

Review article

Second line antiretroviral therapy for treatment of HIV in Asia

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Limited access to virological monitoring has led to a high prevalence of resistance to nucleoside reverse transcriptase inhibitors (NRTIs) at the time of first line failure in most studies from low- and middle-income countries (LMIC). Nevertheless, the current standard of care is to include NRTIs in second line regimens. The activity of tenofovir/emtricitabine following failure of stavudine/lamivudine or zidovudine/lamivudine is dependent on the sensitivity of the monitoring strategy used during first line therapy and the threshold for switching, whereas these factors are less important if the opposite sequencing strategy is used. Boosted protease inhibitors (PIs) are the foundation of effective second-line therapy with demonstrated efficacy in early salvage regimens and high barrier to resistance. Lopinavir/ritonavir and ritonavir-boosted atazanavir have recently been described by the World Health Organization as preferred boosted PIs for use in LMIC. Alternative approaches currently under investigation include boosted PI monotherapy, dual boosted PIs, and the combination of raltegravir (an HIV integrase inhibitor) and a boosted PI.

Keywords: Antiretroviral therapy, HIV, protease inhibitor, second line, treatment failure

The expansion of access to antiretroviral therapy (ART) for people living with HIV has been the largest public health undertaking to date. In the five years to the end of 2008, the number of people receiving ART in low- and middle-income countries (LMIC) increased from 400,000 to 4 million [1]. The prescription of first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART is appropriately the primary focus for HIV treatment programs in these settings. Furthermore, access to second line regimens has to date been extremely limited in many countries [2] and in some settings clinicians have been reluctant to switch to second line treatment due to lack of subsequent treatment options [3]. Nevertheless, as access to first-line treatment improves [1] and as treatment cohorts mature and expand, there is increasing use of second-line therapy

and an appropriate increase in interest in how to optimize therapy for patients failing NNRTI-based first line therapy.

Prevalence of resistance at time of first line regimen failure

In many settings in LMIC, routine HIV viral load monitoring is not available. In these settings, ART efficacy monitoring relies on non-virological markers, particularly clinical disease progression and CD4 counting, with demonstrated poor sensitivity and specificity for virological failure [4, 5]. Thus, many individuals with virological failure of NNRTI-based first line therapy continue on a failing regimen with attendant accumulation of HIV drug resistance. A number of studies from LMIC have demonstrated that patients in these settings have a relatively high prevalence of drug resistance at time of virological failure [6, 7]. With the use of thymidine analogue (zidovudine or stavudine) containing first line regimens the prevalence of thymidine analogue mutations (TAMs), NNRTIs mutations (particularly Y181C and

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K103N), and to lamivudine mutations (the M184V mutation) approximate 30-40%, 50-90%, and 70-90%, respectively [6,7,8]. Stavudine has been associated with a higher probability of type 1 TAMs, which are associated with broad NRTI resistance and inability to construct a potent second-line NRTI backbone. The K65R and Q151M mutations are less common.

Nucleoside reverse transcriptase inhibitors in second line therapy

The standard of care in both high-income countries (HIC) and LMIC is to continue the use of the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class in second line regimens [9,10]. The World Health Organization (WHO) recently recommended that second line NRTIs should consist of tenofovir with either emtricitabine or lamivudine if the first line regimen contained stavudine or zidovudine [11]. If tenofovir was used in the first line regimen, the recommended NRTIs were zidovudine and lamivudine.

The contribution of NRTIs to the efficacy of second line regimens is broadly associated with the sensitivity of the monitoring strategy used during first-line therapy as this determines the prevalence of NRTI resistance at the time of first-line regimen failure [12]. Thus, with a sensitive monitoring strategy and a low switch threshold applied during stavudine or zidovudine containing first line therapy, TAMs will be uncommon and it is very likely that tenofovir will be active when given as part of second line therapy and lamivudine will provide some benefit [13]. However, if a less sensitive monitoring strategy and high switch threshold are used, TAMs will be common at time of failure and some patients will have developed the K65R mutation. Therefore, the contribution of tenofovir to second line efficacy will be substantially reduced in many patients. Didanosine and abacavir are alternatives to tenofovir, but didanosine has a poor toxicity profile and abacavir is more expensive. In addition, the M184V mutation increases tenofovir susceptibility but increases resistance to abacavir and, to a lesser degree, resistance to didanosine.

The contribution of zidovudine and lamivudine to second line efficacy following failure of tenofovir-containing first line therapy is less dependent on the monitoring strategy and switch thresholds used during first line therapy. This is because regimens containing tenofovir and emtricitabine or lamivudine commonly select for the M184V mutation and less commonly the K65R mutation. The prevalence of K65R at time

of failure is substantially lower than TAMs at time of thymidine analogue regimen failure, susceptibility to zidovudine is increased in the presence of K65R and/or M184V and selection of resistance will require multiple zidovudine mutations if these mutations are maintained.

Protease inhibitors in second line therapy

Ritonavir-boosted protease inhibitors (PIs) have demonstrated efficacy in early salvage therapy [14] and seem well suited to use in second line therapy as their high plasma concentrations and high genetic barrier seem to reduce the need for support from other drugs in the regimen [15, 16]. Comparison between protease inhibitors is complicated by the use of different doses, study populations and outcome measures [17]. Furthermore, randomized comparisons of boosted PIs for second line treatment in LMIC are not available.

Recent guidance from WHO describes lopinavir/ritonavir and ritonavir-boosted atazanavir as preferred boosted PIs for use in second line therapy in LMIC [10]. Lopinavir/ritonavir is currently the only co-formulated boosted PI available in most LMIC and in combination with two NRTIs long-term efficacy with an absence of documented PI resistance has been demonstrated in treatment-naïve individuals [18]. In a study of the efficacy of lopinavir/ritonavir-containing second line therapy conducted in Cambodia, 89% of individuals were virologically suppressed after a median of 10.2 months following switch to second line therapy [19].

Atazanavir is dosed once daily and when boosted with ritonavir is non-inferior to lopinavir/ritonavir with less gastrointestinal toxicity and more favorable lipid profile in treatment naïve and experienced individuals [20, 21]. Although the use of un-boosted atazanavir is potentially attractive for LMIC, existing data suggest the absence of ritonavir-boosting may be associated with a moderate reduction in efficacy, particularly in treatment experienced individuals [20, 22, 23] and lower plasma levels when combined with tenofovir.

Alternative approaches to second line therapy

Monotherapy with a boosted protease inhibitor is an attractive option in LMIC as efficacy is independent of any NRTI resistance, NRTI toxicity is eliminated, and drug costs are reduced. However, randomized studies have suggested moderately increased risk of virological failure and drug resistance when compared to the standard combination of a ritonavir-boosted PI and two NRTIs in treatment-naïve individuals [24].

Studies are currently ongoing in Thailand and Africa to investigate the efficacy of this strategy in LMIC, but to date, no study has been reported in individuals failing initial NNRTI-based therapy.

Another nucleoside sparing strategy for second line therapy is the use of dual boosted PIs. A number of studies conducted in HIC demonstrated the significant toxicity of this approach [25-27], as have studies conducted in Thailand and Brazil of lopinavir/ritonavir/saquinavir 400mg/100mg/1000mg twice daily in treatment-experienced individuals [28, 29]. An alternative regimen of atazanavir/saquinavir/ritonavir 300mg/1600mg/100mg daily has been studied in Thailand and found to have adequate pharmacokinetic and virological outcomes, warranting further investigation [30].

New agents in second line therapy

In recent years, a number of new agents have been licensed for the treatment of HIV infection leading to the investigation of alternative approaches to second line therapy in LMIC. Raltegravir is a potent and well-tolerated first-in-class HIV integrase inhibitor, with minimal drug interactions as it is metabolized by glucuronidation rather than by the cytochrome-P450 system. The combination of raltegravir and a boosted PI is likely to be potent and well tolerated based on available data, reduces exposure of NRTIs and is not affected by NRTI or NNRTI resistance present at time of switch. At present, availability of raltegravir is extremely limited in LMIC and the estimated cost of raltegravir and lopinavir/ritonavir is approximately \$1600 per person per year, compared with \$650 per person per year for tenofovir, emtricitabine, and lopinavir/ritonavir [3]. Studies are currently ongoing comparing these two regimens.

The role for other new agents appears more limited at present. Enfuvirtide is expensive and requires subcutaneous injections twice per day. Maraviroc is only effective in individuals with R5-only HIV virus, testing for which is currently expensive and logistically difficult. Etravirine, a new NNRTI, is active against NNRTI-resistant virus, but its efficacy declines with increasing number of NNRTI resistance mutations, as commonly seen with low sensitivity monitoring strategies.

Conclusion

Second line therapy is an increasingly important component of many HIV treatment programs in

LMIC, but there are limited data available to inform optimal treatment strategies. In this context, standard of care continues to be based upon the use of two NRTIs with a boosted PI. WHO recently simplified recommended therapy to one of two combinations from each of these classes. Studies investigating alternative second line strategies that are not affected by the high prevalence of NRTI and NNRTI resistance currently seen with use of low sensitivity monitoring strategies are ongoing.

The author has served on advisory boards for ViiV Healthcare and Tibotec.

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