Editorial

Observing the revolution: A commentary on the new GeSIDA HIV guidelines

Observando la revolución: un comentario sobre las nuevas directrices GeSIDA VIH

Margherita Bracchi\textsuperscript{a}, Anton Pozniak\textsuperscript{a,b,*}

\textsuperscript{a} St Stephen’s AIDS Trust, Chelsea and Westminster Hospital, London, UK
\textsuperscript{b} Chelsea and Westminster Hospital NHS Foundation Trust, London, UK

Who would have predicted what has been recommended in these new GeSIDA HIV guidelines? In the ‘what to start’ section, out go all the old favourites in the preferred list, replaced only by integrase inhibitors (INSTIs).

The new guidance could be interpreted as far-sighted by some and over-ambitious by others, but without doubt is in the vanguard of the ‘revolution’ in HIV guidelines worldwide.

In a way, these Spanish guidelines reflect the ‘end of an era’. AIDS related events, prevention of AIDS progression, and virological failure are, for the majority of patients, troubles of the past. Research is increasingly focusing on issues of ageing, long-term tolerability, impact of antiretrovirals (ARVs) on non-AIDS related morbidity, regimen simplification, drug interactions and, of course, costs. Concerns that are clearly reflected in this new version of the guidelines.

Before moving on to the contentious section of what to start, it has to be said that the sections on switching and virological failure are exemplary. They are comprehensive and guide the clinician clearly through the various options. There is not much new in the sections on acute HIV infection, agreeing with the view of most HIV physicians to treat as soon as possible, and continue long term. The sections on tuberculosis and pregnancy are again similar to those published by other guidelines, reflecting the level of data we have for those conditions. It is surprising that lopinavir/ritonavir is the only treatment of choice mentioned in pregnancy, and that the use of an integrase for those presenting late with a detectable viral load is omitted. The issue of co-infection with hepatitis B and the preferred use of tenofovir/emtricitabine or lamivudine should be highlighted more in the tables and text, as this point is sometimes overlooked by physicians. The dominance of integrases has yet to make it into the section on HIV-2.

Similarly to their previous guidance, and to what is recommended in the DHHS HIV guidelines,\textsuperscript{1} this new version maintains the recommendation to start antiretroviral therapy (ART) in all patients, regardless of CD4+ count. The rationale behind starting ART at high CD4+ lymphocytes is to improve patient’s health by reducing on-going inflammation, diminishing prevalence of non-AIDS defining illnesses, and preserve immune-function. At the same time, it is an essential strategy for the reduction of HIV onward transmission, as ‘Treatment as Prevention’ (TasP). Increasing ART coverage can lead to decline in HIV incidence at a population level, and studies conducted in serodiscordant couples have shown strong evidence of the efficacy of treating the positive partner in reducing probability of transmission to the uninfected one.\textsuperscript{2}

Importantly, while previous evidence on earlier commencement of ART was controversial (as the only data came from large observational studies conducted in North America, Europe and Australia, and from secondary analyses of randomised trials), new evidence has finally been provided by major randomised clinical trials such as TEMPRANO\textsuperscript{3} and START\textsuperscript{4} (‘Strategic Timing of AntiRetroviral Treatment’). In the latter study, 4685 HIV naïve patients with CD4++500, from 35 different countries, have been enrolled to compare immediate versus delayed treatment, evaluating differences in onset of AIDS diagnoses, serious non-AIDS diagnoses, and all-cause mortality. The DSMB recommended stopping the study after an average follow-up of three years, as it showed a lower risk of both AIDS-related events and serious non-AIDS related events in the early treatment arm. Importantly the risk of developing serious illness or death was reduced by 53% (41 events for early group versus 86 events for deferred ART group). Many felt the START trial should not have gone ahead as the answer to ‘when to start’ was to them already clear. However the trial showed that it was not the expected cardiovascular events that occurred in the deferred group but it was tuberculosis, and cancers including lymphoma and Kaposi’s sarcoma, that drove the difference, suggesting immunosuppression and oncogenic viruses rather than inflammation were responsible. It also appears that CD4s are not useful predictors of disease progression above 350 cells. GeSIDA
should feel pleased that they have advocated early treatment for so long, although the reasons for doing so now need to be partly revised.

Earlier ART for all, however, means longer exposure to ARVs throughout a patient’s lifetime. We are in an era where effective and well-tolerated ART is available. Until the perfect regimen, which is simple, with no toxicity or side-effects, no resistance and no drug interactions, exists, guidelines will still have to make choices of which regimens are preferred based on clinical trial data. To date most guideline panels usually include several classes of third agent drugs combined with nucleosides.

This new version of the guidelines introduces a revolutionary change in the recommended first line regimens for naïve patients. Agents that have been preferred options during the past decade, like efavirenz and the protease inhibitors (PIs), are now relegated to alternatives, leaving the podium solely to the INSTI class.

It is remarkable that the same data can be interpreted differently by various guideline panels. For example, these guidelines are different from the current DHHS HIV guidelines, which have kept darunavir in the preferred regimens mainly based on the ACTG 5257 results.3 The DHHS included all INSTIs but the current Spanish guidelines have as preferred first line options only two INSTIs, dolutegravir and raltegravir, and excluded elvitegravir.

The new draft BHIVA guidelines have also demoted efavirenz but kept atazanavir, darunavir, rilpivirine and all INSTIs.

Why is there so much variation? One can understand the rationale of what is ‘in’ when analysing all the trials. Dolutegravir was superior to efavirenz and darunavir at the primary endpoint of SINGLE2 and FLAMINGO, and raltegravir was superior to efavirenz at the 192 week time point in STARTMRK4 and superior to darunavir and atazanavir in ACTG 5257.

But, more interestingly, what are the reasons for drugs that are ‘out’?

Removing efavirenz from first choice is a growing trend for guidelines committees and the DHHS and draft British guidelines have also done the same, no doubt soon to be followed by IAS-USA and EACS, though we need to wait and see!

The tolerability/toxicity that has made efavirenz inferior in the trials has been compounded by the data on increased suicidality linked to efavirenz from the ACTG,5 data not supported by cohort analyses.

However the message of rejecting efavirenz must be confusing to the majority of the world who follow the current WHO guidance. Efavirenz works at all CD4+ counts, has been used for over a decade, has excellent forgiveness and can be used in pregnancy and tuberculosis, so why abandon it? Is there any chance of an efavirenz come back? Although the use of reduced dose efavirenz in ENCORE-1 has an economical advantage, it did not eliminate significantly CNS toxicity. It is unlikely that high resource countries will promote this strategy to ‘preferred option’ in the guidelines, even if it was safe in pregnancy and tuberculosis, unless the European economy became the driving force for recommendations.

We await the new WHO guidance to be released at the end of the year, as it will be difficult for them to ignore the dolutegravir and ENCORE-1 data, and equally difficult for them to abandon the current recommended use of cheap, easily available, efavirenz in a single tablet regimen.

The other non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine has not made the preferred list either, as it is complicated by viral load thresholds, food restrictions, and drug interactions, particularly with proton pump inhibitors. Most guidelines with rilpivirine in the preferred list have footnotes explaining these restrictions, but there seems to be no room for the drug, or any such footnote, in the Spanish HIV treatment ‘Primera División’.

Not having NNRTIs as first choice may appear radical enough, but having no PIs may be a bridge too far for many, including the DHHS who have kept darunavir. PIs are agents of choice in those who need treatment and have no resistance test available. They still have an important role in patients with potential poor adherence, or at high risk for intermittent toxicity, as demonstrated in many years of clinical use. There are notes in this guidance mentioning these qualities, but the danger is that physicians may look to the preferred list and start using dolutegravir, instead of PIs, based on its evolving resistance data.

In defence of the guidance, a logical view of recent data would show that, as raltegravir was superior to both atazanavir and darunavir in ACTG 5257, and dolutegravir superior to darunavir in FLAMINGO, the PIs should be alternatives. However most, if not all, of this superiority was driven by tolerability or toxicity. In ACTG 5257, which was open label, the patients could switch for any tolerability or toxicity issues, and many came off atazanavir because of jaundice, hyperbilirubinemia and gastro-intestinal disturbance. These events occurred mainly in those with grade 3–4 hyperbilirubinemia, which, according to the British guidelines writing group is harmless, and not of clinical significance. Of note is that the rates of switch due to these adverse events in ACTG 5257 was 4–8 times that seen when using atazanavir in ATCG 5202, Gilead 103 and 114, or the BMS CASTLE studies.

Are these older studies less reflective of real life than ACTG 5257? It seems that ‘zero tolerance’ of intolerance is driving the GeSIDA guidelines choice.

Darunavir has also been eclipsed. In ACTG 5257 there were more viral failures on darunavir than atazanavir (115 versus 95), but this does not help in any argument to keep the drug in a recommended position. In FLAMINGO dolutegravir was superior, but the study was open label, and so patients could abandon their arm if they did not get their preferred choice. INSTIs cause rapid drops in viral loads whereas PIs can still be reducing the viral burden even out to 48 weeks and beyond, which can bias some virological endpoints against PIs. No resistance mutations have been seen with virological failure in many naïve studies of darunavir or atazanavir, nor in clinical practice. This characteristic is shared in the naïve trials by dolutegravir, but we need to have more real world data to confirm this. The same genetic barrier story cannot be told about raltegravir, where resistance, cross-resistance to elvitegravir, and partial cross-resistance to dolutegravir, have been observed in both naïve and experienced subjects who were failing, as reported from the STARTMRK, ACTG5257 and the SWITCHMRK studies.

Elvitegravir has also been abandoned to the lower league. It needs to be pharmacoenhanced with cobicistat (thus complicating drug interactions), it has only been non-inferior to efavirenz and atazanavir, and affects serum creatinine (as does dolutegravir). Therefore the reasons for its use appear to be outweighed by its simplicity as a one pill once a day treatment. Again differences in interpretation arise with the DHHS and draft British guidelines, continuing to recommend it.

When looking at the overall clinical trial data, this choice just to have the INSTIs dolutegravir and raltegravir as recommended first line agents is easily understandable. They are potent and have few side effects and drug interactions. Another advantage may be the rapid drop in viral load, and this may be useful to limit the time someone might transmit when used as TasP or in late pregnancy, or possibly in acute seroconversion for symptom relief and, perhaps, in limiting the size of the reservoir. Only dolutegravir comes in a single pill regimen and thus far can be given once a day, limiting any claim that the guidance favours simplicity.

However data on INSTIs has mainly come from asymptomatic Caucasian MSM with low CD4+ counts and high viral loads, who attend good research centres. The Pharma companies are trying hard to do studies in women and people of colour, as well as giving the drugs to late presenters, and those with high cardiovascular
risk. The recent WAVES study\textsuperscript{11} has shown superiority of Stribild over boosted atazanavir in women, and it will be interesting to see how GeSIDA react to it. Pregnancy data is being collected and tuberculosis studies are completed or underway, and it may take a few more years to have the body of evidence and data for INSTIs that we possess for NNRTIs and PIs.

Meanwhile the elephant in the room can no longer be ignored, the GeSIDA choice is an expensive line up. They may be supported by cost-effectiveness studies but few payers concern themselves with the long term and want to know how much things will cost in any financial year. A cost-analysis study conducted to evaluate long-term cost-effectiveness of DTG + ABC/3TC versus EFV/TDF/FTC from a United States (US) payer perspective, (using data from the SINGLE study), has postulated that treatment with DTG + ABC/3TC will result in higher costs, and only slightly increased QALYs over a lifetime. From cost-effectiveness prospective, therefore, it is unknown whether the use of DTG + ABC/3TC may not be advantageous enough to justify the incremental increase in costs.\textsuperscript{12}

According to a cost-efficacy analysis of the 2014 GeSIDA/Spanish National AIDS Plan guidelines for antiretroviral therapy in naive adults,\textsuperscript{13} Eviplera and Atripla were the most efficient in terms of cost/efficacy, with regimens containing integrase inhibitors being less expensive due to higher costs.

Cost differences between antiretrovirals may impact our care more than we expect in the near future, as more antiretrovirals will become available as generic formulations. Patents of efavirenz, abacavir and lamivudine have already expired, and tenofovir, darunavir and atazanavir ones will expire in 2017. A cost analysis performed in the UK shows that systematic switching from patented to generic antiretrovirals could save over £1.1 billion in five years.\textsuperscript{14} How relevant will guidelines be, if payers insist that we do as they say? In London the payers have recommended efavirenz and kivexa as first choice. Few data can defend this, except for those based on cost.

Finally, are these guidelines too restrictive? Do they reflect clinical practice in 2015? Do they interpret the available clinical data and come to rational conclusions?

On balance they do, but as with all documents the devil is in the detail: the text is extremely important, and those that just use the tables to guide their practice may be led astray.

There are footnotes of caution to be added however. Our total experience with INSTIs is limited. For example, there have been case reports of psychiatric disorders on dolutegravir\textsuperscript{15} and ongoing pharmacovigilance is important to ensure that such symptoms are, or not, associated with the drug. Abacavir, once out of fashion, is back, and the argument over cardiovascular risk has not gone away. The practical implications of implementing such guidance in a Europe struggling financially, where cheap generics are available, or on the horizon, may turn the guidelines into a ‘wish list’. It is important to be financially prudent but we hope that the trinity of randomised clinical trial data, expert opinion, and patient involvement distilled into such guidelines will continue to drive our prescribing practices.

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**References**


