Curr Trop Med Rep (2017) 4:6–10
DOI 10.1007/s40475-017-0097-3

A Complex but Exciting Future: New Options for Second-Line Antiretroviral Therapy

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Published online: 18 February 2017

Abstract
Purpose of Review Protease inhibitors have been the bedrock of second and subsequent line HIV therapies for more than a decade, in both high-income and low- and middle-income countries.
Recent Findings WHO's recommendation for 'blind' sequencing from first- to second-line therapies, acknowledging that genotype testing would not be available in many resource-constrained settings, has recently been supported by large randomised studies. The availability of highly potent integrase inhibitors have transformed therapy in places where these combinations are used in first and subsequent line. The resistance barrier conferred by the newer agents in this class is formidable, and it is unclear how this will influence sequencing. WHO has recommended dolutegravir as an alternative first-line agent for first-line therapy in 2015.
Summary The fact that dolutegravir is cheaper in many high-prevalence countries than alternatives, and is amendable to co-formulation, means that debate about and studies looking at how to rationally use the different classes of drugs, balancing cost and toxicity, will be a priority.

Keywords Second-line therapy · Antiretroviral resistance · Sequencing

This article is part of the Topical Collection on *HIV in the Tropical Setting*

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Introduction

Second-line antiretroviral therapy (ART) options are required for both HIV patients failing with resistance, as well as those with toxicities. Increasing evidence that continuing viraemia causes complications and the recognition that aviraemic patients are non-infectious has meant more attention to viral load suppression in people where first-line therapies may be failing. The availability of new, potent drugs has made this possible.

A greater proportion of patients are staying on their regimen longer, as first and subsequent line regimens get more potent and less toxic [1]. People with virological failure or toxicity have an increasing number of alternatives available, especially in high-income countries [2•]. Although the term "second-line" is loosely used to refer to sequencing after virological failure on the first regimen, principles regarding "cycling" of drugs within and between classes have evolved for both resistance as well as toxicity. The historical term "salvage regimen," referring to an often-desperate situation where patients with multi-class resistance had one and, if fortunate, two new drugs added to whatever drugs still predicted by genotype to have some residual activity, is now thankfully a vanishingly small problem.

Simplification, till recently, has been limited in most cases to second and subsequent line therapies, as protease inhibitors (PIs) were the staple in the event of resistance. PIs have not been co-formulated with other classes of drugs, due to the size of the tablet for all PIs; have complex drug interactions; and are relatively toxic and with any dosed twice daily in multi-tablet combinations [2•, 3•]. Fortunately, this has recently changed, with multiple research prongs of attack looking at alternative drugs and regimens that will simplify second line.

This article discusses some of the new thinking around sequencing of regimens, with the advent of new, potent drugs, and the impact on different settings.

WHO and the Public Health Approach to Sequencing

In HIV hyperendemic low- and middle-income countries (LMICs), the exponential increase in ART availability since 2002 has lead WHO to recommend the "public health approach," where simplified algorithms are developed for drug choices, conscious of the low health resources present in many of these countries, and for HIV diagnosis, staging, initiation, monitoring and maintenance of ART [4]. Practically, this has meant adapting a combination of nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTIs) in combination for first-line ART, then changing the NRTIs and combining them with a boosted protease inhibitor, without genotype guidance. These guidelines have been slightly adapted to accommodate safer drugs within these classes as new data became available, and the vast majority of countries continue to follow the NRTI to boosted PI algorithm, even within the private sector.

In higher-income countries till recently, this approach has practically followed a similar sequence (patients with resistance being transitioned to a PI-based regimens for suppression, even where PIs are used in first line), although the availability of genotyping has allowed for the identification of people with no identified resistance, a sign of very low levels of drug pressure on replicating virus, meaning that adherence rather than drug changes becomes the priority intervention. If resistance is identified, availability of increasing number of drugs within more classes allows an experienced clinician to use the genotype results to preserve "sensitive" drugs and combine these with new candidates that have high levels of efficacy [5].

The rapid movement of the HIV field in terms of new drugs and classes has created an evidence gap. Formal evaluation of this approach of using genotyping to identify candidates for recycling and adding new drugs was evaluated over a decade ago, then using drugs largely not used within richer countries anymore [6]. In addition, there has been recognition that certain drug mutations may decrease efficacy to one drug, while mitigating resistance development and increasing efficacy to another, making classic resistance report interpretation of individual drug activity more complex. Studies such as the Europe-Africa Research Network for Evaluation of Second Line Therapy (EARNEST) study discussed below have called into question the use of genotyping in guiding drug section after NNRTI-based first-line failure, but these results are also not easily extrapolated to developed countries, where NNRTIs are no longer recommended as preferred drugs in first line.

Suitable Drugs for Sequencing

NNRTIs

Tenofovir (TDF) and abacavir have become the commonest NRTIs used in first-line regimens throughout the world (the latter used largely in higher-income countries, due to cost and co-formulation availability with certain integrase inhibitors), in combination with lamivudine or emtricitabine, which are regarded as interchangeable by WHO and almost all guidelines [4, 5].

Older NRTIs, such as stavudine and didanosine, have all but disappeared from first- to second-line regimens in the last 5 years anywhere in the world, as the toxicity of these drugs has been recognised, and due to the wide availability of TDF, which, due to its cost and safety benefits over zidovudine (AZT), has consigned the latter to second-line and subsequent line regimens [3•].

In the WHO guidelines, blind cycling has been from TDF to AZT, as there is relatively little resistance overlap between the two drugs, and the resistance mutations are predictable in terms of their impact. Second-line regimens routinely retain lamivudine or emtricitabine, recognising that the M184V mutation associated with this class improves TDF or AZT susceptibility while protecting from further resistance [4, 5].

PIs

Boosted PIs all have a formidable resistance barrier, with patients requiring prolonged exposure to the class to accumulate the sequential mutations required to decrease efficacy, a process that takes years of sub-optimal adherence [5]. For this reason, they have been the mainstay for second-line regimens, until very recently. There is cross-resistance between the drugs within the PI class, and genotyping may be useful to guide movement between them [5].

The class carries significant toxicities, and several older PIs have fallen out of use as safer drugs became available. Common class toxicities include gastrointestinal intolerance and metabolic changes. Currently, lopinavir and atazanavir regimens are preferred in LMICs for cost reasons, while darunavir and atazanavir use is more usual in richer countries [3•]. Darunavir, which has toxicity benefits and resistance barriers over other PIs, is increasingly being prescribed as the preferred PI in places that can afford the drug.

Simplification is difficult with the PI class. The originator versions of darunavir and atazanavir are not co-formulated

with ritonavir, due to patent issues, although generic manufacturers have produced an atazanavir-ritonavir fixed-dose combination and are working on a similar combination with darunavir [3•]. Currently, this means multi-tablet regimens are the norm with PI regimens, sometimes twice daily, a problem when considering that the commonest reason for first-line failure is non-adherence to a single daily tablet. PIs are also not currently co-formulated with other classes, largely due to the size of the tablet. PIs have extensive drug interactions, with potent and complex effects on the CYP systems, especially with the rifamycins, making dosing complex in the presence of TB [4, 5]. Their potency but less than optimal pill dosing and toxicity issues has meant that approaches exploring new strategies, as well as evaluating current ones, are currently being reviewed. One strategy is dose reduction, successfully done with atazanavir, and currently being looked at with darunavir [7, 8].

The Impact of EARNEST

Published in 2014, the EARNEST trial challenged many dogmas on sequencing, challenging the use of genotyping after first-line failures to guide NRTU choice, and tempered calls for more widespread resistance testing availability for LMICs [9••]. The study compared three second-line regimens in five African countries and essentially demonstrated that WHO sequencing approach was highly effective. The study used a pragmatic approach to diagnosing second-line failure, using WHO virologic (viral load), immunologic (CD4), or clinical treatment failure definitions to enrol patients into lopinavir/ritonavir-containing regimens, with the lopinavir/ritonavir co-formulation used alone, or with an NRTI backbone left up to the clinician, or the NRTI replaced with raltegravir, an integrase inhibitor. Stored samples allowed the researchers to retrospectively examine resistance patterns to analyse the impact of mutations on subsequent responses to treatment.

The patients enrolled had evidence of advanced failure, with almost half having a viral load over 100,000 copies/ml, more than half having a CD4 count below 100 cells/μl, and over half retrospectively having moderate or high resistance to NRTIs. The study arm using lopinavir/ritonavir monotherapy was not successful, but there was no difference in the other two arms comparing against raltegravir. There were very high rates of viral suppression achieved in both arms, even in the presence of extensive NRTI resistance, testament perhaps to the potency of boosted protease inhibitors, but also potentially showing the importance of the impact on viral fitness by NRTI mutations.

A similar two-arm study, published just prior to the EARNEST study, was the SECOND-LINE study [10••]. This large, well-conducted study in over 500 patients from 37 middle- and high-income countries compared raltegravir against NRTI backbones, both in combination with boosted darunavir, and was shown to be non-inferior. The study was more representative of high-income country approaches to virological failure, using viral loads as an entry criterion and with over 90% of the patients receiving genotyping. Again, virological success was high in both arms (82% at 48 weeks), despite almost all patients who had resistance testing demonstrating at least one major NRTI at initiation of the new regimen. Resistance testing guiding NRTI resistance did not appear to have impact on virological success.

It is important to remember that raltegravir may not be the optimal integrase inhibitor, just as lopinavir may not be the ideal PI, in future regimens. Lopinavir continues to be the most prescribed PI in LMICs, but the promise of affordable and potent dolutegravir, which is more potent than raltegravir, may change how integrase inhibitors are used in second line, and is discussed below [3•].

However, EARNEST and SECOND-LINE showed how effective WHO approach in sequencing was and also challenged conventional dogma among many clinicians about how they interpreted genotyping results.

Other Drug Classes

Maraviroc, a CCR-5 blocker, is very occasionally used in some rich countries, and has a good toxicity profile, but requires a complex and expensive susceptibility test. Enfuvirtide, an injectable fusion inhibitor with significant toxicity and expense, has almost completely disappeared as more potent oral drugs have come to market [5].

What Will the Impact Be of the Integrase Inhibitors?

Integrase inhibitors have rapidly replaced NNRTIs as the preferred "third" agent in first line in richer countries that have the option, due to side effect benefits over the NNRTIs, specifically efavirenz. The availability soon of injectable combinations allow for interesting future combinations that may allow for addressing complex adherence problems. Raltegravir, the oldest integrase inhibitor, has been steadily replaced by newer, co-formulated combinations containing integrase inhibitors that have simpler dosing and far higher resistance barriers. Dolutegravir, the newest entry, has yet, at the time of writing, to demonstrate failure due to resistance in first-line use, an astonishing feat as the drug has been used in over half a million patients in richer countries [3•, 11•, 12•]. Co-formulations for LMICs that include dolutegravir are currently underway, although the use of the drug in TB and pregnancy is still being evaluated. The new drugs are not perfect; recent neurotoxicity

has been demonstrated as use increases, but there is no debate that they represent a major step forward in treatment [13, 14].

The availability of these newer drugs from a completely different class has offered interesting options for second-line regimens in LMICs. Questions about whether to reserve the class for second line in LMIC or lead with the current data that suggests that failures in first line may be few are currently being pursued. The latter seems likely, as it appears that dolutegravir (as well as new, pending products) may be cheaper than efavirenz to manufacture, and it is clinically clearly preferable [3•, 15•, 16]. WHO has recommended dolutegravir as an alternative in first line and will probably move this to "preferred" status once the various pregnancy, TB, cost, and co-formulation issues are addressed. Botswana has announced that it is moving to first-line dolutegravir-based regimens immediately [17].

Sequencing after newer integrase inhibitor failure needs more data and experience. The fact that the PIs are so potent and have a solid history in second line is a reassuring go-to in the interim, but whether we can sequence integrase inhibitors or retain them between regimens, as we do with the PIs and the cytosine analogues, will need to be addressed in the next few years.

Other New Potential Co-formulations

Several studies are planned or being discussed of different combinations for second line, all in the context of failing NNRTI regimens. A study looking at a "class-sparing" combination of dolutegravir/darunavir will start recruitment in 2017. Other innovative combinations looking at combinations of newer NNRTIs, like rilpivirine with dolutegravir or darunavir, are in discussion, and with the dolutegravir/darunavir study, promise simplified single tablet second-line formulations.

How these studies influence policy is uncertain; there is a chance, as discussed above, that integrase inhibitors may be in first line, making studies evaluating NNRTI-based failures less compelling.

Should We Be Prioritising Genotype Resistance Testing in Second and Subsequent Line?

EARNEST and SECOND-LINE have tempered calls for routine genotyping after first line in LMICs; however, there is increasing use of "third"-line regimens in certain LMICs, as patients fail lopinavir- or atazanavir-based second-line regimens. These regimens usually combine combinations of integrase inhibitors, darunavir and etravirine, based on genotyping, with recommendations being made by experienced doctors. There is little clinical data published on this approach as yet, but the cost of these drugs means that limiting use to only patients who have sufficient resistance to PIs, is likely to continue. Again, the advent of highly effective integrase inhibitors may mean reappraisal of this strategy, as more clinical and genotyping data is acquired.

Pregnancy, Co-infections Like TB and hep B/C

One of the complexities of selecting second-line drugs is that the evidence base in selected populations is relatively small. This may be less important in richer areas, where more drugs that take complex co-conditions into account are available, but LMICs have to factor in common conditions within their populations such as pregnancy, TB and hepatitis.

The use of rifamycins in the treatment of TB makes drug selection in co-infected HIV patients complex, especially in second-line patients. The integrase inhibitors, many newer NNRTIs and even the new pro-drug of TDF, tenofovir alafanemide (TAF), have extensive drug interactions with rifamycins. Lopinavir is generally used when requiring a PI, with double-dosing, with some success recorded in real-world settings [4]. Atazanavir and darunavir are not recommended, although there is interest in doing pharmacokinetic (PK) studies on darunavir to see if it could be used.

Hepatitis B is common in many LMICs, where screening for hepatitis B is unusual, and the TDF-based first-line regimen is a serendipitous benefit in first-line regimens. However, when TDF is changed to another NRTI in the event of failure, this is often done without considering hepatitis B status. TDF-based regimens combined with emtricitabine or lamivudine are potent treatments of hepatitis B, but withdrawal of TDF in HIV/hepatitis B co-infected patients has been associated with several anecdotal cases of fulminant hepatitis [4]. The problem appears rare, as tens of millions of people have been initiated (and many interrupted or switched) on TDF-containing regimens, with hepatitis B levels are reported to be in the order of over 5% [18].

Hepatitis C, common in Asia and Northern Africa, as well as in many richer countries, has enjoyed astonishing progress in treatment, with new programmes expanding access across the globe. First-line and second-line ARV choice is relatively simple currently, for this group, as it is similar to those without hepatitis C, although hepatic and renal monitoring is important, and dose adjustment of hepatitis C drugs and atazanavir, if used, may be important [5].

Conclusions

We are at a puzzling time in discussing second and subsequent line therapies and simplification. The comfortable, evidence spot occupied by the protease inhibitors as the reliable "go-to"

drugs for people with resistance is being challenged. The newer integrase inhibitors, if unbreakable virologically as seems to be the current case, and with a far better side effect profile than currently used NNRTIs, may make the movement to second-line minimal. It is unclear what drugs will be required in second line, and it is even conceivable that the newer potent integrase inhibitors may be recycled. The role of other NRTIs and PIs in second line remains to be seen.

However, even with the older drugs, the biggest challenge for second-line regimens, especially in LMICs, is a health system one—identifying patients failing, whether by virological, immunological or clinical criteria, or due to toxicity, and switching them timeously. In all environments, providing support to adherence will continue to be a priority, even in a world with safer and better drug regimens.

Acknowledgements WDF Venter is supported by PEPFAR/USAID, UNITAID, the Bill and Melinda Gates Foundation, Aids Fonds and the South African Medical Research Council.

Compliance with Ethical Standards

Conflict of Interest Dr. WDF Venter declares grant support for dose optimisation studies from Bill and Melinda Gates Foundation, USAID, UNITAID and South African Medical Research Council; declares the donation of study drug from Viiv Healthcare and Gilead Sciences and declares speaking honoraria from Mylan, Aspen, Gilead Sciences, Adcock Ingram, and J&J Pharmaceuticals. Dr. Venter is a also PI on a second-line dose reduction study (referenced within the paper). He is also on multiple local and international committees advising on antiretroviral regimen selection.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Fauci AS, Marston HD. Ending the HIV-AIDS pandemic—follow the science. N Engl J Med. 2015;373(23):2197–9. doi:10.1056/NEJMp1502020.
2.• Barnhart M, Shelton JD. ARVs: the next generation. Going boldly together to new frontiers of HIV treatment. Glob Health Sci Pract. 2015;3(1):1–11. doi:10.9745/GHSP-D-14-00243. **Excellent summary fo current thinking about how to use new ARVs**
3.• Clinton Health Access Initiative 2016, ARV market report: the state of the antiretroviral drug market in low and middle income countries, 2015–2020, http://www.clintonhealthaccess.org/content/uploads/2016/10/CHAI-ARV-Market-Report-2016-.pdf. Accessed 20 Nov 2016 **This regular report is an extremely useful resource in understanding medication pipelines and volumes, and how ARVs are being used in LMICs**
4. WHO, Geneva, Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, recommendations for a public health approach—second edition; http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed 01 Oct 2016
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 20 Nov 2016
6. Sing T, Däumer M. Interpretation algorithms, in: antiretroviral resistance in clinical practice. London: Mediscript; 2006. Chapter 6.
7. Bunupuradah T, Kiertiburanakul S, Avihingsanon A, Chetchotisakd P, Techapornroong M, Leerattanapetch N, et al. Low-dose versus standard-dose ritonavir-boosted atazanavir in virologically suppressed Thai adults with HIV (LASA): a randomised, open-label, non-inferiority trial. Lancet HIV. 2016;3(8):e343–50. doi:10.1016/S2352-3018(16)30010-8.
8. Venter WDF, Evaluation of low-dose darunavir in a switch study, registered at ClinicalTrials.gov at ClinicalTrials.gov Identifier: NCT02671383
9.•• Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med. 2014;371(3):234–47. doi:10.1056/NEJMoa1311274. **One of the major second line ARV papers, validating WHO's approach in using blind sequencing for second line PI-based therapy**
10.•• SECOND-LINE Study Group, Boyd MA, Kumarasamy N, Moore CL, Nwizu C, Losso MH, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet. 2013;381(9883):2091–9. doi:10.1016/S0140-6736(13)61164-2. **Another major important paper examining sequencing to PIs in second line**
11.• I-Base, Pipeline report 2016, London, http://i-base.info/htb/wp-content/uploads/2016/07/2016-Pipeline-Report.pdf Accessed 20 Nov 2016 **A regular, critical resource on the ARV (as well as hep C, TB and diagnostics/monitoring) pipeline, and how clinical studies on individual drugs are faring**
12.• Brenner BG, Wainberg MA. Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance. Virus Res. 2016. doi:10.1016/j.virusres.2016.07.006. **Major examination of the near-unbreakable genetic barrier seen with dolutegravir, and the implications of this for sequencing**
13. de Boer M, van den Berk G, van Holten N et al., Intolerance of dolutegravir containing cART regimens in real life clinical practice. AIDS 2016
14. Sabranski M, Wyen C, Welz T, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients HIV drug therapy conference, Glasgow 2016
15.• Raffi F, Pozniak AL, Wainberg MA. Has the time come to abandon efavirenz for first-line antiretroviral therapy? J Antimicrob Chemother. 2014;69(7):1742–7. doi:10.1093/jac/dku058. **Critical discussion paper on the future role of efavirenz**
16. Li H, Marley G, Ma W, Wei C, Lackey M, Ma Q, Renaud F, Vitoria M, Beanland R, Doherty M, Tucker JD. The role of ARV associated adverse drug reactions in influencing adherence among HIV-infected individuals: a systematic review and qualitative meta-synthesis. AIDS Behav. 2016
17. Botswana treatment guidelines, Gaborone, 2016 http://www.moh.gov.bw/Publications/Handbook_HIV_treatment_guidelines.pdf. Accessed 15 Nov 2016
18. Firnhaber C, Reyneke A, Schulze D, Malope B, Maskew M, MacPhail P, et al. The prevalence of hepatitis B co-infection in a South African urban government HIV clinic. S Afr Med J. 2008;98(7):541–4.