CHAPTER 3

South African guidelines and introduction to clinical cases

3.1. South African national antiretroviral guidelines

When this book was published in 2012 the current national antiretroviral treatment guidelines were those published by the Department of Health in April 2010[1]. There have, however, been subsequent amendments to the guidelines in response to important developments in the evidence base.

The main goals of the South African Antiretroviral Treatment Guidelines 2010 were to achieve the best health outcomes in the most cost-efficient manner, to implement nurse-initiated treatment, to decentralize service delivery to primary health care (PHC) clinics and to retain patients on lifelong therapy. The objectives of the guidelines were to contribute to the strengthening of the public and private health sectors' capacity to deliver high quality health and wellness services, to ensure timely initiation of ARVs and to minimize unnecessary drug toxicities.

More specific objectives of the 2010 national guidelines were to prioritize ARVs for specific categories of patients: those with CD4+ cell counts < 200 cells/μl or with WHO stage 4 disease irrespective of CD4+ cell count; and TB co-infected patients or pregnant women with CD4+ cell count ≤350 cells/μl. In August 2011 the CD4+ cell count cutoff was increased to 350 cells/μl for all patients[2]. In May 2012 a directive from the national Department of Health recommended that all HIV-infected TB patients be initiated on ART regardless of CD4+ cell count, in line with the National Strategic Plan[3,4]. Table 3.1 summarizes the current eligibility criteria for antiretroviral therapy (ART) in South Africa

TABLE 3.1 *South African eligibility criteria for starting antiretroviral therapy (ART) in adults and adolescents (as of May 2012)*

Eligible to start ART:
1. CD4+ cell count ≤ 350 cells/μl irrespective of clinical stage
2. Stage IV disease irrespective of CD4+ cell count
3. Active TB disease irrespective of CD4+ cell count

For the first six years of the national antiretroviral programme, first-line ART regimens were based on an NRTI backbone of stavudine (d4T) and lamivudine (3TC). Reducing the use of d4T was a specific objective of the South African 2010 guidelines. This was due to the long-term toxicities of d4T, e.g. symptomatic hyperlactataemia/lactic acidosis, peripheral neuropathy, and lipodystrophy. The standardized adult first-line national regimen in the new guidelines was TDF/3TC/EFV or TDF/3TC/NVP. Patients currently on d4T-based regimens with no side-effects were advised to continue the existing regimen. An early switch was suggested if any toxicity was detected or if there was a high risk of toxicity, e.g. high body mass index (BMI), older female. TDF was contraindicated in the presence of significant renal impairment (creatinine clearance <50ml/min) and AZT was recommended for those cases.

In terms of the NNRTI component of the regimen, EFV was preferred for TB co-infection whereas NVP was preferred for pregnant women and women of child-bearing age. In May 2012

this guidance was updated to recommend EFV for all patients (including pregnant women and women of child-bearing age) unless specific contra-indications exist, e.g. unstable psychiatric disease[5]. The rationale for this was based primarily on the evidence of harm from nevirapine, with both liver failure and Stevens-Johnson syndrome increasingly seen as causes of maternal mortality[6].

The South African Antiretroviral Treatment Guidelines 2010 recommended routine laboratory monitoring for patients on ART. Viral load (VL) tests are recommended at months 6 and 12 on ART and then every 12 months in stable patients. The recommended responses to viral load results are illustrated in FIGURE 3.1. The recommended adult second-line regimen was TDF/3TC/LPVr for patients who failed on a d4T- or AZT-based first-line regimen; and AZT/3TC/LPVr for those who failed on a TDF-based first-line regimen.

Third-line or salvage regimens were not specified in the guidelines. The only specification was that patients failing any second-line regimen should be referred to a specialist.

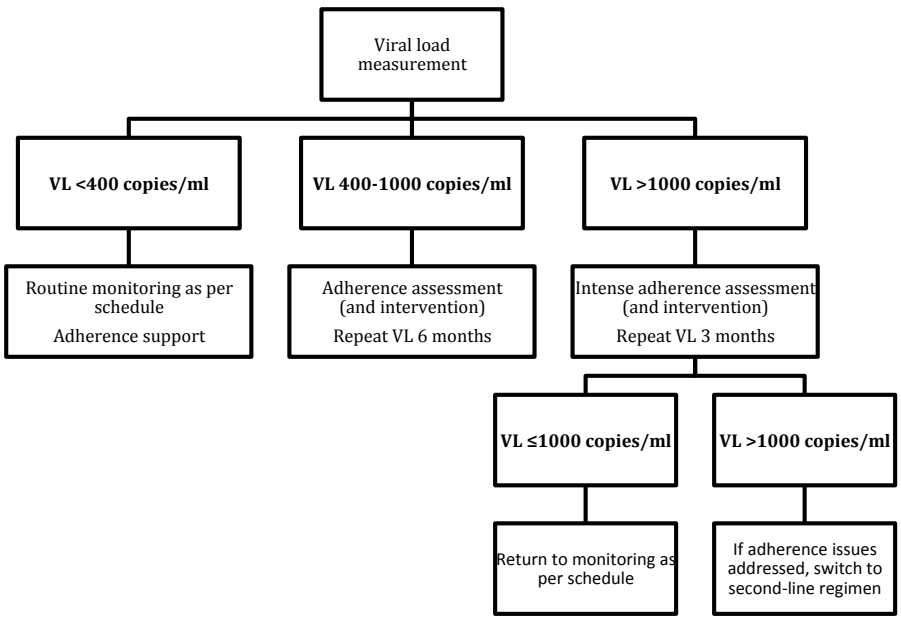


FIGURE 3.1 *Viral load monitoring and recommended responses*

3.2. South African national TB guidelines

The current national TB guidelines (2009) aim to provide guidance to primary health care personnel and managers in addressing the challenges of TB control and successfully managing all clients presenting with TB, including those co-infected with HIV, as well as early detection of drug-resistant TB[7].

The guidelines recommend diagnosis of TB based on sputum AFB smears and culture, with the use of additional investigations for smear-negative pulmonary and extrapulmonary disease. Treatment is based on standardised regimens and benefits from the use of fixed-dose combinations (FDCs):

New cases (regimen 1): 2HRZE/4HR

The national implementation of the Xpert MTB/RIF assay will inevitably lead to changes to the treatment guidelines, with the early identification of drug-resistant disease allowing optimisation of treatment regimens and removal of the standardised re-treatment regimen[8]. The algorithm for Xpert MTB/RIF-based diagnosis and management was shown in FIGURE 2.5. It is likely that this algorithm will be modified as evidence is accumulated about the operational use of Xpert MTB/RIF.

3.3. Integrating HIV and TB guidelines and research in South Africa - National Strategic Plan 2012-2016

To prevent the spread of HIV, STIs and TB infections and to mitigate the impact of the dual HIV and TB epidemics in society, the Department of Health (DoH) has developed a National Strategic Plan (NSP) that will shape the way the department handles these diseases for the next five years (2012 -2016)[4]. What distinguishes this plan from others is the fact that it will treat the epidemics as a state of emergency; the plan includes putting measures in place that will enable everyone to know their HIV status and to be screened for TB.

The integration of TB, HIV and STIs is also a very interesting aspect of the current NSP. This should allow health workers and health professionals to integrate TB and HIV diagnosis and treatment at primary health care. This will ultimately ensure that TB patients who are also infected with HIV are initiated on ART in a timely fashion regardless of their CD4+ cell count. This will hopefully reduce the number of preventable deaths and will also help to fight the stigma associated with HIV and TB.

In April 2012, the DoH invited many of the top researchers and public health officials to a summit in Johannesburg in order to discuss research priorities for HIV & TB as part of the current NSP. At this meeting, research priorities for the next five years were identified and ranked. HIV & TB drug resistance ranked high in the priority list.

The DoH has called on all sectors of society, organizations and individuals to collaborate in the implementation of this strategic plan. We, the authors of this book, support this initiative and are already in talks with the Department of Health, as part of the Southern African Treatment and Resistance Network (SATuRN), to find better solutions to the growing threat of HIV and TB drug resistance. One of the major objectives outlined by the NSP is sustaining the health and wellness of patients on ART and we believe that this open access book will facilitate this task.

3.4. HIV cases introduction

This book presents 14 clinical cases related to HIV-1 drug resistance. These cases were carefully selected from our clinical practice to highlight important points. Many of the cases highlight errors in management that could have contributed to the emergence of drug resistance but these are all real and we believe it is only by collectively learning from our mistakes that we can advance our clinical practice and ultimately benefit our patients.

"The only real mistake is the one from which we learn nothing" (John Powell)

A common feature of all the HIV cases is that they used the SATuRN RegaDB Drug Resistance Database to construct a complete clinical chart and resistance report for each patient[9]. The SATuRN/RegaDB database allows all of the laboratory results, treatment regimens and clinical information to be collated to construct a clinical chart for the patient (FIGURE 3.2). The clinical chart presents four pieces of information: treatment regimen (i.e. drug names, start and stop date), the date of the drug resistance test, clinical test results for CD4+ cell count and viral load.

For example, FIGURE 3.2 illustrates the treatment history for a patient who in May 2008 started a first-line regimen of d4T/3TC/EFV. These drugs are represented in grey at the bottom of the figure. The patient's pre-initiation CD4+ cell count was 108 cells/μl. This patient had a suboptimal initial virological response to antiretroviral therapy (ART) with VL 1300 copies/ml at six months, but then exhibited virological suppression (VL < 25 copies/ml) at 12 months. Subsequently, she had three VL >5000 copies/ml despite step-up adherence counselling. Genotypic resistance testing was performed in June 2011. This is represented by the vertical dotted line in graph.

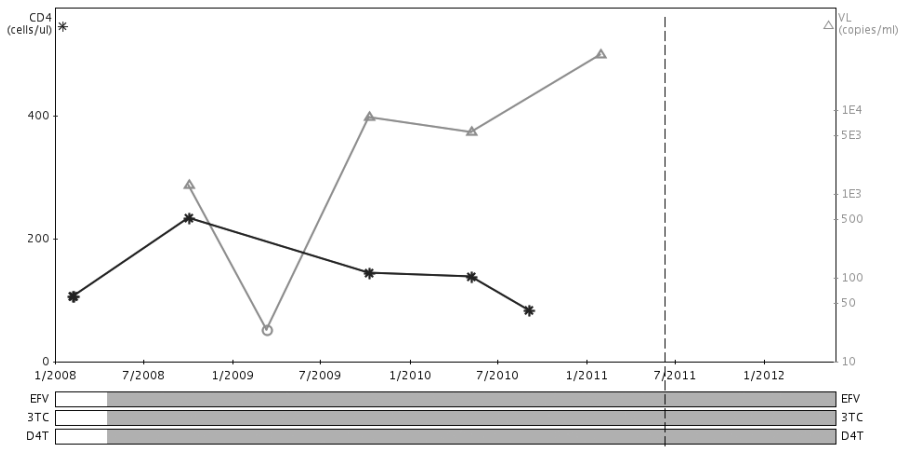


FIGURE 3.2 *Patient clinical chart*

RegaDB SATuRN database also interprets the drug resistance genotype using the Stanford HIVDB algorithm[10]. The drug resistance interpretation results are normally presented in table format (TABLE 3.2), which contains the drug resistance mutation lists, the interpretation of the resistance levels per drug, the level of the resistance and the genotypic susceptibility score (GSS).

TABLE 3.2 *HIV-1 drug resistance interpretation table*

Drug	Mutations	Description	Level	GSS
zidovudine	None	Susceptible	1	1.0
zalcitabine	N/A	N/A	N/A	N/A
didanosine	None	Susceptible	1	1.0
lamivudine	None	Susceptible	1	1.0
stavudine	None	Susceptible	1	1.0
abacavir	None	Susceptible	1	1.0
emtricitabine	None	Susceptible	1	1.0
tenofovir	None	Susceptible	1	1.0
nevirapine	None	Susceptible	1	1.0
delavirdine	None	Susceptible	1	1.0
efavirenz	None	Susceptible	1	1.0
etravirine	None	Susceptible	1	1.0
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r	None	Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r	None	Susceptible	1	1.0
nelfinavir	None	Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r	None	Susceptible	1	1.0
lopinavir/r	None	Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r	None	Susceptible	1	1.0
tipranavir/r	None	Susceptible	1	1.0
darunavir/r	None	Susceptible	1	1.0

TABLE 3.2 summarises the resistance level. This table has been generated using the Stanford HIVDB 6.0.5 algorithm[10]. The result shows that no HIV-1 drug resistance mutations were detected in this patient. Her HIV population is still susceptible to all ARVs. The level of resistance for all drugs is 1 (values range from 1 to 5, where 1 denotes susceptible and 5 denotes high-level resistance). The GSS score for all drugs is 1.0 (values range from 0 when the drug is considered likely to be inactive due to complete resistance and 1.0 when the drug is likely to be fully active).

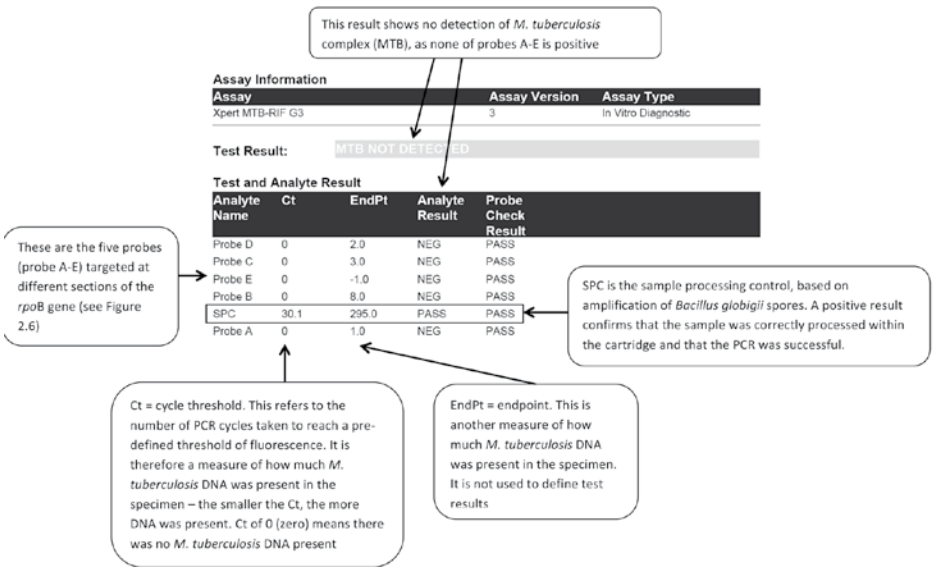
Each HIV case is presented with the clinical chart and drug resistance tables with accompanying interpretation and clinical recommendations from an expert clinician, as provided in real time through the programmes supported by SATuRN. Each case also contains a questions and answers section, which is followed by key learning points and references.

3.4. TB cases introduction

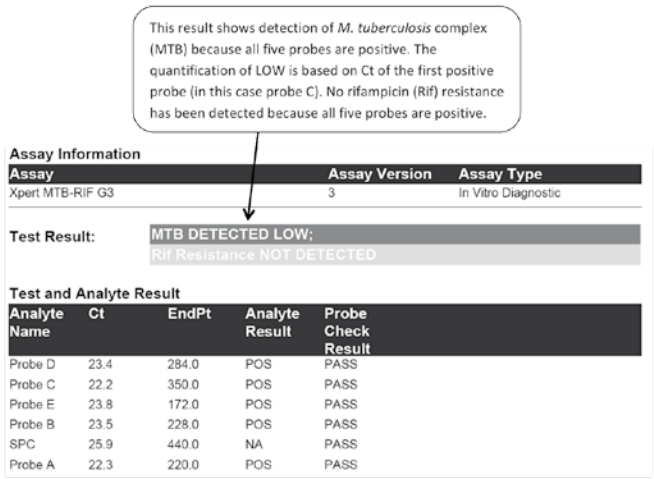
The six TB cases have been selected to highlight certain points about the diagnosis of drug-resistant TB. Five of the cases include the use of the Xpert MTB/RIF test and some cases also involve the use of the Genotype MTBDR*plus* assay (line probe assay). Guidelines and algorithms do not always cover every clinical situation that we face in our work at clinics and hospitals and the rapid roll-out of these new technologies presents new challenges for the health care workers on the ground that are tasked with interpreting diagnostic test results and making management decisions for individual patients. The aim of these cases is to enable health care workers to familiarize themselves with these tests and to highlight not only the key strengths but also some of the limitations of these technologies.

FIGURE 3.3 shows results generated by the Xpert MTB/RIF assay, with explanation of the different elements. FIGURE 3.4 demonstrates the Genotype MTBDR*plus* assay. These are included for educational purposes but it should be noted that a standard laboratory result is likely to report only a positive or negative result for the presence of TB and as susceptible or resistant with respect to drug resistance.

A



B



C

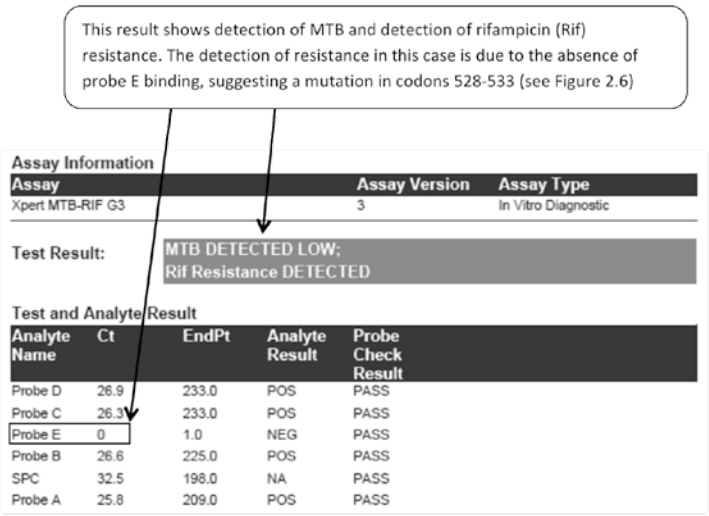


Figure 3.3 *Results of Xpert MTB/RIF test: Xpert negative (A); Xpert positive, rifampicin susceptible (B); Xpert positive, rifampicin resistant (C)*

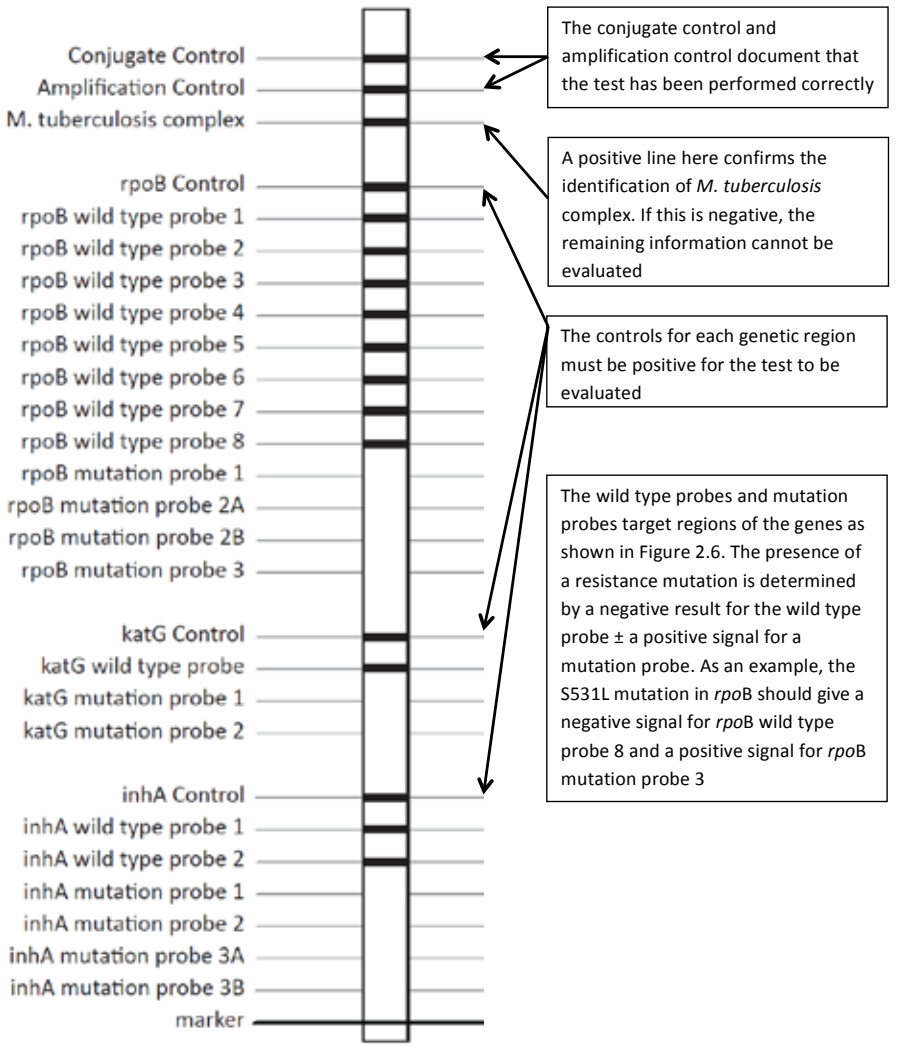


Figure 3.4 *Example of Genotype MTBDRplus assay*

3.5. References

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