Overview of the HIV/AIDS antiretroviral medicines pipeline and existing products on the market: a focus on suitability for use in resource-limited settings

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
API	Active product ingredient
ARV	Antiretroviral
ART	Antiretroviral treatment
ATV	Atazanavir
AZT	Zidovudin
BMI	Body mass index
BMS	Bristol-Myers Squibb
CCR5	C-C chemokine receptor type 5
CHAI	Clinton Health Access Initiative
CNS	Central nervous system
COBI	Cobicistat
CXCR4	C-X-C chemokine receptor type 4
ddI	Didanosine
d4T	Stavudine
DHHS	Department of Health and Human Services (United States)
DNDi	Drugs for Neglected Diseases initiative
DRV	Darunavir
DTG	Dolutegravir
EC90	90% effective concentration
EFV	Efavirenz
EMA	European Medicines Agency
ETV	Etravirine
EVG	Elvitegravir
FDA	Food and Drug Administration (United States)
FDC	Fixed dose combination
GSK	GlaxoSmithKline
FTC	Emtricitabine
HIV	Human immunodeficiency virus
IMPAACT	International maternal pediatric adolescent AIDS clinical trials
INI	Integrase inhibitor
LPV	lopinavir
MSF	Médecins Sans Frontières
MVC	Maraviroc
NGO	Non-governmental organisation
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PACTG	Pediatric AIDS Clinical Trials Group
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetics
PEPFAR	President's Emergency Plan for AIDS Relief (United States)
PI	Protease inhibitor
RAL	Raltegravir
RTV	Ritonavir
RLS	Resource limited setting
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
UGT	UDP-dependent glycosyl transferase
UN	United Nations
WHO	World Health Organization

INTRODUCTION

For those with access to antiretroviral treatment (ART), HIV is now a manageable condition and last year's results from HPTN 052 showed ART can reduce onward transmission by a considerable 96% in serodiscordant couples (NIAD, NIH 2011).

Twenty-six antiretroviral (ARV) drugs are currently approved by the United States Food and Drug Administration (FDA) to treat HIV, alongside a further seven combination products. In addition, the pipeline looks hopeful, with several promising new compounds and formulations in phases 2 and 3 of development.

At first glance, the antiretroviral market may already seem quite crowded (FDA 2012). However, only a limited number of these ARVs are recommended for use in resource-limited settings (RLS) in the World Health Organization (WHO) guidelines, and fewer still are in routine use in national programmes in those settings. Furthermore, although existing antiretrovirals have saved millions of lives, most have significant shortcomings (WHO 2010).

This report provides an overview of existing and pipeline products used and with potential for use in RLS for adults and children. **The focus of this report is on the clinical suitability of antiretroviral treatments. Other key factors determining access to these products have been described elsewhere (see "further reading", below).** Information and analysis are current as of November 2012.

The discussion in this report is based on the target of having drugs and regimens that are suitable for easy use in decentralized care with minimal laboratory requirements. Ideal products must be tolerable, durable, heat stable, safe and effective for use across all CD4 strata, with high viral load, in men and women, in pregnancy, in children and with tuberculosis or viral hepatitis co-infection. They need also be available at the lowest possible cost.

Section 1 provides an overview of existing products and their limitations in their clinical and programmatic use and describes ongoing research into ways that these products and regimens could be optimized.

Section 2 looks at the nearer end of the pipeline with an emphasis on "high potential" products that are closer to market launch and/or could provide improvement over the existing products.

Further reading

The i-Base/TAG Pipeline Report reviews the latest developments in HIV, hepatitis C virus (HCV), and tuberculosis (TB) drugs, diagnostics, vaccines, and preventive technologies in development and is available as a regularly updated web report or PDF: http://www.pipelinereport.org

Some elements of this report have been adapted from the Pipeline Report 2012, with a particular emphasis on treatment in low- and middle-income countries.

Other sources of information that complement the clinical focus of this report include:

Untangling the Web of Antiretroviral Price Reductions, produced by Médecins Sans Frontières (MSF) Access Campaign. Includes details of pricing and patents: http://utw.msfaccess.org

ARV Ceiling Pricing List produced by Clinton Health Access Initiative (CHAI). Also focuses on antiretroviral pricing: http://www.clintonhealthaccess.org/news-and-information/ARV-Ceiling-Price-List-May-2012

The Patent Status Database for selected HIV Medicines of the Medicines Patent Pool. Provides information on the patent status of selected antiretrovirals in many low- to middle-income

countries: http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs

SECTION 1: EXISTING PRODUCTS

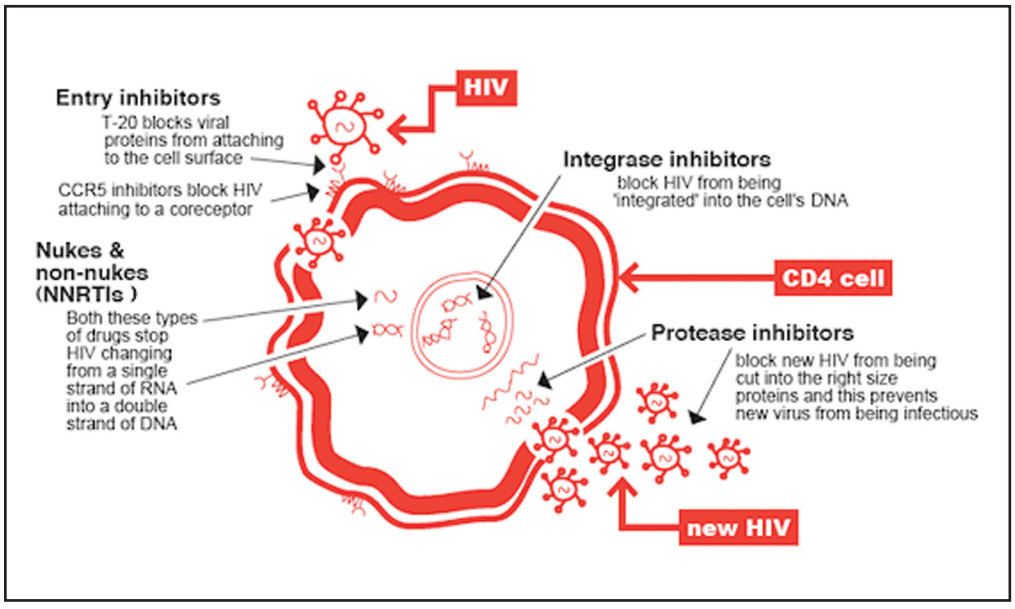
1.1 Overview of existing ARVs

There are five main classes of antiretrovirals that each work at a different stage of the HIV lifecycle (see Figure 1). These are nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTI/NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (INI), and entry inhibitors.

The drugs are given in combination, usually including three active drugs. Two NRTI/NtRTI and an NNRTI are most commonly given in RLS as a first-line regimen, as recommended by WHO. Protease inhibitors are used in second-line treatment (and more rarely first line).

Only one ARV is currently approved as a single agent in the newer integrase inhibitor class (raltegravir) and is very seldom used due to cost constraints. The FDA recently approved the elvitegravir-containing fixed-dose combination (FDC) Stribild (formerly QUAD, a combination product containing tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat), but its price is expected to also limit its use (Collins 2012). Entry inhibitors are still rarely used. Maraviroc, a CCR5 inhibitor, has the potential for wider use; enfuvirtide [T-20] is reserved for a tiny minority of extensively resistant patients (WHO 2010, DHHS 2012).

Figure 1: HIV lifecycle – how antiretrovirals target different stages



Introduction to Combination Therapy (April 2012), i-Base.

Regimens are facilitated by a choice of single and dual agents, fixed-dose combinations (FDCs) and co-blister packs. The WHO prequalification programme now includes up to 278 finished pharmaceutical products in the list of prequalified antiretrovirals, with 88 of them being coformulations (including 37 triple FDCs or co-packs for first-line regimens, and quadruple copack formulation for second line) (WHO 2012). Likewise, the FDA has already provided approval (or tentative approval) for 156 generic single adult and paediatric antiretroviral formulations, including 32 triple FDCs and co-blister packs, for treatment in RLS programmes, including PEPFAR (FDA 2012).

The majority of generic products are single, dual and combinations of NRTI/NtRTI and NNRTIs with a few protease inhibitors.

Table 1: *WHO recommended ARVs: Medicine class, year of adult approval and role in current standard of care*

Compound	Class	Year of approval by FDA for adult use	Originator	Comments
Didanosine (ddI)	NRTI	1991	Bristol-Myers Squibb	2nd line if no other options. Preferably replaced by 3TC.
Emtricitabine (FTC)	NRTI	2003	Gilead	Recommended for both 1st and 2nd line. Considered interchangeable with 3TC.
Lamivudine (3TC)	NRTI	1995	Viiv Healthcare	Recommended for both 1st and 2nd line.
Stavudine (d4T)	NRTI	1994	Bristol-Myers Squibb	No longer recommended.
Tenofovir (TDF)	NRTI	2001	Gilead	Recommended in 1st or 2nd line (if not used in 1st line).
Zidovudine (AZT)	NRTI	1987	Viiv Healthcare	Recommended in 1st or 2nd line (if TDF used in 1st line).
Efavirenz (EFV)	NNRTI	1998	Merck and Co	Preferred NNRTI in 1st line.
Etravirine* (ETR)	NNRTI	2008	Janssen	Tentative recommendation for 3rd line.
Nevirapine (NVP)	NNRTI	1996	Boehringer Ingelheim	Alternative to EFV in 1st line (widely used for PMTCT).
Atazanavir (ATV)	PI	2003	Bristol-Myers Squibb	Preferred 2nd line.
Atazanavir/ ritonavir (ATV/r)	bPI	2011	Mylan	Preferred 2nd line. Co-formulated heat stable generic.
Lopinavir/ritonavir (LPV/r)	bPI	2000	Abbott	Preferred 2nd line. Most widely used PI.
Darunavir* (DRV)	PI	2006	Janssen	Tentative recommendation for 3rd line.
Ritonavir (RTV/r)	PI	1996	Abbott	Recommended as booster.
Raltegravir* (RAL)	Integrase inhibitor	2007	Merck	Only currently approved drug in this class. Tentatively recommended for 3rd line.

*WHO current recommendation for 3rd line but this recommendation is subject to access.
Please, consult Medicines Patent Pool database for information on current patent status of each product (http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/).
Sources: WHO 2010, FDA 2012, MSF 2012.

First-line regimens

WHO currently recommends an NNRTI-based first-line regimen, in which the preferred option is tenofovir/lamivudine/efavirenz formulated as a once daily FDC (WHO 2011). Use of efavirenz/tenofovir-based regimen for first line in RLS represents treatment that is on a more equal footing with that in US or Europe, for example, where the recommended first line is tenofovir/emtricitabine/efavirenz, given as a once daily FDC (Atripla) (DHHS 2012).

Second-line regimens

Second-line treatment – based on boosted heat-stable protease inhibitor-based regimens – is not yet facilitated by convenient FDC formulations (or co-blister packs where co-formulation is not feasible). The WHO Expert Committee on the Use of Essential Medicines lists protease inhibitor-based FDCs as key missing formulations. Currently lopinavir/ritonavir is the most widely used boosted protease inhibitor (Medicines Patent Pool 2011).

WHO suggests an atazanavir/ritonavir-based second-line regimen could be the preferred option for treatment optimization (WHO 2011). A heat stable generic atazanavir/ritonavir-based FDC is now available and has been tentatively approved by FDA since November 2011, being marketed at lower prices ($304 per person per year) (MSF 2012) than, for instance, the third PI option, darunavir, for which no co-formulation is yet marketed.

Third-line regimens

A second generation NNRTI, etravirine, the boosted protease inhibitor darunavir and ritonavir, and the integrase inhibitor raltegravir are tentatively recommended for use in nucleos(t)ide-sparing combinations for third-line treatment. These are all currently extremely costly, with $913, $1137, and $675 minimum prices per person per year, respectively (MSF 2012). Third-line recommendations are currently less clear than those for first or second line; there are no generic compounds or FDCs, and access is extremely limited.

1.2 First- and second-line treatment

1.2.1 Shortcomings in current first- and second-line treatment

Although currently used and recommended options have saved millions of lives, toxicities, monitoring requirements, and inadequate suitability for use across all populations mean that better alternatives are still required to make it possible to treat all those in need.

Toxicity is a major cause of discontinuation of treatment. Dose reduction studies of existing drugs may help to improve tolerability. New drugs will need to have superior tolerability to those currently used. It should be noted that in RLS many people receiving treatment are using stavudine-based combinations. A recent London study reported that twenty percent of participants discontinued tenofovir/emtricitabine/efavirenz for central nervous system (CNS) side effects associated with efavirenz (Zheng 2011) (see Table 2: Limitations of WHO recommended first and second-line ARVs).

Table 2: *Clinical Limitations of currently recommended first and second-line ARVs*

Compound	Cautions	Comment
Zidovudine (AZT)	• Gastrointestinal, proximal myopathy • Bone marrow suppression: macrocytic anaemia or neutropenia • Lipoatrophy • Skin and nail hyperpigmentation with black skin • Insulin resistance/diabetes mellitus	• Low CD4 and low BMI associated with increased risk of anaemia • Twice-daily dosing
Tenofovir (TDF)	• Low cumulative renal toxicity (<5%) • Moderate reduced bone density during first 6 months then relatively stable • Potentially easier resistance pathway for K65R in subtype C • Active against hepatitis B • TDF level increased by PIs	• Renal monitoring may be more important in elderly, those with low weight; those taking concomitant renal toxic drugs or with diseases such as diabetes and hypertension • Once-daily dosing
Lamivudine (3TC)	• Active against hepatitis B	• Generally well tolerated and widely used ARV as part of a three-drug regimen • Once-daily dosing
Emtricitabine (FTC)	• Hyperpigmentation/skin discoloration • Active against hepatitis B	• Generally well tolerated and widely used ARV as part of a three-drug regimen • Once-daily dosing • Considered interchangeable with 3TC

Table continued on next page

Compound	Cautions	Comment
Efavirenz (EFV)	• CNS side effects (abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Risk may increase with drug levels (genetics, high fat meal). ~ 20% people discontinue • Caution during first trimester of pregnancy • Interactions with oral contraceptives (not ethynyl estradiol) • Dyslipidemia. Metabolic body fat changes • Rash, Stevens-Johnson syndrome, and hepatotoxicity • Drug interactions include rifapentine, cisapride, midazolam, triazolam	• CNS side effects generally reduce within 2-4 weeks but may persist indefinitely in some patients • Once daily dosing. Not with high fat meals
Nevirapine (NVP)	• Rash, Stevens-Johnson syndrome, and hepatotoxicity. Higher risk in women • Not recommended as starting treatment when CD4 >250 (women) and >400 (men) • Drug interactions include rifapentine	• Once or twice daily (approved twice-daily, often used once-daily in stable suppressed patients)
Lopinavir/ ritonavir (LPV/r)	• Gastrointestinal, diarrhoea • Dyslipidemia • Insulin resistance/diabetes mellitus • PR interval prolongation • Metabolic body fat changes • Broad potential drug interactions include rifampin, rifapentine, some statins, cisapride, midazolam, triazolam, tenofovir	• Once or twice daily dosing (depending on resistance)
Atazanavir/ ritonavir (ATV/r)	• Gastrointestinal, diarrhoea • Hyperbilirubinemia • PR interval prolongation • Metabolic body fat changes • Dyslipidemia (with RTV boosting) • Nephrolithiasis • Broad potential drug interactions include rifampin, rifapentine, some statins, cisapride, midazolam, triazolam, PPIs and H2 receptor antagonists, tenofovir	• Generally well tolerated • Hyperbilirubinemia (may be managed by dose modification (+/- ritonavir) • Once-daily dosing

Table continued on next page

Compound	Cautions	Comment
Antiretrovirals no longer recommended by WHO but widely used		
Stavudine (d4T)	• Lipoatrophy (irreversible) • Peripheral neuropathy (irreversible) • Lactic acidosis. 50% fatal. Increased risk in women, high BMI) • Insulin resistance/diabetes mellitus	• Remains in use by >30% of people on treatment globally • Lipoatrophy (stigmatising) and neuropathy (debilitating pain) reported in >30% when reported • Reduced dosing (30 mg/20 mg twice daily only approximately halves incidence of side effects when reported)
Didanosine (ddI)	• Nausea and gastrointestinal • Lactic acidosis (increased risk in women, high BMI) • Pancreatitis, steatosis, prolonged exposure linked to noncirrhotic portal hypertension • Retinal changes • Insulin resistance/diabetes mellitus	• Remains second-line option in many countries where no other option is available • Dosing by body weight >/<60kg

Sources: WHO 2010, DHHS 2012

1.2.2 Strategies to optimize first- and second-line treatment

Discussions about dose optimization of antiretrovirals – particularly through appropriate dose reduction – have been ongoing for over a decade (Hill 2001, Hill 2010). More recently, research into these strategies has gained momentum given the potential to make treatment available to more people who need it at the lowest possible price. WHO has endorsed dose optimization as part of their commitment to the broader Treatment 2.0 initiative and have conducted consultations to consider future medium-term opportunities for optimizing ARVs and ART regimens. Based on existing research and the current ARV pipeline, CHAI have undertaken the execution and co-ordination of related research projects and the Bill and Melinda Gates Foundation are providing substantial donor support (WHO 2011, WHO 2012, CHAI 2012, Gates 2012).

There may be opportunities for dose optimization for several currently-approved antiretrovirals. These strategies offer several advantages:

- Reduction of the active pharmaceutical ingredients (API) used in a compound leads to reduction in price (API accounts for approximately 70% of the price of generic ARVs);
- Potential reduction in toxicities; and
- Reduction in volume that can make co-formulation easier (in resource limited settings, 80% of people are treated with FDCs).

Dose optimization mechanisms

There are several ways in which dose optimization might be accomplished:

Dose reduction: In order to achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (phase 3) – similar to those conducted by industry for the approval of a new drug – need to be conducted. It would take approximately three to six years to generate sufficient data to file with regulatory agencies, in addition to the time required for approval (about three months to a year). The estimated cost would be $15 to 22 million.

Reformulation: This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug. A reformulated compound will need bioequivalence studies (phase 1) with the approved formulation. The estimated time frame to regulatory filing is two to three years; the estimated cost would be $2 to 8 million.

Process chemistry: It may also be possible to alter the manufacturing process leading to more efficient and less expensive API production. For this strategy to be successful regulatory authorities would only need to see equivalent stability and purity data. This would take about one to two years at an estimated cost of $1 to 2 million.

Source: Crawford KW et al. Optimizing the manufacturing, formulation, and dosage of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement. Lancet Infect Dis. 2012;12(7):550–60.

A number of dose optimization strategies for antiretrovirals are currently ongoing or in discussion.

Tenofovir

Tenofovir is preferred as part of first-line treatment (in combination with lamivudine and efavirenz). It is currently broadly considered to be the best NRTI/NtRTI on the market and this is likely to continue for several years. In recent years the price of tenofovir has dropped considerably. A WHO prequalified generic tenofovir/lamivudine/efavirenz FDC is available at $172 per person per year (MSF 2012). There are, however, limits to further decreasing the price due to the high milligram dose (300 mg) used in the current formulation. This also makes it less easy to co-formulate with other antiretrovirals.

CHAI is currently working on reformulation of tenofovir in partnership with a generic manufacturer. Although the new dose has yet to be determined, the researchers anticipate a reduction by about a third. Additionally there are two new pro-drugs of tenofovir in development (see below).

Zidovudine

If tenofovir remains the preferred first-line NRTI/NtRTI, zidovudine is likely to be used second line in the short term. Although zidovudine is generally is better tolerated over the long-term compared to stavudine, its hematological toxicities (anaemia/neutropenia) remain a concern in many RLS.

The ongoing MiniZID study is assessing 200 mg versus 300 mg zidovudine twice daily (as part of a regimen with lamivudine plus an NNRTI), with reduction of anaemia as the primary endpoint. This 48-week phase 2 study in 136 treatment-naive patients is sponsored by the University of Geneva and is being conducted at the Hôpital de la Caisse Nationale de Prévoyance Sociale, Yaoundé, Cameroun. Recruitment began in August 2011 (clinical trials.gov NCT01540240). The study will not generate sufficient data for regulatory approval of the lower dose, but rather will provide proof of principle.

Some Asian countries such as Thailand and India already use the zidovudine 250 mg tablet twice daily. Thailand is already using 200 mg twice daily in patients weighing less than 50 kg.

Stavudine

Of all the dose optimization strategies proposed or ongoing, stavudine is the most controversial. Unlike the other antiretrovirals for which these strategies are being proposed or conducted, stavudine is no longer a preferred option due to its toxicity profile.

A proposed phase 3b study plans to compare 20 mg stavudine twice daily to 300 mg tenofovir once daily in approximately 1000 patients. The primary objective is to demonstrate the non-inferiority of stavudine to tenofovir (both in a regimen with lamivudine plus efavirenz) in treatment-naive patients, as determined by the proportion of patients in each regimen with undetectable viral load (< 200 copies/mL) at 48 weeks. The secondary endpoints are to evaluate the tolerability, overall safety and efficacy of 20 mg stavudine compared to tenofovir. The proposed trial would be conducted at sites in India, South Africa and Uganda and be sponsored by the Gates foundation.

This trial is concerning to many as it will not answer the long-term toxicity questions about stavudine. The 20 mg stavudine dose might be acceptable in a short-term 48- or even 96-week virologic endpoint study, but because mitochondrial toxicity is both dose- and time-dependent, many of stavudine's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. Although it looks at lipoatrophy, this study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

The stavudine parallel track programme, in which over 10,000 patients were randomized to receive 40 (30) mg or 20 (15) mg between October 1992 and February 1994, showed a higher incidence of neuropathy in the high-dose arm (21%). Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15%) (Anderson 1995).

In addition to concerns about cumulative toxicities, stavudine-related cost savings may become irrelevant by the trial's end. Through other dose optimization strategies and the expected approval of promising pipeline compounds (e.g. GS-7340 and dolutegravir, both described below), alternatives are likely to become available in a similar time frame that could drive regimen costs down with less risk to patient safety.

It is important to note that stavudine is unpopular with communities. For example the Malawi Network of People Living with HIV/AIDS (MANET+) held a press briefing to discuss concern over the slow pace phase-out of this drug in Malawi. Despite the funding crisis, the Malawi government has prioritized completing stavudine phase-out by June 2012. The Treatment Action Campaign in South Africa has also been very vocal in its opposition to the trial (TAG 2011, Goldacre 2011, Nkhoma 2011, Andrieux-Meyer 2012, Dubula 2012).

Efavirenz

Efavirenz is currently the preferred anchor drug. Price and possibly CNS toxicities could be reduced if a lower than the currently recommended 600 mg dose is possible.

The ENCORE 1 study, which began recruitment September 2011, is looking at 600 versus 400 mg of efavirenz in 630 treatment-naive patients. The ENCORE studies are designed to compare lower to approved doses of antiretrovirals[1] (clinicaltrials.gov NCT01011413). The primary endpoint for ENCORE 1 is the between-group comparison of the proportion of patients with viral load < 200 copies/mL 48 weeks. The complete follow up period is 96-weeks and there are sites in Europe, Australasia, Latin America, Asia and Africa. The trial is fully recruited and results are expected in 2013. ENCORE 1 has two sub studies designed to look at PK and CNS exposure (clinical trials.gov NCT01451333, NCT01271894).

If successful, this trial will generate sufficient data to gain regulatory approval and change WHO and other key treatment guidelines.

[1] Pharmacokinetic studies of lamivudine and lopinavir (ENCORE 2 and 3) have already been conducted as part of this programme with the conclusion that neither is a suitable candidate for dose optimisation
(J Antimicrob Chemother 2011; 66: 635–640 doi:10.1093/jac/dkq468 Advance Access publication 17 December 2010; http://aac.asm.org/content/early/2011/12/13/AAC.05599-11.abstract)

There are concerns about the drug/drug interaction with rifampicin TB/HIV coinfection if the efavirenz dose is reduced. The high API content of efavirenz is due in part to its poor water solubility. CHAI is in discussion about reformulation work to improve this.

Atazanavir

Dose reduction may also be possible with atazanavir. The HIV Netherlands Australia Thailand Research Collaboration, with some support from the Kirby Institute, is conducting a trial that will provide some evidence for this strategy (clinicaltrials.gov NCT01159223).

The low dose atazanavir/ritonavir versus standard dose atazanavir/ritonavir (LASA) study is comparing the efficacy and safety of atazanavir/ritonavir at either 200/100 mg or 300/100 mg once daily in Thai patients in combination with two NRTIs. This non-inferiority, phase 4 study with about 600 patients began recruiting in March 2011 and has a similar timeline to ENCORE 1. The study is enrolling patients who are already virologically suppressed to switch to the lower or standard dose of atazanavir.

This research is important for Thailand, as patients generally have a lower body weight and hyperbilirubinemia occurs quite frequently. It will be difficult to generalise the results from this study beyond the study population, but positive results would provide good reason to conduct a study in treatment-naive patients from a broader population.

This second-generation protease inhibitor is also poorly water-soluble and CHAI is looking at the possibility of reformulation.

Darunavir

Darunavir is generally considered to be the most durable protease inhibitor; however, there is no generic formulation and cost has been a barrier to its wide use. It also has differing approved doses for treatment-naive (including experienced but with no darunavir-associated mutations) and PI-experienced patients. Treatment-naïve patients receive darunavir and ritonavir at an 8:1 (800/100 mg) ratio once daily and experienced patients receive it at a 6:1 (600/100 mg) ratio twice daily. There may be potential for dose reduction to 400/50 mg.

The ratios also vary for children depending on their weight band and treatment experience. The establishment of single ratios for adults and children would make a simpler darunavir-based regimen and formulations more feasible.

CHAI is also looking at optimizing the formulation.

Ritonavir

It may also be possible to give atazanavir and darunavir with a lower boosting dose of ritonavir. Lower doses could be better tolerated, cheaper, and easier to co-formulate with PIs than the current dose.

If a 50 mg heat stable tablet of ritonavir could be manufactured, or if 50 mg ritonavir could be coformulated with either protease inhibitor, new bioequivalence trials would be needed to ensure the boosting effects were similar to those that have been achieved previously in small pharmacokinetic trials with the liquid formulation. A 50 mg ritonavir tablet would also be very useful for paediatric dosing, as the liquid is expensive, impractical (particularly for resource limited settings) and highly unpalatable (Hill 2011).

Lopinavir

The current tablet formulation of LPV/ritonavir is 118% bioavailable compared to the original gel capsule formulation. Taking a regulatory approach using existing data may be sufficient for the approval of a lower dose with this compound and this strategy has been discussed. Although lopinavir is currently the most widely used protease inhibitor, both atazanavir and darunavir could be considered to be better options, so this approach may not be pursued as it is of lower priority.

Table 3: *Approved ARV compounds with potential for dose optimization*

ARV Compound (current approved dose)	Drug class	Potential approaches	Outcomes	Comments
Tenofovir (300 mg once daily)	NtRTI	Reformulation	• New dose to be determined by research • >30% dose reduction anticipated	• Phase 1 likely to start Q4 2012/Q1 2013 • Possible reduction on incidence of renal and bone toxicities • Also promising pro-drugs GS-7340 and CMX-157 in development
Zidovudine (300 mg twice daily)	NRTI	Dose reduction	• Dose reduced to 200 mg twice daily • Potential $25 saving per person per year	• MiniZID Phase 3 study recruiting • Possible reduction of anaemia incidence
Stavudine (30 mg twice daily)	NRTI	Dose reduction and comparison with TDF	• Dose reduced 20 mg twice daily	• Likely to maintain unacceptable side effects even at lower dose because of the cumulative effect • Other drug developments likely to make this cost saving strategy unnecessary within the timeline for study and approval • Low acceptability by activists and doctors
Efavirenz (600 mg once daily)	NNRTI	Dose reduction Reformulation	• Dose reduced to 400 mg once daily • Potential $20 saving per person per year	• ENCORE 1 phase 3 study currently ongoing • May reduce CNS side effects (although not primary endpoint) • May be possible to reduce dose further still (300 mg) • Concerns about the impact on efficacy of TB/HIV co-treatment because of RMP interactions
Atazanavir/ritonavir (300/100 mg once daily)	PI	Dose reduction Reformulation	• Dose reduced to 200/100 • or 200/50 mg once daily • Potential $70 saving per person per year	• LASA Phase 3 study of 300/100 versus 200/100 • Potential for lower ritonavir boosting dose • Already cheapest PI

Table continued on next page.

ARV Compound (current approved dose)	Drug class	Potential approaches	Outcomes	Comments
Darunavir/ritonavir (800/100 mg once daily or 600/100 mg twice daily)	PI	Dose reduction Process chemistry	• Dose reduced from 800/100 to 400/50 mg once daily	• Best tolerated PI. Dose optimisation potential for PI-naive patients, but not for patients with PI resistance • Potential for lower ritonavir boosting dos • Dependent on regimen sequencing in patients who are PI-naive, dose reduction possible, but not if they have used a PI previously
Lopinavir/ritonavir (400/ 100 mg twice daily)	PI	Regulatory approach	• Daily lopinavir dose reduced from 800 to 665 mg (with current formulation)	• Registration trials were with earlier soft gel capsule formulation. Newer tablet formulation has better bioavailability (118%) with approved dose. Possible to reduce the lopinavir dose by 20% • Taking a regulatory approach is under discussion
Ritonavir (100 mg)	Booster	Dose reduction	• Boosting dose of darunavir and atazanavir reduced to 50 mg • Potential $20 saving per person per year	• Under discussion

Sources: CHAI, clinical trials.gov, Hill A 2012.

1.3 Third-line treatment

Even with the generally high response rate from first-line treatment, and the hope that second-line treatment, where it is available, will sustain most people for many years, an increasing number of people in RLS will need third-line antiretroviral treatment. With current third-line options severely limited based on cost and lack of generic formulations, current national guidelines either ignore this patient group or marginalize the description of their care to a few sentences.

In high-income countries, third-line treatment is based on second-generation protease inhibitors (darunavir, and to a much lesser extent tipranavir), integrase inhibitors (raltegravir) or, to a lesser extent, second generation NNRTIs (etravirine). Clinical response rates to subsequent combinations in RLS are generally expected to remain lower than those seen in settings where treatment changes are prompted by early virological failure.

In settings where each combination is maintained until clinical failure (defined by significant CD4 decrease or clinical symptoms), the impact of extensive development of resistance to all drugs in a combination, especially the accumulation of complicated patterns of reverse transcriptase and protease mutations, severely impairs the ability for other drugs from these classes to effectively contribute to the antiviral potency of subsequent combinations (Hosseinipour 2010). This is further supported by the very high early failure rate of the second-generation NNRTI etravirine in RLS due to the lack of available active drugs in the background combination (Ruxrungtham 2008). This concern will limit the use of integrase inhibitors, which have a vulnerability to resis-

tance similar to NNRTIs, if used in a sub-optimal combination, perhaps suggesting their future use in first-line treatment.

The development of different treatment algorithms for countries with limited or no access to viral load and resistance technology is likely to be required. Additionally, treatment strategies with non-standard combinations might have a specific role in these settings. In RLS, access to generic formulations of newer drugs for use earlier, in first or second lines (darunavir, raltegravir, and integrase inhibitors in development) has the potential to reduce the demand for third-line and later combinations by increasing the durability and success of first- or second-line regimens.

1.4 Paediatric treatment

Antiretroviral options currently recommended for children depend on age, exposure to nevirapine in prevention of mother to child transmission, a paediatric indication and an appropriate formulation.

Although fewer antiretrovirals are approved for children than adults, the market is highly fragmented with over 45 paediatric formulations available.

Despite incentives and penalties from regulatory agencies to originator manufacturers designed to ensure that children across all age groups benefit from these medicines, the disincentives to develop and manufacture them are considerable. Paediatric markets are smaller and less interesting to industry than those of adults. There is negligible demand for products in high-income countries – where paediatric HIV has been virtually eliminated – and the global demand will be unaffected by the growing case to provide treatment as prevention.

If maternal health and prevention of mother to child transmission programmes become more effective, the advantages to child health that this brings will reduce demand further in the paediatric market.

Despite all this, there has been significant progress in recent years in both pediatric research and treatment scale-up. UN agencies, international organizations like MSF and CHAI, UNITAID, and other major donors have made a concerted effort to highlight paediatric HIV and ensure children have access to the medicines they need.

Innovation from generic manufacturer Cipla – in the form of reduced strength tablets of the first adult FDC of nevirapine, lamivudine and stavudine – meant that young children in RLS could be treated with simpler and less expensive formulations than the liquids used largely in high income countries. But although these paediatric FDCs have saved many lives, the combination is not ideal, particularly as WHO extends the recommendation for use of protease inhibitors as first line for infants. Currently, WHO recommends lopinavir/ritonavir and two NRTIs as first-line regimen for children under two years with nevirapine exposure, and nevirapine and two NRTIs for those without known exposure (WHO 2010). This recommendation may change to a protease inhibitor-based first line for this age group regardless of exposure, and could even be extended to under 3 years old. To date, nevirapine-based regimens have been used most widely, especially as there is wider access to many age-appropriate FDCs for this combination than for protease inhibitor-based combinations.

There are now limited data to guide efavirenz use in children under three years of age, including with TB treatment, from IMPAACT 1070 (Bolton 2012). They suggest though that optimal use of EFV in this age group requires pre-treatment genotyping, clearly not feasible in most RLS. Dosing and formulation difficulties remain with this age group, with significant variability. The bioavailability of the oral formulation is reduced by 30% compared to the tablets. High doses, meaning large volumes of liquid, are needed to achieve adequate concentrations in plasma. Despite this, the drug will remain important until an alternative is found, as both nevirapine and protease inhibitors have drug-drug interactions with rifampicin, which complicates the treatment of HIV/TB co-infected children.

The recommended second-line treatment for children is lopinavir/ritonavir-based for children starting with an NNRTI, and NNRTI-based for those starting with lopinavir/ritonavir.

NRTI options have been more limited in children. Stavudine, zidovudine and abacavir are used most widely and included in FDCs with lamivudine. Similar toxicities to those seen in adults have been shown in all age groups of children receiving stavudine (Innes 2012, Shiau 2012).

The preferred adult option, tenofovir (approved for adults in 2001), has been slow to gain paediatric approval. This has been due in part to difficulties with the development of paediatric formulations, and also bone toxicity and maturation concerns. The FDA approved tenofovir for paediatric patients aged two to twelve in January 2012 (Gilead 2012). The approval includes three once-daily tablets in doses of 150 mg, 200 mg and 250 mg for children aged six to twelve years. The agency also approved an oral powder formulation for children aged two to five years.

WHO recently performed a review of the current published and unpublished data on the safety and efficacy of tenofovir in children (WHO 2012). This review found that based on the available data, tenofovir is effective in children and adolescents at current FDA-approved doses, but further studies are needed to confirm the dose and investigate the side-effects of tenofovir (decreased bone mineral density, and glomerular and renal tubular dysfunction for which data in children are very sparse).

If there is increased reassurance about the safety of tenofovir for children, it is expected that guidelines will begin to recommend, and programmes introduce, this drug more widely. Suitable solid formulations – to facilitate weight band dosing – of tenofovir/lamivudine/ efavirenz would help to align treatment for older children with that of adults.

The FDA approved the oral suspension of darunavir for children aged three to six years in December 2011 (FDA 2012). A heat stable darunavir/ritonavir-based FDC for children over three is a priority for second line, where lopinavir has been used in first-line treatment. There is not yet a single ratio of darunavir to ritonavir, which is needed in order for appropriate combination products to be developed.

For younger children, a better option than the current formulation of lopinavir/ritonavir is urgently needed. The syrup needs to be refrigerated, has very high ethylene glycol and ethanol content, and a highly unpalatable taste. A heat stable “sprinkle” formulation is currently in development.

Heat stable 25mg ritonavir for super boosting lopinavir/ritonavir during concomitant TB treatment is also a priority for children.

Importantly, last year, the Drugs for Neglected Diseases initiative (DNDi) – a collaborative, patients’ needs-driven non-profit drug research and development (R&D) organization – was asked by several international organizations to apply its expertise to the development of paediatric formulations of antiretrovirals to address the dearth in R&D focused on the needs of children with HIV/AIDS in RLS.

DNDi recently announced a new collaboration with Cipla to develop two optimized first-line regimen FDCs of lopinavir/ritonavir sprinkles, with one of two nucleoside backbones (either abacavir/lamivudine or zidovudine/lamivudine), as well as a super-booster ritonavir formulation for TB-coinfection.

The aim is to gain approval by 2015, to make the product affordable in the public sector in poor countries and to assist with registration and implementation.

SECTION 2: ANTIRETROVIRALS IN THE PIPELINE

There are currently a number of adult ARVs in the pipeline. This list is not exhaustive, but includes compounds that are filed with regulatory agencies, close to filing, and/or that might have the potential to offer advantages over existing products.

2.1 Nucleos(t)ide reverse transcriptase inhibitors

BMS-986001

This compound is an NRTI with a chemical structure similar to stavudine, but initial studies suggest that BMS-986001 could have a comparatively improved toxicity profile, as it is a weak inhibitor of DNA synthesis in cell studies. Bristol-Myers Squibb (BMS) acquired development and marketing rights to BMS-986001 from Oncolys BioPharma in December 2010 (BMS 2010).

Results from a phase 1b-2a dose escalation study were presented in September 2010 (Cotte 2010). BMS-986001 monotherapy was given for ten days to four groups of eight treatment- experienced patients currently not on treatment (6 active:2 placebo) using once-daily doses of 100, 200, 300, and 600 mg.

Mean reductions in viral load at day 10 were 0.87, 0.98, 1.36 and 1.22 log10/copies/mL in the 100, 200, 300, and 400 mg groups, respectively (vs -0.07 in the placebo group) from baseline levels. No pattern of side effects appeared over 10 days, with all grade 2-4 side effects judged unrelated to the study drug. No new reverse transcriptase mutations emerged at days 10 and 17.

A phase 2b safety, efficacy, and dose-finding study in treatment-naive patients is now underway evaluating 100 mg, 200 mg, 400 mg, and a comparison with 300 mg tenofovir, in once daily regimens with efavirenz and lamivudine (clinical trials.gov NCT01489046).

Apricitabine

The Melbourne-based biotechnology company Avexa is developing an NRTI that could have a potential role in multiple drug resistance. The development programme for apricitabine closed in 2010 but has since been resumed. Analysis of the data from the phase 2b/3 trial has been completed and presented to the FDA, together with plans for an alternative study. Avexa were able to secure agreement upon an expedited path to approval, which requires further data (Avexa 2011). Avexa is currently seeking partners to complete this final stage.

GS-7340

GS-7340 is a pro-drug formulation of tenofovir currently in development by Gilead that achieves higher levels of the active metabolite in lymph tissue and targets cells including peripheral blood mononuclear cells (PBMCs). GS-7340 has higher potency compared to equivalent doses of the existing formulation of tenofovir, while maintaining reduced plasma concentrations (approximately 100-fold lower).

This compound has the potential to require less API, increase antiviral activity, compared to the current formulation, and reduce systemic-related toxicity. Data presented recently from a 10-day monotherapy study, using 8 mg, 25 mg, and 40 mg with the current formulation of tenofovir and placebo arms as controls, showed respective time-weighted average change in viral load at day 11 of -0.76, -0.94, -1.08, -0.48 and -0.01 log copies/mL (Ruane 2012). Median viral load reductions were -1.08, -1.46, -1.73, -0.97 and -0.07, respectively. As such, the 8 mg dose of GS-7340 resulted in about the same viral load reduction as the current formulation of tenofovir and the two higher doses resulted in significantly greater viral load reductions.

Another recently-presented pharmacokinetic study showed GS-7340 and tenofovir exposures were approximately two- to three-fold higher with cobicistat boosting as compared to the elvitegravir/cobicistat/emtricitabine/GS730 FDC formulation (Ramanathan 2012). This interaction is driven by the inhibition of intestinal P-glycoprotein-mediated intestinal secretion of GS-7340 by cobicistat. Elvitegravir/cobicistat/emtricitabine/GS730 10 mg provided comparable GS-7340 and tenofovir PK as GS-7340 25 mg single agent.

Two phase 2 studies that are already ongoing or soon to enroll are using a 10 mg dose for development in two FDC formulations. One substitutes GS-7340 for the current formulation of tenofovir in Stribild with elvitegravir, cobicistat and emtricitabine and a second in a coformulation with darunavir, cobicistat and emtricitabine to be the first once-daily single-pill PI combination. Both compare the GS-7340-based regimens to Stribild (clinicaltrials.gov NCT01497899, NCT01565850).

A safety question has emerged over whether increased intracellular concentrations of GS-7340 accumulate in renal tubule cells. Although no renal concerns were seen after 10 day exposure, this will be an important focus of further studies.

The potential for this compound looks very promising. The dose for the single agent is likely to be 25 mg.

CMX-157

CMX-157 is a lipid conjugate of tenofovir in development by Chimerix, designed to take advantage of natural lipid uptake pathways and to achieve high intracellular concentrations of the active antiviral, with the aim of increasing the effectiveness of tenofovir. It binds directly to HIV and has significantly more activity in target cells.

In vitro data showed CMX-157 to be greater than 200-fold more potent than the current formulation of tenofovir against wild type-HIV and clinically relevant mutations. It may have potential as a long acting formulation (Lanier 2010).

A phase 1 pharmacokinetic study has been completed but not presented (clinical trials.gov NCT01080820). Recently Chimerix signed a worldwide license with Merck for the development of CMX-157 (Chimerix 2012).

2.2 Non-nucleoside reverse transcriptase inhibitors

Lersivirine

Lersivirine is an NNRTI, previously in development at Pfizer and amalgamated into the ViiV antiretroviral portfolio. Forty-eight-week results have been presented from a dose-finding study comparing lersivirine to efavirenz in treatment-naive patients. The percentage of patients with viral load less than 50 copies/mL was 79%, 79% and 86% in the 500 mg, 750 mg and efavirenz groups, respectively. Although the study was not powered to detect difference in efficacy among the lersivirine arms, it suggested a poorer response overall compared to efavirenz. The combined safety analysis reported a similar incidence of side effects in each group but fewer grade 3/4 events in the lersivirine groups compared to efavirenz (Pozniak 2011).

A long-term safety and efficacy study is ongoing (clinicaltrials.gov NCT01254656).

Rilpivirine Long-Acting

Rilpivirine is currently approved at a dose of 25 mg once daily in a single tablet formulation for use in antiretroviral regimens for treatment-naive adults. It is also approved as part of a FDC with emtricitabine and tenofovir.

As an oral treatment, this drug is not considered high priority as more virological failure was observed in two phase 3 studies, in people with higher pre-treatment viral loads (greater than 100,000 copies/mL) receiving rilpivirine compared to efavirenz (Cohen 2011, Molina 2011).

Rilpivirine Long-Acting (RPV-LA), developed by Tibotec/Janssen with support from the Gates Foundation, is a novel parenteral formulation – a nanosuspension – containing 300 mg/mL, allowing prolonged plasma exposure and potentially monthly or less frequent dosing.

Preliminary data was recently presented from a phase 1 study in which female and male healthy volunteers received a single intramuscular dose of rilpivirine (Jackson 2012). Twenty women received 300 mg, 600 mg and 1200 mg by injection. Plasma was collected for rilpivirine concentrations on up to 84 days post dose as well as genital tract fluid. Vaginal biopsies were also taken at days 14, and 7 or 28 for tissue pharmacokinetics.

Six men in a small substudy received an intramuscular dose of 600 mg, with a similar schedule of plasma pharmacokinetics and rectal biopsies at days 7 and 14.

All three doses showed prolonged plasma and genital tract exposure. The women had higher concentrations in genital tract fluid than plasma and slightly lower in vaginal tissue compared to genital tract fluid. In the men the rectal tissue concentrations mirrored that of plasma.

Rilpivirine-LA will be explored further as a PrEP agent. Multiple doses of the formulation will now be studied to look at safety, pharmacokinetics and pharmacodynamics.

2.3 Integrase inhibitors

Elvitegravir

Gilead has developed elvitegravir to be used both as a boosted agent and as part of Striblid, the recently FDA-approved FDC combining elvitegravir/cobicistat/tenofovir/emtricitabine (FDA 2012). Elvitegravir is currently filed with the FDA for approval as a boosted agent.

Dolutegravir

Shionogi-ViiV is developing dolutegravir as a once-daily integrase inhibitor that also overcomes resistance to raltegravir with twice-daily dosing. It will be dosed at 50 mg once a day in treatment-naive patients.

Dolutegravir has several positive attributes, including once-daily dosing, no boosting, low PK variability, few expected drug interactions, potentially distinct resistance profile to raltegravir, and high potency at a low milligram dose.

Ninety-six week results from the phase 2 dose-ranging study comparing dolutegravir/abacavir/lamivudine to efavirenz/tenofovir/emtricitabine in treatment-naive patients achieved similar virological efficacy with 50 mg dolutegravir compared to efavirenz, with differences between the two arms driven by slightly higher discontinuations in the efavirenz arm related to efavirenz side effects (Stellbrink 2012).

In this study, 205 subjects were randomized to receive dolutegravir at 10 mg, 25 mg, or 50 mg once daily compared to efavirenz. At week 96 the proportion of subjects with viral load < 50 copies/mL was 79%, 78%, and 88% in the 10 mg, 25 mg, and 50 mg arms, respectively, vs 72% in the efavirenz arm. Only two people discontinued dolutegravir due to adverse events (one in each of the 25 mg and 50 mg arms) compared to five in the efavirenz group.

A phase 1 pharmacokinetic study in HIV-negative people showed that an increased dolutegravir dose (50 mg twice-daily) overcomes an interaction with rifampin (Dooley 2012).

Top line results were also recently released from the SPRING-2 phase 3 study in treatment-naive adults reporting dolutegravir to be non-inferior to raltegravir (Shionogi-ViiV 2012).

Dolutegravir is also being coformulated in a fixed dose combination with GSK/ViiV nucleosides abacavir and lamivudine (clinical trials.gov NCT01366547).

S/GSK-1265744

S/GSK-1265744 is a second-generation integrase inhibitor, also from Shionogi-ViiV, with potential as a long-acting formulation. It has similar attributes to dolutegravir, with a long plasma half-life of approximately 30 hours (about twice that of dolutegravir).

In a previous three-part phase 1-2a dose escalation study in healthy volunteers and HIV-positive patients using doses ranging from 5 mg to 50 mg oral suspension or placebo, 88% of HIV-positive patients receiving 30 mg S/GSK1265744 monotherapy were virologically suppressed to less than 50 copies/mL at 14 days (Min 2009).

The compound is now being studied in a phase 1 study as an intramuscular, long-acting parenteral intramuscular injectable suspension formulation in doses of 100 mg, 200 mg, 400 mg, and 800 mg (clinical trials.gov NCT01215006).

S/GSK1265744 has potential for once-monthly dosing and possible uses for both treatment and PrEP are under discussion.

2.4 Boosters

Cobicistat

The pharmacokinetic booster cobicistat has so far reported similar boosting efficacy and side effects compared to ritonavir, without residual direct antiretroviral activity. The latest clinical data comes from elvitegravir studies and a direct booster comparison to ritonavir. It is also a component of Stribild.

An agreement was announced by Gilead in June 2011 to collaborate on a co-formulation of cobicistat with Tibotec's darunavir (Gilead 2011). A co-formulation with atazanavir is also in development under an agreement between Gilead and BMS announced in October 2011 (BMS 2011).

2.5 Entry inhibitors

BMS-663068

BMS-663068 is an entry inhibitor in development from BMS, active against the gp120 binding site on the CD4 cell. The first investigational compound to target the initial step in HIV attaching to the CD4 cell receptor, BMS-663068 works by binding to the HIV-1 envelope glycoprotein gp120, thereby interfering with its attachment to the CD4 receptor.

A randomized open-label proof-of-concept study using BMS-068 evaluated five dose combinations using BMS 068 1200 mg once-daily and either 600 mg or 1200 mg twice-daily, with and without ritonavir boosting (Nettles 2011). The trial's 50 participants were either antiretroviral treatment-naive or treatment-experienced but off treatment for the previous eight weeks. Pharmacokinetic data showed ritonavir to have a relatively modest impact on boosting BMS-068. A pharmacokinetic analysis of the dose-response rate reported that the baseline EC90 as a marker for drug susceptibility has a stronger correlation to virological response than pharmacokinetic exposure and that EC90 values were wide in the monotherapy study.

BMS-663068 is currently being studied in a phase 2b pharmacokinetic trial evaluating a dose range from 400 mg to 1200 mg , once and twice daily with raltegravir and tenofovir (clinical trials.gov NCT01384734).

Table 4: *Antiretroviral pipeline*

Compound	Company	Class	Formulation and dose	Status and Comments
Elvitegravir (EVG)	Gilead	Integrase inhibitor	150 mg once daily	• 48-week Phase 3 data demonstrated non-inferiority to raltegravir • Needs boosting with COBI • Filed with FDA (as boosted single agent) December 2011
Cobicistat (COBI)	Gilead	PK booster	150 mg boosting dose	• Phase 3 • 48-week Phase 2 results comparing to ritonavir showed similar efficacy • Filed with FDA for use as a boosting agent
Dolutegravir (DOL)	ViiV/Shionogi	Integrase inhibitor	50 mg once daily	• Phase 3 treatment-naive study compares 50 mg QD with EFV • Phase 3 non-inferior to raltegravir • Further Phase 3 to report in treatment-naive patients, treatment experienced patients and integrase inhibitor resistant treatment-experienced patients • Phase 2b data 50 mg BID effective in people with raltegravir resistance • Filing anticipated in 2012
Lersivirine	ViiV	NNRTI	500, 750 and 1000 mg once daily	• Phase 2 • Phase 2 data similar activity to EFV in treatment-naive people at 48 weeks • Long-term safety study ongoing
BMS-986001	BMS	NRTI	100, 200 and 400 mg once daily	• Structurally close to d4T but hopefully without associated toxicity • Phase 2b dose finding study in treatment-naive people underway
Apricitabine	Avexa	NRTI	800 mg twice daily	• Phase 2 • Recently resumed development. Structurally close to 3TC/FTC
BMS-663068	BMS	Attachment inhibitor (gp120)	400 mg and 800 mg twice daily 600 mg and 1200 mg once daily	• Phase 2b • New therapeutic class. Study in treatment experienced currently ongoing
GS-7340	Gilead	NRTI	10-25 mg, to be determined for single agent	• Phase 2 • New formulation (oral pro-drug) of tenofovir suggesting improved PK

Table continued on next page.

Compound	Company	Class	Formulation and dose	Status and Comments
CMX-157	Chimerix	NRTI	To be determined	• Phase 1 • Long acting pro-drug of tenofovir.
GSK-1265744	ViiV/Shionogi	Integrase inhibitor	To be determined Oral doses of 10, 30 and 60 mg are being evaluated Dose ranging of long-acting formulation underway: 100, 200, 400 and 800 mg Intramuscular injectable	• Phase 2 • 30-hour half-life, so potential for long acting formulation with possible monthly dosing. Also possible PrEP agent
Rilpivirine-LA (RIL)	Janssen	NNRTI	300 mg/mL 300, 600 and 1200 mg Intramuscular injectable	• Phase 1 • Long acting formulation of rilpivirine • Potentially monthly or less frequent dosing • Currently being evaluated as a potential PrEP agent
Pipeline for combined products, including FDCs				
Darunavir/ cobicistat	Licensing agreement between Gilead (COBI) and Janssen (DRV)	PI/booster	Film coated once daily tablet: 800/150 mg	• Once daily boosted PI
Darunavir/ cobicistat/ emtricitabine/ GS-7340	Licensing agreement between Gilead (COBI/ FTC/GS-7340) and Janssen (DRV)	PI/booster/ 2 N(t)RTIs	Film coated once daily tablet: DRV 800 mg/COBI 150 mg/FTC 200 mg/ GS-7340 10 mg	• Phase 2 study planned in treatment-naive patients • First PI-based FDC • Interaction with COBI increases GS-7340 exposure 2-3 fold • GS7340 small molecule makes co-formulation with a PI possible
Elvitegravir/ cobicistat/ emtricitabine/ GS-7340	Gilead	INI/booster/ 2 N(t)RTIs	Film coated once daily tablet: EVG 150 mg/COBI 150 mg/FTC 200 mg/ GS-7340 10 mg	• Phase 2 study recruiting in treatment-naive patients • Interaction with COBI and GS-7340
572-Trii Dolutegravir/ abacavir/ lamivudine	Shionogi/ViiV	Integrase inhibitor/ 2 NRTIs	Film coated once daily tablet: DTG 50 mg/600 mg/ 300 mg	• PK completed but not presented • Phase 3 with treatment-naive patients begun

Sources: 2011 i-Base/TAG Pipeline Report, Clinical trials.gov.

2.6 Paediatric pipeline

When drugs are approved for children, multiple label changes may take place because paediatric populations are studied in sequence. As paediatric investigation plans work in de-escalated age bands, the youngest age group may have the longest delay in labeling. Sometimes there is no indication or appropriate formulation for the very youngest children, complicating the implementation of universal treatment as early as possible in infancy.

A compound may occasionally receive a waiver from regulatory agencies; for example, darunavir will not be investigated in children bellow three years, due to dangerously high concentrations and in turn adverse events in juvenile rats in preclinical studies. Even without a waiver, toxicity concerns can delay approval – as was the case for tenofovir, which presented concerns related to bone maturation. There may also be difficulties producing an appropriate formulation for younger children, which is the case for efavirenz and tenofovir.

It is mandatory, however, for new compounds to be studied in children. The FDA extends six-month patent protection to companies that perform the requested paediatric studies and the EMA enforces penalties for those that do not provide a paediatric investigation plan as part of their application (or request a waiver).

Several of the compounds now in the paediatric pipeline have development plans and appropriate formulations for the youngest children, including combination products.

The following approved and investigational compounds are currently undergoing paediatric investigation.

Non-nucleoside reverse transcriptase inhibitors

Etravirine

The recommended etravirine dose per weight band for children and adolescents aged six to 17 is based on 5.2mg/kg twice daily. The FDA recently approved dosing recommendations for etravirine for treatment-experienced paediatric patients 6 to 18 years of age weighing at least 16 kg, as well as for the scored 25 mg tablet (FDA 2012).

IMPAACT P1090 will evaluate the drug in both treatment-naive and experienced children aged two months to six years (clinical trials.gov NCT01504841).

Rilpivirine

The PAINT trial is currently recruiting treatment-naive adolescents, aged 12 to18 years, weighing more than 32 kg and receiving 25 mg once daily plus two N(t)RTIs. The trial will evaluate the steady state pharmacokinetic profile and short term antiviral activity in this age group (clinicaltrials.gov NCT00799864).

TMC278-C220 is an open-label single-arm trial using the granule formulation, planned in children aged two to 12 years. This trial is taking a staggered approach and will study the drug in de-escalated age groups, down to two years of age.

Protease inhibitors

Atazanavir

The atazanavir capsule formulation is approved for children in the United States aged six years and older who are treatment-naive and weigh 15 kg or more and for treatment-experienced children weighing 25 kg or more. In the EU it is approved for both treatment-naive and treatment-experienced children aged six years and older and weighing 15 kg or more.

Treatment-naive and experienced children aged three to six months receiving atazanavir unboosted and boosted with ritonavir are being studied in PRINCE 1 and 2 and PACTG 1020A (Clinicaltrials.gov NCT01099579, NCT01335698, NCT00006604).

Lopinavir/ritonavir

The generic manufacturer Cipla is developing a sprinkle formulation of lopinavir/ritonavir (see section 1.5). The formulation (40/10 mg lopinavir/ritonavir) consists of a finite number of mini-tablets in a capsule, which is opened and sprinkled on soft food.

Data from a randomized crossover pharmacokinetic study in healthy adults comparing a single dose of sprinkles from 10 capsules of lopinavir/ritonavir with a single dose of 5 mL Kaletra oral solution (each mL containing 80 mg lopinavir and 20 mg ritonavir) were recently presented (Gogtay 2012). Both formulations were administered with about 150 g porridge and 240 mL water. Most of the pharmacokinetic parameters fell within the conventional bioequivalence range of 80–125% in this study. Where they fell outside, the differences were not large.

CHAPAS-2 compared twice-daily sprinkles to tablets in children ages 4 to 13 years, and sprinkles to syrup in infants ages 3 to 12 months, in a randomized cross-over PK study. Initial data found high variability in the younger cohort with both sprinkles and syrup, with no significant difference in subtherapeutic concentrations between formulations (Keishanyu 2012). In the older children, lopinavir/ritonavir concentrations were lower in children receiving sprinkles than in those who got the tablets.

Acceptability data showed storage, transport, and conspicuousness were less problematic for sprinkles compared with syrups, but for older children, several caregivers commented about the number of capsules needing to be used.

At week 8, when they could choose which formulation to continue with, 10 out of 14 (71%) caregivers chose to continue sprinkles rather than syrups for the infants, but only 7 of 29 (24%) of the older children chose sprinkles over tablet, with taste particularly to blame.

The CHAPAS-2 study comparing syrups to sprinkles in one- to four-year-olds is ongoing.

Integrase inhibitors

Dolutegravir

The IMPAACT P1093 study of dolutegravir will work with de-escalated age bands of children down to six-week-old infants. The older children will receive tablets and the younger ones the paediatric formulation.

A granule dolutegravir formulation has been developed and a phase 1 pharmacokinetic study in healthy adult volunteers was recently presented (Patel 2012). The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water. Subjects received a single dose of dolutegravir as 50 mg (adult tablet) and in 10 g of granule given: direct to mouth with no liquid; with purified water; with mineral water containing high caution concentrations; or with infant formula milk.

Dolutegravir exposures of the granule formulation were all moderately higher than the tablet formulation with or without liquids. Exposure was highest when the granule formulation was given with formula milk.

The granule formulation is being studied further in children in IMPAACT P1093. A reduced strength FDC of dolutegravir, abacavir, lamivudine is also planned.

Elvitegravir

The 183-0152 study of elvitegravir was a phase 1b open-label, nonrandomised trial in treatment-experienced adolescents receiving elvitegravir 150 mg once daily plus a PI-optimized background regimen. Of the 21 subjects enrolled in the 10-day pharmacokinetic study, 9 of 11 eligible subjects continued elvitegravir plus ritonavir-boosted PI-containing optimized background regimen and completed 48 weeks of treatment.

The paediatric committee of the EMA granted positive opinion toward the cobicistat and Stribild paediatric investigational plan in April 2011.

Boosted elvitegravir will be studied in de-escalated weight bands and a suspension formulation is in development for the youngest children.

The Stribild study will start after a review of data for elvitegravir and cobicistat. Age-appropriate formulations are planned.

Raltegravir

The raltegravir adult 400 mg film-coated tablet is approved in the United States for use in adults and children aged 6 to 18 weighing > 10 kg; 100 mg and 25 mg chewable tablets are approved for children > 2 to < 12 years old at a maximum dose of 300 mg.

The paediatric programme is ongoing in IMPAACT P1066 and an oral granule formulation is being studied in the youngest children and babies. Intensive PK data, along with preliminary 24 week safety and efficacy data for 6-month- to < 2-year-olds receiving the raltegravir oral granule formulation, was recently presented (Spector 2012). In this dose-finding study of treatment-experienced children, participants received weight-based raltegravir oral granule suspension at ~6 mg/kg, twice daily. The pharmacokinetic values achieved were similar to those observed in 2 to < 12-year-old children receiving chewable tablets. At week 12, 78% of the 9 children achieved virologic suppression; by 24 weeks, 85% achieved virologic suppression.

The dose of 6 mg/kg every 12 hours was chosen for continued study in this age group.

IMPAACT P1097 is a washout (passive) pharmacokinetic and safety study. This is the first clinical trial of an investigational antiretroviral to evaluate neonatal pharmacokinetics. Raltegravir crosses the placenta wall. It is metabolised primarily by an enzyme in the liver (UGT-1A1) that is immature in neonates. UGT pathways increase dramatically in activity in the first weeks of life. This study is recruiting mothers already receiving raltegravir in pregnancy (the infants are not dosed directly). The infants will be sampled at intervals up to 30 to 36 hours after dosing.

To follow a review of pharmacokinetic and safety data from both trials, the company is planning a study of infants born to HIV-positive mothers from immediately after the time of birth until their HIV status has been confirmed.

CCR5 receptor antagonists

Maraviroc

The A4001031 study of maraviroc is ongoing in children two to 18 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). Use of this drug requires a tropism assay, as it will not work for people with the CXCR4-tropic virus or in mixed-virus (CCR5/CXCR4) populations (clinicaltrials.gov NCT00791700).

Preliminary data showed body surface area based doses of maraviroc provided adequate exposures when administered with a protease inhibitor as part of their background regimen, in 29 children. Children who were not receiving a boosting agent in their background regimen required at least doubling of the initial dose (Vourvahis 2011).

Table 5: *Paediatric ARV pipeline*

Compound	Company	Class	Formulation and dose	Status and comments
Atazanavir (ATV)	Bristol-Myers Squibb	PI	Oral powder 50 mg sachet Capsule 100, 150, 200, 300 mg	• Ongoing phase 2 • naive and experienced with or without RTV from • 3 months to 6 years of age
Dolutegravir (DTG)	Shionogi/ViiV	INI	Older children tablets 10, 25, 50 mg Granule formulation being evaluated for younger children	• Phase 1 and 2 from 6 weeks to 18 years of age • Exposure of granules with different liquids exceeded that of tablets in healthy adults so can be given without liquid restriction or directly to mouth
Dolutegravir/ abacavir/ lamivudine (572-Tri)	Shionogi/ViiV	INI/2NRTIs FDC	Paediatric specific formulation development planned (dosing to be determined)	• Development dependent on ongoing studies confirming dose of DTG in children and potential for once daily dosing of ABC/3TC in children
Elvitagravir (EVG)	Gilead	INI/booster	Reduced strength tablets and suspension in development	• Phase 1 PK in healthy adults healthy adults planned • Needs boosting • PK completed 12-18 years of age RTV boosted • RTV and COBI boosted EVG to be studied in all age groups
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir (Stribild)	Gilead	INI/ booster/ 2 N(t)RTIs FDC	Reduced strength tablets in development	• Phase 1 PK (vs adult Quad) in healthy adults planned • Studies planned in treatment experienced 6 to 18 years of age once sufficient data available from individual compounds
Etravirine (ETR)	Janssen	NNRTI	Dispersible tablets 25 (scored), 100 mg	• FDA approved for experienced children >6 years of age weighing >16 kg • Phase 1&2 treatment-naive and experienced 2 months to 6 years of age planned
Lopinavir/ ritonavir (LPV/r)	Cipla	Boosted PI	Sprinkles 40/10 mg (equivalent to 0.5 mL liquid)	• Similar PK to liquid in healthy adults • PK in children being evaluated • Sprinkle regimen for use in infants <2 years in RLS in development

Table continued on next page.

Compound	Company	Class	Formulation and dose	Status and comments
Maraviroc (MVC)	Pfizer/ViiV	CCR5 receptor antagonist	Oral suspension 20 mg/mL	• Phase 4 • Experienced CCR5 tropic 2 to18 years • Requires tropism assay
Raltegravir (RAL)	Merck	INI	Oral granules for suspension 6mg/kg (100 mg sachet) 100 mg and 25 mg chewable tablets	• FDA approved 400 mg tablet for children aged 6 to 18 weighing >10 kg, and chewable tablets for aged >2 to <12 at a maximum dose of 300 mg. Awaiting EMA approval • Granules Phase 2, 2 weeks to 2 years of age • Achieved good target exposure in 6 months to <2 years of age, similar to that with older children • Neonate passive PK study
Rilpivirine (RIL)	Janssen	NNRTI	Oral granules 2.5mg base/g	Phase 2 planned 0-12 years

Sources: 2011 i-Base/TAG Pipeline report, clinicaltrials.gov.

2.7 "High potential" products closer to market launch

The integrase inhibitor dolutegravir, currently in phase 3, with expected approval in 2013, has been identified as a product with high potential. It is predicted to cost $30 per patient per year – 90% less expensive than raltegravir. It is a small molecule (50 mg), compared to elvitegravir (150 mg once daily plus boosting agent) and raltegravir (400 mg twice daily), with once-daily dosing in treatment-naive patients. It appears to be well tolerated and could replace efavirenz in first-line treatment or be used in second-line treatment. Trials in children are planned, including neonates, and a granule formulation is in development.

Further down the pipeline, but also with high potential is the tenofovir prodrug GS-7340. With doses 10 times or more lower than that of the existing formulation of tenofovir, the cost of GS-7340 is predicted to be appropriately lower than the current formulation and may reduce the toxicity profile.

Both compounds could be used as components of FDCs.

2.8 Improving current formulations

With the potential to completely alter the standard of care, early development of long-acting formulations is also underway – for monthly or weekly depot injections. Potential candidates might include rilpivirine and GSK-1265744, both in early stages of development, plus CMX-157, which also has a long half-life. There is currently little clarity on the target product profile, however; nor is it clear if the right combination of drugs required to construct a suitable regimen are available or even in development (MSF 2012).

Finally, the possibility of nanoformulations of ARVs is very attractive – of which the long acting formulation of rilpivirine is the first to be considered. Nanotechnology is already established in many areas of medicine, with over 40 products approved and widely used to treat a diverse range of serious illnesses. Nanoformulations of ARVs, based on their properties of improved pharmacokinetics (requiring significantly lower volumes of API for the same antiviral activity) and more efficient drug targeting, have the potential to vastly increase the number of people currently being treated globally at standstill cost (i.e., at today's capped budgets). While this potential has been foreseen in research extending back at least 15 years, this area will need to become a funding priority if disparate and isolated groups of scientists with expertise in this field are to be supported and if a structured pathway is to be charted for developing these exciting potential ARV compounds.

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