Kingdom of Cambodia

Nation Religion King

Ministry of Health

Switching Protocol for Phasing Out

The Use of d4T among HIV Patients on ART in Cambodia

November 2013

National Center for HIV and AIDS, Dermatilogy and STI (NCHADS)

Preface

Base on clear recommendation of World Health Organization (WHO) on long-term toxicities of d4T and with the objective of treating all eligible HIV-infected patients in Cambodia with optimal ARV regimens, the Ministry of Health has approved the demotion of d4T-based first line regimens. This phase out of d4T-based regimens constitutes the latest effort in Cambodia to align with the international guidance and growing evidence of poor treatment outcomes among patients who remain on sub-optimal regimens, such as first line containing d4T regimens, for extended periods.

The Ministry of Health also appreciates the National Center for HIV/AIDS, Dermatology and STD (NCHADS), and all development partners for their leadership and contribution in developing this d4T phase-out and switching protocol. This protocol will provide guidance to all implementers, including clinicians, pharmacists and program implementers to smoothly phase out d4T-based regimen in adult and pediatric HIV patients.

The Ministry of Health has officially endorsed this protocol and is confident that all concerned stakeholders will follow and support the implementation of the protocol to ensure that Cambodian HIV-infected patients are offered with an optimal ART regimen associated with better tolerability and patient outcomes in the long term.

Phnom Penh, ๒๕ November 2013

Prof. ENG HUOT
SECRETARY OF STATE

Acknowledgements

The National Centre for HIV/AIDS Dermatology and STD (NCHADS) would like to appreciate and express our thanks to all NCHADS, AIDS Care Unit staff, FHI 360, CHAI, UNICEF, US-CDC and WHO staff who have actively contributed to the successful development of the d4T Switching Protocol for Cambodia.

Our special thanks to the CHAI country team in Cambodia for their active participation in collecting and compiling inputs from local and international experts to develop this important protocol.

Phnom Penh, 13 November 2013

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1 Background

Cambodia's response to the HIV epidemic has been one of of the most successful in the Western Pacific Region: HIV incidence has decreased from its peak at 20,978 new HIV infections in 1995 to 1,780 new infections in 2010. This decline continues each year, with a projection of 1,007 new infections in 2015. It is estimated there are 75,000 people living with HIV, of whom 51,000 are in need of ART. Cambodia has achieved the universal access target for HIV treatment, with over 90 percent of adults and children in need receiving ART and approximately 95 percent on first line treatment.

The National Center for HIV/AIDS, Dermatology and STD (NCHADS) has been very adaptable and responsive to new evidence and international guidance. In many regards Cambodia has anticipated WHO recommendations and already implemented appropriate changes to its ARV program, for example through expanding ART to all asymptomatic HIV positive individuals including pregnant women and individuals with HIV/TB regardless of CD4 count.

The 2010 WHO guidance recommended the demotion of d4T as a non-preferred first line regimen. Nevertheless, in Cambodia a substantial proportion of patients remain on d4T based first line regimens. At the end of quarter one of 2013, there were approximately 20,238 adult patients on d4T-based first line regimens, representing 44% of all adult patients on ART in Cambodia. Similarly, approximately 68% of pediatric patients were on d4T based regimens at the end of Q1 2013, despite the recommendation in the Cambodian national guidelines that AZT be used as a preferred first line NRTI. As the long term toxicities of d4T are widely recognized, Cambodia is now actively preparing to transition first line patients on to preferred regimens.

2 Rationale

The main rationale for phasing out the use of d4T in both adult and pediatric patients is due to the long-term toxicity of d4T experienced by patients in Cambodia.

One of the most common side effects of d4T is lipodystrophy. A study of lipodystrophy in pediatric HIV patients in Thailand found that 9 percent had developed some form of lipodystrophy after 48 weeks, 16 percent after 72 weeks and 65 per cent by 144 weeks

on d4T[1]. A recently published follow up study monitoring 45 of these children showed that by 48 weeks after switching from d4T to zidovudine, 59 percent of children with fat atrophy and 40 percent of children with abnormal fat accumulation had recovered.[2]

Changes in body fat distribution (lipodystrophy) have been reported to occur in 1%–33% of children with HIV infection in clinic-based case series.[3] It has been found more commonly in adolescents than in pre-pubertal children.[4]

HIV infected children may be more prone to d4T toxicity in the long run due to their longer exposure to d4T because of initiating ARV at a younger age. In order to prevent d4T long-term toxicities in children who have been on d4T for at least a year, it is important to develop a systematic approach to switching d4T to AZT before toxicities develops and become irreversible.

A 2012 retrospective study [5] conducted by the Sihanouk Hospital Center of Hope (SHCH) in Phnom Penh provided estimates of long-term toxicity related to stavudine (d4T) up to six years after treatment initiation. In a cohort of 2,581 adults initiating a d4T-containing regimen, 7% of patients experienced peripheral neuropathy within the first year. After the first year, lipoatrophy became predominant with a cumulative incidence of 56% by year 3 and 72% by year 6. Use of d4T also significantly increased the risk for lactic acidosis among people on concurrent TB treatment. Isoniazid use has increased for preventive therapy against incident tuberculosis and has overlapping toxicity risk of peripheral neuropathy.

In addition, in light of the 2013 WHO consolidated guidelines for the use of ARV for the treatment and prevention of HIV infection[6] and due to more recent updates on the use of tenofovir (TDF) for Treatment as Prevention and for prevention of mother-to-child transmission, NCHADS plans to use TDF as a preferred first-line (1L) regimen for adult

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[1] Aurpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-54

[2] Aurpibul L, Puthanakit T, Taejaroenkul S, Sirisanthana T, Sirisanthana V. Recovery From Lipodystrophy in Human Immunodeficiency Virus-infected Children After Substitution of Stavudine With Zidovudine in a Non-nucleoside Reverse Transcriptase Inhibitor-based Antiretroviral Therapy. Pediatr Infect Dis J. 2011 Nov 23.

[3] Babl FE, Regan AM, Pelton SI , Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals. Lancet, 1999. 353(9160):1243-4.

[4] Beregszaszi M Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children.J Acquir Immune Defic Syndr, 2005. 40(2):161-8.

[5] Phan V et al. Incidence of Treatment-Limiting Toxicity with Stavudine-Based Antiretroviral Therapy in Cambodia: A Retrospective Cohort Study. *PLoS ONE* 7(1): e30647 (2012)

[6] WHO consolidated guidelines for the use of ARVS for the treatment and prevention of HIV infection, 2013

patients on ART and AZT as a preferred first-line (1L) regimen for pediatric patients in 2013 onwards. Although the WHO 2013 guidelines recommend TDF for children older than 2 years, there is currently no generic product available for pediatric patients.

TDF-containing regimens have a lower pill burden for adult patients and a once daily dosing frequency. Patients are more likely to adhere to simpler, less toxic regimens. Better adherence improves treatment outcomes and prevents drug resistance from developing and slowing the need for more complex and expensive second-line regimens.

A TDF-based regimen is recommended for HIV/hepatitis B (HBV) co-infection. Long-term treatment with TDF has been shown to achieve profound and durable HBV virological suppression leading to less liver damage and improved function in Asian populations [7], whereas d4T has no activity against HBV.

Most importantly, the longer patients are kept on d4T, the more their second-line options are compromised, especially if they are failing their first-line regimen because of the accumulation of thymidine analogue mutations (TAMs). Unlike d4T, TDF does not confer TAMs accumulation; therefore, people taking TDF can stay on a failing regimen much longer without compromising efficacy of AZT as component of a second-line therapy[8].

From a pharmaceutical supply chain management perspective, proper planning is also needed to minimize or avoid drug wastage through expiries. It is also important to plan for the switch of new and existing patients from d4T to more optimal regimens to ensure uninterrupted availability of both drugs for patients at sites and to avoid any stock outs of ARVs.

3 Objective of protocol

This protocol provides guidance for clinicians, pharmacists and program implementers to phase out d4T-based regimens in adult and pediatric patients. The sections below will describe the clinical and programmatic steps for clinicians to proactively demote the use of d4T in all first line patients in their cohorts. Section 4 addresses how to demote d4T

[7] Pan CQ, Hu KQ, Tsai N. Long-term therapy with nucleoside/nucleotide analogues for chronic hepatitis B in Asian patients. Antivir Ther. 2012 Nov 23. doi: 10.3851/IMP2481. [Epub ahead of print]
[8] http://www.sajhivmed.org.za/index.php/sajhivmed/article/view/813/652

in first line for Adults and Section 5 addresses how to demote d4T for Pediatric patients according to the following subsections:

- Who to switch to or initiate on TDF-based First Line regimen
- What to switch to or initiate among First Line patients
- When to switch to or initiate a TDF-based First Line regimen
- How to switch or initiate a TDF-based based First Line regimen

4 Implementing the Drug Transition for d4T adult patients

4.1 Who to switch to or initiate on TDF-based First Line ART

- All new adult patients initiating ART for the first time should be prescribed a TDF-based First Line regimen
- All existing adult patients on a d4T-containing first-line regimen should be prescribed a TDF-based First Line regimen
- Patients on second line regimens should not be switched

4.2 What to switch to or initiate among First Line adult patients

All eligible existing first line adult d4T patients and all new patients should be started on or switched to:

TDF+3TC+EFV (triple fixed-dose combination ARV)

4.3 When to switch to or initiate a TDF-based First Line regimen

Clinicians should begin switching adult patients to TDF-based regimens during regular patient consultations from November onwards. The aim is to switch 20% of existing d4T patients to TDF every month until all patients have been switched based on available supply of TDF products.

4.4 How to switch to or initiate a TDF-based First Line regimen

Step 1: Before initiating or switching to TDF-based regimen:

- As a general rule, when considering switching d4T- to a TDF-containing regimen, clinicians should:
    - Review adherence to current regimen
    - Review CD4 cell count data

- Review viral loads if available (especially if suspected treatment failure)
- Review risk factors for underlying renal dysfunction or diseases

All new and existing patients should be evaluated for the following risk factors for TDF-associated renal dysfunction:

- Older age (> 50 years)
- Low body weight (< 50 kg)
- Untreated diabetes
- Uncontrolled hypertension
- Previous history of renal disease
- Use of nephrotoxic drugs

- If the patient presents with one or more risk factors from the list above, they may have underlying renal diseases or kidney dysfunction, and it is therefore recommended to draw a blood test for serum creatinine levels before initiating or switching to a TDF-based regimen.

- Patients can only be initiated or switched to TDF-based regimens if their creatinine clearance is greater than 50 ml/min.

- If serum creatinine testing is not available, clinicians are advised to assess for presence of glycosuria and/or proteinuria by urine dipstick analysis.

- For existing patients on a d4T regimen, clinicians must also ascertain that they are not already failing their d4T regimen by assessing their CD4 count or Viral Load levels, in accordance to national guidelines. Adherence counselling should be provided to support the switch to TDF.

Step 2: Initiation of TDF-based regimen

- If the patient does not have any underlying renal diseases, clinicians may then proceed to start the new patient on a TDF-based first line regimen.

- Patients should be prescribed a once-daily triple fixed dose combination (FDC) containing TDF/3TC/EFV 300/300/600mg. If patients develop intolerance to EFV, clinicians may consider the use of nevirapine (NVP) as an alternative NNRTI. In this case, patients should be prescribed AZT/3TC/NVP (as TDF/3TC+NVP is a non-preferred regimen).

- If patients are not eligible to switch to TDF, they may be switched to an AZT-based regimen as an alternative. Patients should be evaluated for anemia risk factors prior to initiating AZT.

Step 3: After initiating or switching to a TDF-based regimen:

- For all patients initiating TDF, draw a serum creatinine blood test six months after initiation to assess patient's renal function and then every 12 months thereafter.

- All patients must have a urine dipstick analysis to test for Fanconi syndrome 6 months after initiating TDF, and every 12 months thereafter.

How to calculate creatinine clearance:

Creatinine Clearance should be calculated using the ***Cockcroft-Gault formula:***

(140-age) x (wt in kg) x (0.85 if female)/(72 x creatinine pl.* mg/dL)

µ-mol to mg conversion rule: µ-mol x 0.113 = mg

Examples of calculation:

1. *For a 35-year old man, weight = 55kg with a plasmatic creatinine at 0.7 mg/dl:*
   Creat. Cl = (140-35) x (55)/(72 x 0.7)= 114.6 ml/min

2. *For a 30-year old woman, weight = 50kg with a plasmatic creatinine at 1.5 mg/dl:*
   Creat. Cl = (140-30) x (50) x 0.85/(72 x 1.5)= 43.3 ml/min

** Creatinine used in this formula is from a blood test. Creatinine monitoring is essential prior to starting a TDF-based regimen.*

Notes for clinicians:

- Selection of an appropriate TDF-based regimen is dependent on the patient's medical history on ART and must be considered on a case-by-case basis

- Avoid administering TDF with concurrent or recent use of nephrotoxic drugs (such as NSAIDS (e.g. aspirin, ibuprofen), aminoglycoside antibiotics (e.g. gentamicin, amphotericin and TB antibiotics like rifampicin)

- All existing adult patients on a d4T-containing first-line regimen should be switched to an alternative NRTI, where clinically appropriate. However, priority should be given to those already exhibiting long-term d4T toxicities such as lipodystrophy and neuropathy.

Serum Creatinine:

- While the serum creatinine gives an indication of renal function, patients can have significantly reduced renal function with a serum creatinine in the high normal range. This is particularly the case in older people and those with low body weight where the serum creatinine is a poor indication of renal function. Therefore, it is essential to calculate the creatinine clearance in all patients with:
    - Age > 50 years
    - Weight < 50kg
    - Serum creatinine > 100 micromol/L (or 11.3 mg/L)

- In all other patients where serum creatinine is < 100 the calculated creatinine clearance is likely to be > 50 ml/min and they can safely start Tenofovir.

- Creatinine may be elevated in acute illness, and repeat measurement when the patient has recovered may give a better reflection of clearance.

4.5 Potential TDF side effects after switching

TDF is classified as a nucleotide reverse transcriptase inhibitor but functions as an NRTI equivalent in ART regimens. It is very well tolerated with few side effects. Nausea, vomiting and diarrhea can occur and are usually mild. TDF has been associated with Fanconi syndrome and decreased creatinine clearance, including in rare cases, acute renal failure (about 7/1000). Because HIV disease can cause renal impairment, ARV treatment (including with TDF regimens) is associated with improved renal function[9].

[9] National guidelines on use of antiretroviral therapy in adults and adolescents in Cambodia, 2012

4.6 Drug Interactions with TDF

- **Didanosine:** The association with ddI is highly not recommended as it might have a negative effect on the immune reconstitution.
- **Atazanavir:** Coadministration decreases atazanavir concentrations and increases TDF concentrations. Use atazanavir with TDF only with additional ritonavir. Monitor for evidence of TDF toxicity.
- **Lopinavir/ritonavir:** Coadministration increases TDF concentrations. Monitor for evidence of TDF toxicity.

5 Implementing the Drug Transition for d4T pediatric patients

5.1 Who to switch to or initiate on AZT-based First Line ART

- All new pediatric patients initiating ART for the first time should be prescribed an AZT based first line regimen
- All existing pediatric patients on a d4T-containing first-line regimen should be prescribed an AZT based first line regimen
- Patients on Second Line regimens containing d4T should not be switched

5.2 What to switch to or initiate among First Line pediatric patients

All eligible existing first line d4T patients and all new patients should be started on or switched to:

AZT+3TC+NVP

5.3 When to switch or initiate patients on AZT-based First Line ART

Clinicians should begin switching pediatric patients to AZT-based regimens from December onwards based on sufficient supply of AZT-based products.

5.4 How to switch or initiate AZT-containing first-line ART

Step 1: Before initiating or switching to AZT-based regimen:

- All new and existing patients should be evaluated for any potential anemia if they present with the following signs and symptoms:

- **Symptoms:** dizziness, tiredness, weakness, shortness of breath, headaches
- **Signs:** pallor (of the skin, tongue, conjunctiva); weak, elevated or irregular pulse, poor capillary refill

- For all patients it is necessary to draw a blood test for hemoglobin levels before initiating or switching to an AZT-based regimen.

- Patients can only be initiated or switched to AZT-based regimens if their hemoglobin level is greater than Hb ≥ 7.5 g/dl.

Step 2: Initiation of AZT-based regimen

- If the patient does not have any anemia, clinicians may then proceed to start the new patient on an AZT-based first line regimen.

- For existing patients on a d4T regimen, clinicians must also ascertain that they are not already failing their d4T regimen by assessing their CD4 count and % or Viral Load levels, in accordance to national guidelines.

- All new pediatric patients initiating ART for the first time should be prescribed AZT+3TC+NVP (triple fixed-dose combination ARV)

- All existing pediatric patients on a d4T-containing first-line regimen, should be switched to AZT+3TC+NVP (triple fixed-dose combination ARV)

- Patients should be prescribed a triple fixed dose combination (FDC) containing AZT/3TC/NVP, with the appropriate dosage according to their weightband.

- Efavirenz (EFV) is not currently recommended for use in those under 3 years or under 10 kg due to the lack of clear pharmacokinetic data to guide dosing in these children.

- In children older than 3 years and over 10 kg, EFV is the NNRTI of choice when receiving rifampicin-based TB therapy. In this case, they should be prescribed the dual FDC of AZT/3TC plus a single EFV tablet.

- For children who cannot tolerate AZT-based regimens, ABC based regimens should be used as alternative First Line. Refer to guidelines for detailed guidance.

Step 3: After initiating or switching to a AZT-based regimen:

- AZT requires monitoring of hemoglobin levels 8 weeks after treatment initiation

- Clinicians should consult the National Guidelines or seek expert advice if they are unsure about complex patient cases.

Notes for clinicians:

- Selection of an appropriate AZT-based regimen is dependent on the patient's medical history on ART and must be considered on a case-by-case basis
- AZT should not be used in cases of severe anemia Hb < 7.5g/dL), in which case patients should be switched to ABC-containing regimens (for guidance on NNRTI selection clinicians should refer to the National Guidelines for Use of Pediatric ART in Cambodia).
- AZT requires monitoring of Hb 8 weeks after treatment initiation.
- Clinicians should consult the National Guidelines or seek expert advice if they are unsure about complex patient cases.

When switching a patient to an AZT-based regimen, clinicians should:

- Review side effects with the patient or caregiver
- Discuss how to manage common AZT side effects, including ways to contact clinic staff for advice
- Educate the patient or caregiver on the reasons for switching
- Review the appropriate dose and show the patient or caregiver the new formulation so they are familiar with it
- Switching can occur directly at the right dose; there is no need for a gradual or "lead-in" transition
- Schedule a follow-up in 2 weeks to assess for intolerance.

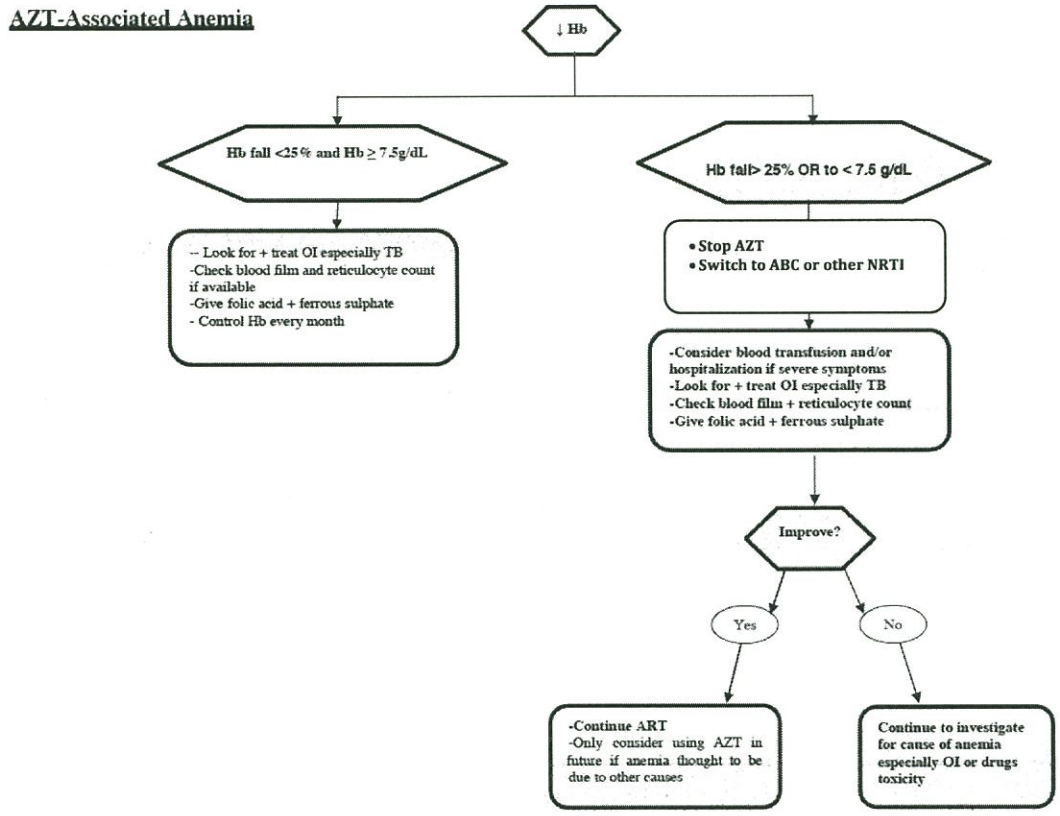
5.5 Management of potential AZT side effects after switching

Mild side effects of AZT include nausea, vomiting, headache and fatigue. More severe side effects include myopathy, anemia and mitochondrial toxicity. During follow-up, AZT side effects should be managed as follows depending on their severity:

Notes for clinicians:

- Clinicians are advised to consult the National Guidelines for the use of ART in children, particularly, Annex H: Flow diagrams for clinical management of AZT toxicities
    - AZT-associated anemia

Figure 1: Management of AZT-associated anemia[10]



6 Logistic and Supply Management

6.1 Timeline for switching

Clinicians should plan to switch 20% of already enrolled d4T adult patients every month (starting November 2013 to proactively switch the majority of patients by end of March 2014) to TDF-based first line regimens.

Clinicians should plan to switch 20% of existing pediatric d4T patients every month (starting January 2014) to achieve the phase-out of d4T in the majority of patients AZT by April 2014.

[10] National guidelines for the use of pediatric antiretroviral therapy in Cambodia, 2011

6.2 Supply plan

The estimated time of delivery of the next shipment of TDF drugs is November 2013. This will coincide with the dissemination of a NCHADS Official Letter during October 2013 to allow d4T switch to start in November 2013.

6.3 Communication

It is important for the clinicians at all Pre-ART/ART sites to communicate with the purchasing pharmacists regarding the estimated changes in patient numbers who will be switched from d4T to TDF (for adults) or to AZT (for pediatrics) so that accurate adjustments to the quarterly ARV request to NCHADS may be made in advance.

For any clarification of the supply and distribution plan, please contact NCHADS Logistic Management Unit.

6.4 Monitoring drug transition

Clinicians at Pre-ART/ART sites are advised to monitor the rate of switching based on the actual number of patients on d4T-based First Line regimens and number of patients switched to a TDF-based First Line regimen on a monthly basis.

At the national level, NCHADS would be tracking the progress across all sites similarly so as to ensure that the target for phasing out the use of d4T is reached.

7 Timeline and action plan

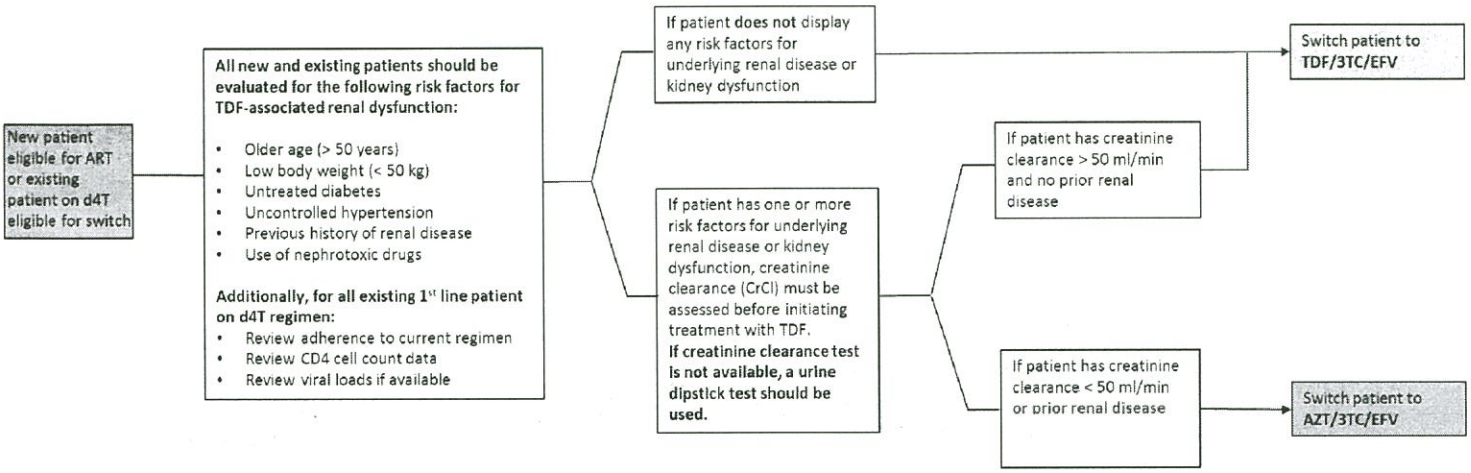
Below is an overview of the timeline and key activities in 2013 and 2014 to support the national phase out of d4T in Cambodia.

Timeline and action plan	
Revised forecast for 2013	January to February
Develop protocol on d4T switch	March
Development of monitoring tool	October
National Orientation Workshop on phasing out d4T	November

Dissemination of job aids for clinicians	November
NCHADS issue official instruction to all sites to switch all existing d4T patients	November
Monitoring and evaluation of switch in terms of patient numbers and consumption trends	November 2013 to June 2014
Final status report on d4T switch	July 2014

8 Decision tree

8.1 How to switch adult patients to TDF-based First Line regimens



8.2 How to switch pediatric patients to AZT-based First Line regimens