TDF - 80% No HBV drug - 53% TDF+FTC/3TC associated with higher likelihood of HBV viral suppression at time of visit than any of the other groups, including tenofovir monotherapy (p=0.02) HBeAg loss - not reported HBsAg loss - not reported	Study looking at treatment-experienced HIV/ HBV co-infected patients showing improved outcomes with combination tenofovir therapy

Legend: HBsAg - hepatitis B surface antigen, HBeAg - hepatitis B e antigen, RCT - randomized controlled trial, 3TC - lamivudine, TDF - tenofovir, AZT - zidovudine, FTC - emtricitabine

Table 1: Selected studies involving HBV/HIV co-infected patients in resource-limited settings.

intention-to-treat analysis. There was no significant difference between any regimen when undetectable HBV viral load (<170 copies/mL) was used as a primary outcome, but the authors found a significant difference when the cutoff for HBV suppression was set at 1,000 copies/mL. Tenofovir-based regimens were found to be superior to lamivudine alone (p=0.013), but there was no significant difference between tenofovir alone versus tenofovir plus lamivudine at this cutoff. Thirty-three percent of HBeAg positive subjects lost HBeAg, and 8% experienced HBsAg loss over the observation period. Median overall CD4 count was 36 cells/μL and increased to 202 cells/μL at 48 weeks. There was a significantly higher CD4 increase in the tenofovir plus lamivudine arm compared to either lamivudine or tenofovir alone (+195 cells/μL, +141 cells/μL, +118 cells/μL respectively, p=0.048). HIV viral suppression (<50 copies/mL) was 84% overall at 48 weeks, with no significant difference between groups.

Avihingsanon and colleagues [7] in a randomized controlled trial looked at HBV responses to patients initiating ARV treatment with an HBV-active component composed of either emtricitabine alone versus a tenofovir plus emtricitabine combination. Sixteen HBsAg positive patients (69% HBeAg positive) were enrolled with 48 weeks follow-up time. Unlike the Matthews et al. study [6], they found a significantly higher viral suppression rate of HBV with the combination arm with undetectable viral load (<170 copies/mL) as an outcome (90% vs. 33%, p=0.036). Median time weighted area under the curve reduction in HBV viral load was greater for tenofovir plus emtricitabine combination compared to emtricitabine alone (p=0.03). HBeAg loss was 36% overall with no significant difference between either regimen. HBsAg loss was not reported. The authors suggested that the use of emtricitabine was synergistic with tenofovir as seen in previous in-vitro models, accounting for the superior results compared to tenofovir plus lamivudine in previous studies. They also stated that a tenofovir monotherapy arm would have been helpful to differentiate the effect of tenofovir alone versus combination therapy but this was not incorporated into the study design. CD4 count increases between the emtricitabine (+120 cells/μL) and the tenofovir plus emtricitabine group (+192 cells/μL) at 48 weeks were not significantly different. HIV viral suppression (<50 copies/mL) was not significantly different between either group (FTC alone 83%; TDF+FTC 100%).

Khamduang et al. [8] conducted a five-year prospective cohort of 30 HBsAg positive HIV patients in Thailand which evaluated HBV suppression rates defined as less than 150 IU/mL (840 copies/mL) with lamivudine as the sole HBV agent in the ARV regimen. The higher cutoff was used since some samples were diluted 1:10 due to insufficient volume of sample. They found that all patients who were HBeAg negative (11/30, 37%) successfully suppressed their HBV viral loads, but only 47% of HBeAg positive patients successfully suppressed at 12 months, for a total long-term suppression rate of 67%. At the end of the observation period, only nine patients (30%) had undetectable viral load, composed of seven HBeAg negative and two HBeAg positive subjects. Median CD4 count at baseline was 100 cells/μL and increased to 247 cells/μL at 12 months and 472 cells/μL at five years. HIV viral suppression (<50 copies/mL) was achieved in 73% of patients at 12 months.

A prospective cohort from Kenya by Kim et al. [9] looked at 27 HBsAg positive HIV patients, the majority of whom were HBeAg negative (24/27, 89%) and were treated with lamivudine as the sole HBV agent upon initiating ARVs. At 18 months, they had five deaths. The causes of death could not be ascertained. Among the evaluable patients remaining, they found an 89% undetectable HBV viral load (17/19, 89%) using an in-house RT-PCR with a limit of detection of 10 IU/mL (56 copies/mL), and defined HBV suppression as HBV DNA < 100 IU/mL (<560 copies/mL). CD4 count baseline at was 122 cells/μL. No cohort data for HIV viral load or CD4 count was reported at the end of 18 months. Compared to non-HBV co-infected patients (N=362), HBV-co-infected patients were found to have higher mortality (21.7% versus 8.9%, p=0.032).

Treatment-Experienced Studies in RLS

We reviewed one trial which included a RLS in an ARV treatment-experienced cohort. Matthews et al. [10] conducted a large, multinational cohort study with HBV co-infected, ARV-experienced HIV patients over three countries (Thailand, United States, Australia) with 165 subjects and looked at undetectable HBV DNA as a primary outcome in patient with ARV regimens containing tenofovir plus emtricitabine, lamivudine or emtricitabine, or tenofovir. Only Thailand was an RLS country in this study, and it accounted for 28.5% of the

total patients. Patients were followed over a median of 2.8 years. HBeAg was positive in 49% of patients. Undetectable HBV DNA was defined as less than 357 IU/mL (2000 copies/mL) because three different assays were used and this was the lowest common threshold across the assays. Univariate analysis showed that patients from Thailand were less likely to be have detectable HBV DNA (OR 0.22, $p=0.04$) although this was not significant in multivariate analysis (OR 0.31, $p=0.05$). Multivariate analysis showed that tenofovir plus emtricitabine or lamivudine was more likely to suppress HBV DNA compared to any kind of monotherapy, including monotherapy with tenofovir alone ($p=0.02$). The major caveat of this study was that patients were treatment-experienced with lamivudine, and may have had pre-existing lamivudine resistance mutations. However, this does not explain the higher HBV viral suppression with combination therapy versus tenofovir alone. Other factors that were found to influence the presence of detectable HBV DNA included less than 95% adherence to the ARV regimen (even when HIV was undetectable), detectable HIV RNA, presence of HBeAg, duration of ARV treatment <2 years, and CD4 count less than 200 cells/ μ L.

Recent Treatment Studies In Resource-Rich Settings

HIV treatment guidelines in the United States and Europe have always recommended the use of dual HBV-active NRTI treatment (tenofovir plus lamivudine/emtricitabine) in treatment-naïve patients despite a dearth of evidence for this approach [11,12]. A recent meta-analysis and systematic review [13] confirmed the major role of tenofovir in the treatment of HBV in HIV co-infected patients. The meta-analysis included 23 studies of various designs, including six randomized controlled trials (RCTs) with a total of 550 patients. However only two of the included studies were done in RLS [6,7], and may therefore be less applicable to developing countries due to major epidemiological differences in transmission and genotypes, as well as availability and affordability of antiretrovirals [4,8]. The meta-analysis concluded that tenofovir is effective for suppressing HBV to undetectable levels in a majority of HIV and HBV co-infected patients, and that the proportion of patients with suppressed HBV DNA increases over time. This was irrespective of prior lamivudine or emtricitabine treatment. Finally, the authors concluded that the addition of lamivudine or emtricitabine to tenofovir offered no additional benefit, in contrast with established guidelines.

A more recent retrospective cohort study involving 150 HBV co-infected HIV patients in the United States who were followed over 240 weeks showed even more discordant results compared to guideline recommendations. The two arms of the study compared lamivudine as the sole anti-HBV agent versus dual treatment with either tenofovir plus lamivudine or tenofovir plus emtricitabine. There was a trend towards HBV suppression for dual treatment but, overall there was no significant difference in treatment. No patients were treated with tenofovir as the sole anti-HBV agent [14].

HIV-HBV Co-Infection and Disease Progression

HBV co-infection in HIV-infected patients is associated with decreased HBV clearance as well as an increased risk of progression to chronic hepatitis [1]. Mortality from all causes, as well as liver-related conditions are increased in HBV co-infected HIV patients regardless of the use of ARVs. The impact of HBV on HIV progression is less clear-cut, although there is some evidence that is suggestive of decreased ARV response and faster time to development of AIDS [15]. While the progression to HCC may at least be partially due to the prevailing genotype [2], the overall prevalence of HCC in HIV co-infected

patients is nearly three-fold increased compared to HIV-seronegative patients [15]. This has become more apparent with increased survival times on ARVs, such that the overall incidence of cirrhosis and HCC has increased in this patient population [4].

HBV genotype is known to affect clinical outcomes and response to treatment [16]. For instance, genotype C is more likely to be associated with HCC than other genotypes, while genotype A is more likely to be responsive to interferon treatment than other genotypes [2]. Less is known about the interaction of HIV clades with different HBV genotypes, but there is likely an effect because of the variability of progression to AIDS of the different HIV clades [17]. The two treatment-naïve studies [8,9] that used lamivudine as the sole active HBV agent showed much higher rates of HBV suppression at one year than most studies with HBV/HIV co-infection treated with lamivudine as a sole agent in developed countries. Genotype A1 was the sole genotype for the Kenyan cohort, while the Thai cohort was mostly made up of genotype C with one genotype B subject [6-9]. While HIV clade B is prevalent for the United States and Europe, the predominant clade for Thailand is CRF01_AE and that for Kenya are clades A and D [17]. While biological responses in the context of these variables may account for some of the observed differences in outcomes of treatment in RLS, the complexities of these interactions and the dearth of studies is such that consistent conclusions on the effect of HIV clades and HBV genotypes on therapeutic outcomes cannot be made at this time.

Hepatitis B Vaccination in HIV-infection

Vaccination for HBV in HIV-infected patients can be challenging due to the decreased immune response to the vaccine, especially in those with severe immunosuppression [4]. In addition to checking that a patient is negative for HBsAg, an HBV core antibody (anti-HBc) should be checked to look for occult infection since these occur more frequently in HIV-infected patients [5]. In RLS that are highly endemic for HBV, childhood vaccination with HBV vaccine is recommended. However, HBV vaccination history may be unreliable and so all HIV patients should be checked for immune status to HBV with an anti-HBs antibody at baseline as well as after vaccination, if possible. The schedule of vaccination in non-HBV immune HIV patients should follow the same three-dose recommendation (20 μ g x three doses intramuscularly at zero, one and six months) as HIV-seronegative subjects with a few caveats. In the event that HBsAg and anti-HBs testing reveals non-immune status, even if there is a history and documentation of childhood vaccination to HBV, the initiation of a full course of HBV vaccination is recommended. In HIV patients with high CD4 counts, vaccination should be given as soon as possible to ensure adequate response before CD4 counts decline, with documentation of anti-HBs response one to two months after the final dose. In those with CD4 counts below 350 cells/ μ L, vaccination may be delayed until significant immune reconstitution has occurred on ARVs, weighed against the risk of acquiring de novo HBV infection while waiting for CD4 counts to rise. In the event that HBV status and CD4 status cannot be determined due to severe resource constraints, we recommend going ahead with a full course of HBV vaccination from a public health standpoint, and because the comorbidity of newly-acquired HBV infection in an HIV-infected patient can be considerable.

While there is some evidence that double-dose and intra-dermal administration of HBV vaccine is associated with increased efficacy, more clinical research is needed prior to institution of these alternative modalities. In addition, the utility of giving boosters beyond the original schedule has not been determined, and cannot be routinely recommended at this time [4].

Guidelines for Antiviral Therapy for HIV-HBV Co-Infected Patients in RLS

Looking at the four treatment-naïve studies done in RLS, only tenofovir plus emtricitabine showed a convincing superiority over emtricitabine alone, as seen in the Avihingsanon study [7]. There was no difference in tenofovir versus tenofovir plus lamivudine in the Matthews study [6], and even the treatment endpoint had to be increased to show superiority of a tenofovir-based regimen compared to lamivudine. There was no clear effect of improved immunological reconstitution seen with some ARV regimens on HBV clinical outcomes. The last two studies [8,9], both prospective cohorts with lamivudine alone as the HBV-active agent, showed surprisingly high rates of HIV suppression, especially among HBeAg negative patients. These findings suggest that, if available, tenofovir plus emtricitabine is the best option in HBV/HIV co-infected patients in RLS. However, the benefit of addition of lamivudine to a tenofovir-containing regimen is uncertain since the Matthews study [6] did not show any difference between either arm, and the Avihingsanon [7] study used emtricitabine only.

If tenofovir is in limited supply, HBeAg testing should be done and lamivudine or emtricitabine as the sole HBV active agent in an ARV regimen can be offered to HBeAg-negative treatment-naïve patients for up to five years. HBeAg positive patients should be prioritized to start a tenofovir-containing regimen. While previous studies [18,19] have shown that tenofovir monotherapy is more durable than lamivudine monotherapy for treatment of HBV in terms of a lower tendency to develop resistance mutations, a negative HBeAg, at least in HIV co-infected patients in RLS, is predictive of more durable suppression rates even with lamivudine monotherapy [8,9].

For lamivudine-experienced HBV/HIV co-infected patients, combination tenofovir plus emtricitabine or lamivudine is the regimen of choice, and is superior to tenofovir monotherapy as shown by the treatment-experienced study by Matthews and her colleagues [10]. This is in contrast with findings of the meta-analysis by Price and his colleagues which concluded that in treatment-experienced patients, there was no benefit to the addition of lamivudine or emtricitabine [13]. Of note, the Matthews study [10] was not included in the Price meta-analysis, nor were any treatment-experienced RLS studies, and therefore this recommendation is new for RLS.

Despite international recommendations to begin ARVs at increasing CD4 counts in RLS, economic considerations result in ARVs being started only in those with low CD4 counts. In these settings, it may be necessary to consider treatment with monotherapy using HBV active agents such as lamivudine, clevudine, entecavir and tenofovir if there is clinically active hepatitis B but the threshold for ARVs have not been reached. This may then adversely impact subsequent ARV regimens and be associated with the emergence of drug resistance, especially in countries where ARV drug repertoires are limited. In the Philippines, where HBV population prevalence is 17%, HIV testing prior to treatment of HBV with NRTI monotherapy is not routine [20]. While historical rates of HIV have been low, it currently has one of the fastest growing HIV epidemics in the world, and haphazard prescription of NRTI monotherapy for HBV infection is not only widespread, but occurs without the benefit of an HIV test [21].

Finally, with regard to occult HBV infection in HIV patients, at least one study done in RLS [22] found high rates of occult HBV infection (10.6%) in HIV patients and recommended using dual HBV-active treatment for these patients without any prospective evidence for this. However, a more recent prospective study done in the Netherlands (not

an RLS) looked at treatment responses of occult HBV viremia to ARV initiation with lamivudine-containing regimens as HBV monotherapy. This study showed that all occult HBV viremia patients with low CD4 counts resolved with ARV treatment [23]. It remains to be seen whether RLS patients will respond in a similar way, and more research is needed to determine whether a combination regime is superior to monotherapy in the case of occult HBV infection.

Conclusions and Recommendations

In conclusion, treatment of HBV/HIV co-infection in RLS may substantially differ from treatment based on mostly developed-country trials. Tenofovir in combination with emtricitabine has the strongest evidence for efficacy for HBV suppression in RLS, and uncertainties remain about tenofovir monotherapy in ARV treatment-naïve patients. Combination treatment with tenofovir plus lamivudine or emtricitabine in treatment-experienced RLS patients is supported by prospective data, in accordance with most published guidelines.

The option of using lamivudine alone as part of the ARV regimen as the initial therapy for co-infected patients who are HBeAg-negative may be preferable for countries who are still struggling with budget-limitations brought about by a larger ARV rollout as recommended by the most recent WHO guidelines. While there is some evidence for this approach, the data supporting this recommendation remains relatively weak due to the small sizes of the clinical studies performed. Further research needs to be done on the feasibility of this strategy, as other gaps in knowledge, including the treatment of HBsAg negative occult HBV infection, and country-specific RLS experiences. Nevertheless, the current evidence, while limited is promising, and can be utilized by program managers in RLS while awaiting larger and more comprehensive data.

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