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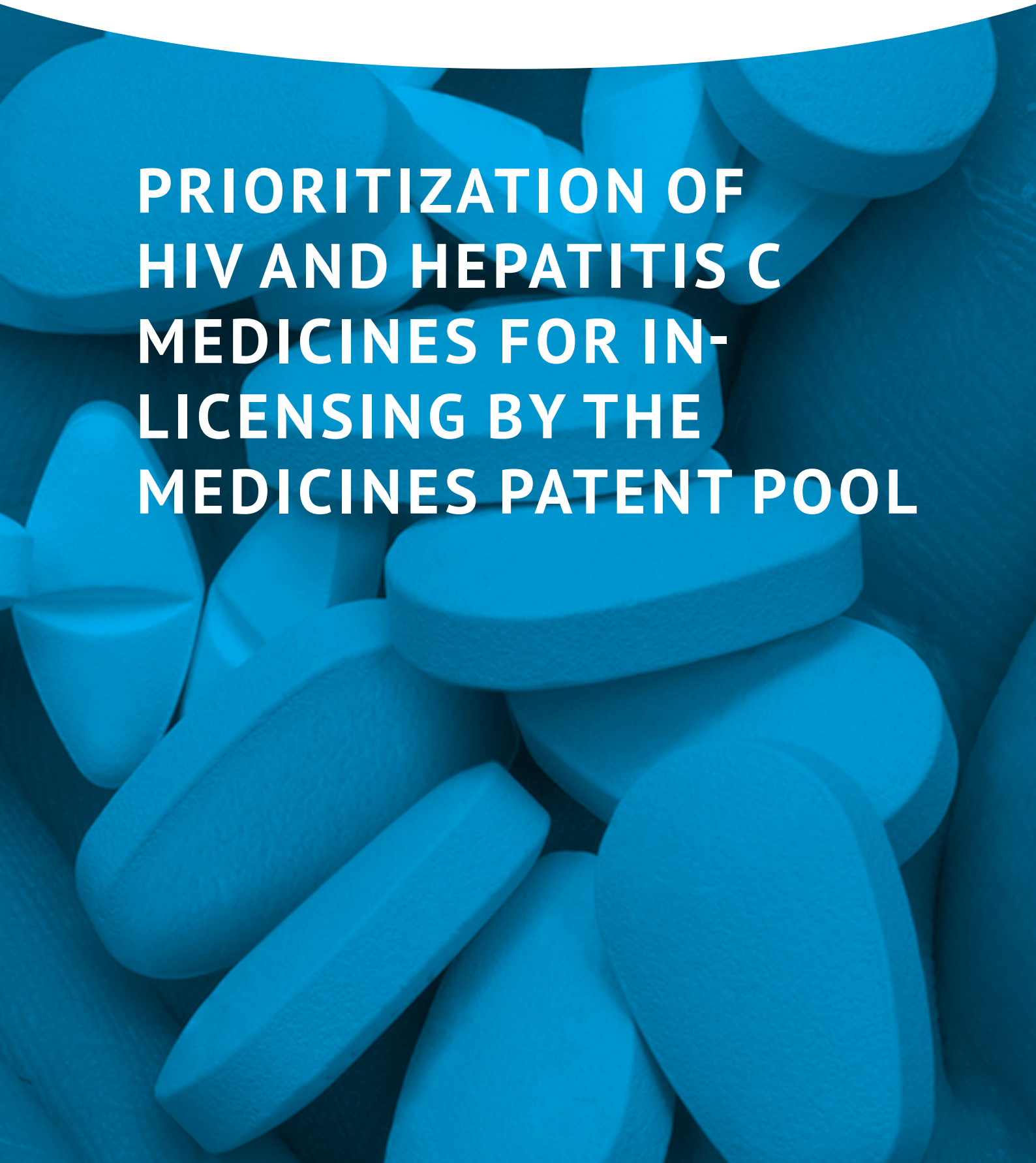

PRIORITIZATION OF HIV AND HEPATITIS C MEDICINES FOR IN-LICENSING BY THE MEDICINES PATENT POOL

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1. INTRODUCTION

This document outlines the methodology used by the Medicines Patent Pool (MPP) to select priority HIV and hepatitis C Virus (HCV) medicines for in-licensing and the list of priority medicines based on that methodology[1]. The prioritization is based on four sets of criteria:

1. **Clinical criteria**: to assess the clinical importance of candidate medicines. The assessment is based on World Health Organization (WHO) treatment recommendations for marketed medicines and published clinical trials data for pipeline candidates.

2. **Intellectual property criteria**: to analyse the extent to which the medicines are protected by patents in developing countries. The assessment is based on the information that the MPP has gathered from patent offices and patent holders and made publicly available through its public database, MedsPaL.

3. **Licensing criteria**: to capture whether there already are licences for the candidate medicines in place and to anaylse their scope and room for improvement. The assessment is based on publicly available information on existing licences and public commitments made by licensors on their licensing policy.

4. **Market criteria**: to analyse the current and future market for the medicines and the potential for reducing the price of treatments through an MPP licence. The assessment relies on public information on the products, the MPP/WHO market forecast for antiretrovirals (ARVs), and pricing information gathered from the WHO Global Price Reporting Mechanism.

While the criteria are similar for both diseases (HIV and HCV), some of the sub-criteria are specific to each disease area. This is particularly the case for the clinical sub-criteria.

The MPP prioritizes HIV and HCV medicines that are either already on the market but have not yet been licensed to the MPP[2], or are in late-stage clinical development (phase 3) and could potentially be licensed to the MPP prior to or shortly after approval.

The MPP, therefore, considered and evaluated 10 anti-HIV compounds and eight direct-acting antiviral (DAA) regimens applying the methodology contained in the annexes.

The evaluation will be repeated on an annual basis to re-assess priorities based on new clinical evidence, updates in WHO recommendations, changes in patent status, evolution in licensing practices and changes in prices or market forecasts for HIV and HCV medicines.

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1 The MPP is grateful to the experts that provided inputs that contributed to the development of this methodology, the refinement of the criteria or a better understanding of the potential of specific drugs. These include Arnaud Fontanet, Elaine Abrams, Fernando Pascual, Pedro Cahn, Shing Chang, Mark Cotton, Nathan Ford, Graham Foster, Manal Hamdy El-Sayed, Nagalingeswaran Kumarasamy, Karine Lacombe, Maud Lemoine, Martina Penazzato, Anton Pozniak, Homie Razavi, George Siberry, Mark Sulkowski, Mark Thursz, Ingo van Thiel, Stefano Vella, Francois Venter, Marco Vitoria, Benjamin Young and members of the MPP Expert Advisory Group for HIV and HCV (Labeeb Abboud, Isabelle Anderieux Meyer, Jonathan Berger, Alexandra Calmy, Philippa Easterbrook, Ludmila Maistat, Nelson Otwoma, Raquel Peck, Achal Prabhala, Violeta Ross Quiroga and Ellen 't Hoen). Special thanks to Fernando Pascual, Karine Lacombe and Stefano Vella who undertook a detailed review of the clinical methodology and to S Padmaja and Pascale Boulet who contributed to understanding the intellectual property (IP) status of individual medicines. The final assessment is the responsibility of the MPP alone.

2 The MPP currently has licences for abacavir (paediatric), atazanavir, cobicistat, daclatasvir, dolutegravir, elvitegravir, emtricitabine, lopinavir, raltegravir (paediatric), ritonavir, tenofovir alafenamide, tenofovir disoproxil fumarate and several combinations containing these medicines. In addition, it has obtained a licence on patents that are relevant to darunavir and collaborated on commitments not to enforce patents for darunavir (paediatric) and nevirapine.

2. FINDINGS

Based on the methodology contained in the annexes, the MPP selected five investigational ARVs and two pipeline direct-acting antiviral (DAA) regimens as immediate priorities for in-licensing. In HCV, four additional DAA regimens, which are currently in phase 2, will be actively monitored by the MPP and are also listed below in view of their current potential. These will be assessed in late 2017 once results of ongoing clinical trials become available.

2.1 HIV Prioritization

The scope and quality of the published clinical data on the pipeline HIV medicines varied and phase 3 results for candidates have not yet been publicly announced. While the methodology attempts to incorporate these limitations, it is likely that assessments will evolve as more clinical data become available (e.g. following major scientific conferences).

Based on evidence presently available, the HIV priorities for in-licensing are listed below in alphabetical order[3]. All of these compounds are currently in phase 3 testing:

- Bictegravir
- Cabotegravir
- Doravirine
- Fostemsavir
- Rilpivirine (long-acting injectable; LAI)

TABLE 1 – SUMMARY ANALYSIS OF HIV PRIORITIES

ARV	SUMMARY ANALYSIS
Bictegravir	Bictegravir (BIC) is an integrase inhibitor that is being investigated as part of a single-tablet regimen of BIC/TAF/FTC with a dose of 50 mg once daily in adults. BIC has a barrier to resistance emergence similar to that of dolutegravir. It was shown *in vitro* to have greater potency than raltegravir, elvitegravir and dolutegravir against a panel of patient-derived HIV-1 isolates that had high-level INSTI resistance-associated mutations. When combined with TAF/FTC in phase 2, BIC was safe and well tolerated, and showed high virologic response rates comparable with that of DTG in native patients, showing no treatment-emergent resistance through week 48. Additionally, it is worth noting that BIC/TAF/FTC is already being studied in virologically suppressed adolescents and children in phase 2/3. Our clinical assessment of BIC will be updated once further efficacy and safety data become available. Patents on bictegravir expire in 2033 and have been filed in key countries of ARV manufacture.
Cabotegravir	Cabotegravir is an integrase inhibitor. Cabotegravir long-acting injectable (CAB-LAI) is being tested together with rilpivirine LAI for long-term maintenance of virologically suppressed patients and could be injected monthly (or less frequently following oral induction). CAB-LAI is also under active investigation as a bimonthly injectable for PrEP. The main patent on cabotegravir has been filed or granted in the leading countries of manufacture of ARVs and expires in 2026. The product has not yet been licensed for generic production.
Doravirine	Doravirine is an NNRTI which requires a smaller dosage and has less common adverse events and an improved resistance profile as compared to efavirenz. Additionally, doravirine was shown to have an efficacy non-inferior to DRV/r in naïve patients regardless of baseline viral load both in combination with 2 NRTIs. Patents on doravirine have been filed in many of the leading countries of manufacture of ARVs and expire in 2031/33. The product has not yet been licensed for generic production.
Fostemsavir	Fostemsavir is the prodrug of temsavir, the first in this new class of attachment inhibitors. Unlikely to be cross-resistant with other classes of ARVs, fostemsavir could play a role in salvage therapy. Patents on this compound have been granted in leading manufacturing countries and expire in 2025.

[3] It should be noted that these priorities are based on available clinical data and will likely evolve over time as more data becomes available and depending on whether the medicines are eventually recommended in WHO treatment guidelines.

Rilpivirine (focus on long-acting injectable)	The oral formulation of rilpivirine was approved in 2011 and has had very limited uptake in developing countries. The LAI formulation is being studied as part of a maintenance strategy in combination with CAB-LAI. In addition, RPV-LAI also holds PrEP potential. RPV-LAI injected every two months is safe, well tolerated and acceptable in low-risk HIV-negative women. Patents on rilpivirine expire in 2022 (combinations in 2024). Licences have been granted to several generic manufacturers for the oral formulation but products are not yet on the market.

2.2 HCV Prioritization

The HCV prioritization focused on regimens, rather than on individual compounds. Based on presently available evidence, the HCV priorities for in-licensing are therefore as follows, in alphabetical order[4]:

- Glecaprevir/pibrentasvir
- Ravidasvir (with sofosbuvir)

In addition, the MPP is actively monitoring the following four HCV regimens, each with pangenotypic potential:

- Simeprevir/odalasvir/AL-335
- Odalasvir / AL-335
- Grazoprevir/ruzasvir/MK-3682
- Ruzasvir/MK-3682

TABLE 2 – SUMMARY ANALYSIS OF HCV PRIORITIES

DAA REGIMEN	SUMMARY ANALYSIS
Glecaprevir / pibrentasvir	Glecaprevir and pibrentasvir have improved resistance profiles over first-generation NS3/4A and NS5A inhibitors, respectively. Phase 3 studies demonstrated pangenotypic efficacy of this regimen with the potential of reducing treatment duration to eight weeks, at least in treatment-naïve patients. Unlike many marketed DAAs, this combination appears to be safe and efficacious in HCV patients with severe kidney diseases. Patents on these compounds expire in 2031 and 2030 respectively and have been filed or granted in several developing countries. There are currently no licences on the products contained in this regimen.
Ravidasvir (with sofosbuvir)	Ravidasvir is an NS5A inhibitor. Having demonstrated high efficacy in genotype 4, ravidasvir in combination with sofosbuvir (SOF) will be assessed across all genotypes in a phase 2/3 study led by the Drugs for Neglected Diseases *i*nitiative (DND*i*). Patents on this regimen expire in 2030 and have been filed or granted in several developing countries. A licence has been issued to one manufacturer on ravidasvir.

[4] It should be noted that these priorities are based on available clinical data and will likely evolve over time as more data becomes available and depending on whether the medicines are eventually recommended in WHO treatment guidelines.

3. ANNEX 1 - HIV PRIORITIZATION METHODOLOGY

The following table provides a detailed overview of the criteria used for assessing the candidate HIV medicines and explanations on how such criteria have been applied. The focus is primarily on ARVs but the methodology is also applicable to non-ARVs being tested for the treatment or prevention of HIV.

3.1 Clinical Criteria

PART A Clinical criteria for ARVs already in the WHO Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. (Second Edition 2016)		
SUB-CRITERIA	**KEY QUESTION**	**COMMENTS**
Inclusion in WHO adult & adolescent guidelines	Is the ARV: Recommended for first-line treatment? Recommended for second-line treatment? Recommended for third-line treatment? Recommended for Pre-Exposure Prophylaxis (PrEP)? Recommendation for Post-Exposure Prophylaxis (PEP)?	ARVs recommended by the WHO as part of a preferred regimen are assessed more favourably than those recommended as part of an alternative regimen. The assessment also takes into account if ARVs are recommended for more than one line of treatment or for treatment plus PrEP or PEP.
Inclusion in WHO paediatric guidelines (<10 years of age)	Is the ARV: Recommended for first-line treatment? Recommended for second-line treatment? Recommended for third-line treatment? Recommended for infant prophylaxis?	Same principle as above.
PART B **Clinical criteria below only apply to ARVs not yet in the WHO HIV Guidelines.[5]**		
SUB-CRITERIA	**KEY QUESTION**	**COMMENTS**
Efficacy	Has the ARV shown efficacy comparable to the standard-of-care (SOC) as per WHO recommendations regardless of the patient viral load?	ARVs with efficacy comparable to or better than SOC, regardless of patient viral load, rate most favourably under this criterion. The quality of evidence is reflected in our assessment. If the quality of evidence is not optimal at the time of our assessment (i.e. data from phase 2 studies or earlier), the ARV is assessed less favourably until more complete data become available.
Safety & tolerability	Does the ARV have a more favourable safety/tolerability profile than the SOC as per WHO recommendations?	Safety/tolerability comparable to SOC is the base case scenario and improvements over SOC score higher. The quality of evidence is reflected in our assessment. If the quality of evidence is not optimal at the time of our assessment (i.e. data from phase 2 studies or earlier), the ARV is assessed less favourably until more complete data become available.

[5] For these clinical criteria, the standard-of-care (SOC) is to be interpreted as the WHO-preferred regimen(s) for the relevant line of treatment. In the event the WHO-recommended regimen(s) is not included in a clinical study, the actual comparator arm in the study serves as the reference point for this assessment.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Durability	Does the ARV show a high genetic barrier to resistance and have a long half-life so as to minimise the impact of missed doses (in other words, good "forgiveness")?	A new ARV that is effective against HIV strains resistant to existing ARVs from the same class scores higher. Novel mechanisms of action or first-in-class are addressed in another section of this table.
Convenience and adherence	Does the ARV have the potential for being more convenient than SOC? Does the ARV demonstrate favourable adherence in comparison with SOC?	Favourable characteristics may include: no food requirement (particularly no calorie requirement); no need for pharmacokinetic booster; potential for making fixed-dose combinations with WHO-recommended ARVs; small pill size; simple dosing (e.g. once-a-day); no need for cold-chain storage or transportation; no dose adjustment or contraindication in case of renal or hepatic impairment; and, no need for baseline genetic sequencing.
Suitability for specific subpopulations	Are there any problematic drug-drug interactions (DDIs) with companion ARVs (particularly WHO-recommended ARVs) and the most widely used medicines for important comorbidities (including tuberculosis, hepatitis, non-communicable diseases)?	Problematic DDIs with WHO-recommended regimens for key comorbidities that commonly affect resource-limited settings (RLS), particularly contraindication with a WHO-preferred regimen, are undesirable. Some DDIs can be addressed by simple dose adjustment or by switching to a WHO-recommended, albeit alternative, regimen although avoidance of treatment adjustment is the best-case scenario.
	Has the ARV been shown to be suitable for use in pregnant and breastfeeding women and men whose female partners are pregnant?	In general, efficacy and safety data in pregnant and breastfeeding women may not be available for pipeline ARVs. If there are no adequate human or animal data at the time of assessment, the ARV is not assessed against this particular criterion. Clinically established safety in this population is the best-case scenario. In the absence of clinical data, results from relevant animal studies are evaluated. Contraindication in pregnant or breastfeeding women or men whose female partners are pregnant receive a low score under this criterion.
	Has the ARV been clinically proven to be highly effective for preventing mother-to-child transmission (PMTCT) of HIV?	An ARV that is proven effective at preventing mother-to-child transmission of HIV is assessed more favourably.
	Potential for use in children and infants (< 10 years of age per WHO definition) a) Is this ARV being developed for paediatric use? b) Does this ARV represent a clinically important new option for children? c) Is the formulation appropriate for use in children in resource-limited settings (RLS)?	Paediatric investigation for a new compound typically lags behind testing for adult use. For pipeline medicines or medicines with recent approval for adults and adolescents only, there is often limited or no clinical data in children at the time of assessment. However, given that paediatric treatment development is a high priority for the MPP, this criterion aims to enable early assessment of the basis of commitment/progress of paediatric development, the clinical relevance of a new ARV for children, and the formulation's appropriateness for use in children in resource-limited settings. Reports from the Paediatric AIDS Drug Optimization (PADO) group are factored into this assessment. The more weight/age bands covered in paediatric investigation, the more favourable it is assessed under this criterion.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Potential for PrEP	Apart from HIV treatment, does the ARV also have PrEP potential?	If in addition to HIV treatment, an ARV also has potential for PrEP with good adherence, it is assessed favourably. High quality of evidence (clinical as opposed to preclinical) or prioritization by CADO is desirable. This criterion will be refined in the future as the field evolves. If an ARV can only be used for PrEP but not for treatment, it can be assessed using a similar set of clinical criteria as above, but with TDF/FTC as the SOC for comparison.
Other public health gaps	Does the product meet any important public health gaps or improved options for other niche populations in RLS?	This section serves to capture innovations that offer an opportunity for improving options for treating or preventing HIV in resource-limited settings. This could be, for example, a novel mechanism of action to combat growing drug resistance issues, novel drug delivery (e.g. long-acting injection administered once monthly or less frequently) or a paradigm-shifting strategy (e.g. maintenance strategy) that could improve or simplify HIV prevention and care. Innovations could also include additional indication of ARVs for diseases that are prevalent in resource-limited settings (e.g. hepatitis B).

3.2 Intellectual Property Criteria

SUB-CRITERIA	KEY QUESTION	COMMENTS
Time to expiry of patents blocking all or main formulations containing the ARV	When do patent(s) on the molecule and/or main formulation(s) expire?	Products that have longer time to patent expiry score higher. This criterion focuses on patents on the molecule itself or patents that cover the main formulations containing the ARV.
Additional years of exclusivity provided by (i) Secondary patents that block some formulations only or (ii) patents that may be blocking main formulations but may potentially be invented around ("quasi blocking patents")	When do secondary patent(s) on specific formulations or "quasi blocking patents" expire?	As above, products that have longer time to patent expiry score higher. This criterion focuses on additional years of exclusivity provided by patents on specific formulations (e.g a paediatric formulation, a fixed dose combination or an extended release formulation), or by other secondary patents that may potentially block the development of generics (e.g. certain process patents or patents on polymorphs).
Geographical coverage of patents blocking all or main formulations containing the ARV	How widely has the patent(s) been filed/granted?	Products for which patents have been filed or granted in countries that are home to a higher percentage of people living with HIV score higher. Given India's role as the manufacturing base for most ARVs that meet international quality requirements, products that are patented in India are given high priority.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Geographical coverage of secondary patents	How widely has the patent(s) been filed/ granted?	As above, products for which patents have been filed or granted in countries that are home to a higher percentage of people living with HIV score higher.

3.3 Licensing Criteria

SUB-CRITERIA	KEY QUESTION	COMMENTS
Licensing status	Has the medicine been licensed to generic manufacturers for manufacturing and sale in developing countries? How many companies have licences to develop the ARV and is this likely to be sufficient in light of forecasted needs?	ARVs for which there are no licensees or only a limited number of licensees score higher. The assessment considers the line of treatment for which the ARV is recommended or being developed, as the minimum licensees required to ensure robust generic competition depends on the line of treatment and the size of the market. It also takes into consideration the number of manufacturers of the active pharmaceutical ingredient (API) that have a licence. The assessment takes into account licences and commitments to licence.
Geographical coverage of licences	What is the geographical scope of current licences (or licensing policy of the patent holder) and is there significant scope for expansion under an MPP licence?	Geographical scope is one of the key features in access-oriented voluntary licences. ARVs licensed with a limited geographical scope are considered a higher priority, as there may be greater room for improvements by the MPP. This criterion takes into consideration countries explicitly included in the licence as well as additional countries that may be able to benefit in light of specific provisions in the licence.
Transparency of licence	Has the licence been made publicly available in full form?	This criterion takes into consideration the importance of transparency in licensing terms and conditions as this is another area in which the MPP has been able to improve on existing licences.
Restrictions in licence	Are there any important restrictions in the licence that could be improved by the MPP if it were to seek a licence?	In addition to geographical scope, there are many other terms and conditions in a licence that can impact on access to medicines. This would include, for example, provisions that provide maximum flexibility to licensees; provisions that ensure complementarity with other access strategies; clauses relating to anti-diversion; and clauses enabling development of adapted formulations. Where detailed terms and conditions of the licence are not available, the assumption is that there are several restrictions in the licence that could potentially be addressed through an MPP licence.

3.4 Market Criteria

SUB-CRITERIA	KEY QUESTION	COMMENTS
Size of market (current and future)	How large is the market for this medicine or for formulations containing this medicine?	The size of the market depends on the likely place in treatment for a given medicine (e.g. first-, second- or third-line). For pipeline medicines, the assessment is based on the positioning of the ARV in clinical trials (e.g. treatment-naïve, highly experienced patients).
Market trend (for marketed products)	What is the market trend for this product over the coming five years?	This criterion takes into consideration the likely evolution in demand for this product over the coming years. Is demand rising, stable or decreasing?
Price differential between originator and generic (for marketed products)	What is the current price differential between the originator product in low- and middle-income countries (LMICs) in which it is patented and the generic version in countries in which it is available?	This criterion is used only for ARVs that are already on the market. It prioritzes products that have a higher price differential between the originator product and generics and where an MPP licence enabling generic market entry could have a major impact.
Potential for low price as compared to standard of care (for pipeline products)	Does the ARV have the potential for being made available at low(er) prices?	This criterion is used for pipeline ARVs only. Reasons why an ARV may have the potential for lower price may be low dosage; less frequent dosing; no need for booster; simple(r) manufacturing processes. Where possible, the assessment considers projected price within five years of projected introduction.

4. ANNEX 2 - HCV PRIOTIZATION METHODOLOGY

The following table provides a detailed overview of the criteria used for assessing the candidate DAA regimens and explanations on how such criteria have been applied.

4.1 Clinical Criteria

SUB-CRITERIA	KEY QUESTION	COMMENTS
Recommendation in WHO HCV Treatment Guidelines	Is this DAA regimen recommended by the WHO for HCV treatment? If so, for how many genotypes is it recommended?	The assessment reviews WHO recommendations for different genotypes and assesses favourably those DAA regimens that are recommended by the WHO. Preferred DAA regimens are assessed more favourably than alternative regimens. Treatment of HCV patients with liver cirrhosis is discussed separately in this table. Any DAA that was previously recommended by the WHO but has been removed from the most recent WHO guidelines is no longer assessed and is not considered a priority for the MPP.
Safety and tolerability	Does the DAA regimen have a favourable safety and tolerability profile?	The DAA regimens are assessed according to their safety/tolerability profile and compared to WHO preferred regimens. DAAs with an inferior safety/tolerability profile than WHO-preferred IFN-free regimens receive a lower score. The quality of evidence is also reflected in the assessment. If the quality of evidence is not optimal at the time of assessment (i.e. data from phase 2 studies only), the DAA is assessed less favourably.
Pangenotypic efficacy	Does the DAA regimen have potential for use across all six major genotypes of HCV as an IFN-free, ribavirin-free combination regimen? Specifically: a) Is this DAA regimen being clinically studied across all six genotypes as an IFN-free and theoretically pangenotypic regimen? b) For how many genotypes have the DAA regimen(s) demonstrated high efficacy in clinical studies? c) Has a Stringent Regulatory Authority (SRA) approved the pangenotypic indication (genotype 1-6) of such regimen(s)?	Clinically proven high efficacy across all six major genotypes of HCV without reliance on IFN score favourably, particularly when pangenotypic indication has been approved by a SRA. If no clinical data are available at the time of assessment, the regimen receives a preliminary score for being under active investigation against all six genotypes. The quality of evidence is also reflected in the assessment. If the quality of evidence is not optimal at the time of our assessment (i.e. data from phase 2 studies), the regimen is assessed less favourably to take into account uncertainty with respect to a compound that is still under development. Assessment under this section relates to HCV mono-infection studies only. Treatment of HCV patients with coinfections or liver cirrhosis are discussed in other sections of this table.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Treatment duration in non-cirrhotic people with HCV?	What is the average treatment duration of this DAA regimen in non-cirrhotic patients?	DAA regimens with a duration that is longer than 12 weeks (the current standard of care) score less favourably. The same applies to DAAs that require adjustment of treatment duration depending on the patient condition as it could be difficult to be put into practice in resource-limited settings. This may include variations by genotype, presence of baseline resistance-associated variants (RAVs), or previously failed treatment. Issues relating to RAVs are discussed in more details below. Treatment specific to liver cirrhotic populations is discussed in another section of this table.
Genetic barrier to resistance	Does the regimen offer high genetic barrier to resistance? Does the marketing authorization by an SRA require a patient to be genetically tested for baseline resistance-associated variants (RAVs) prior to being prescribed this DAA regimen?	DAAs regimens with high genetic barrier to resistance score favourably. The average resistance profile of WHO-recommended IFN-free regimens serves as the base case for comparison. Regimens clinically shown to be poorly effective in presence of certain RAVs score less favourably, as it may result in requirement for baseline genetic testing, which could be difficult to carry out in RLS.
Ease of administration	Can the DAA regimen be administered conveniently?	DAA regimens score lower if they require any of the following: more frequent than once-daily administration, food, pharmacokinetic booster, or cold chain storage/transportation. In line with inputs from experts consulted during the development of this methodology, the assessment did not consider crucial the potential of a DAA to be co-formulated with other DAA(s) into fixed-dose combinations. It is therefore not considered for this evaluation. The need for dose adjustments for some DAA regimens due to drug-drug interactions is discussed in another section of this table.
Treatment of HCV patients with liver impairment, including liver cirrhosis	Can the DAA regimen be used in HCV patients with liver impairment? If so, does it require substantial changes to the regimen?	Liver cirrhotic patients comprise an important subpopulation among HCV patients and one that is often prioritized for treatment. Additionally, in resource-limited settings, where HCV screening capacity is likely limited, HCV infection and its resultant liver damage may often not be early detected. For the above reasons, a regimen contraindicated in HCV patients with moderate to severe liver impairment scores unfavourably. Regimens shown to be equally effective without adjustments regardless of cirrhotic status represents the ideal scenario. Requirement for either longer treatment duration or the addition of ribavirin is common, including in WHO-recommended regimens, and therefore serves as a base case. However, requirement for both or dose adjustment of DAA receive a lower score.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Specific subpopulations	a) Are there any problematic drug-drug interactions (DDI) with medicines commonly prescribed for co-morbidities, such as WHO-recommended antiretroviral therapies?	Assessment reflects whether it is easy to address potential DDI issues. HIV/HCV co-infection is discussed below by way of example. Most of the new DAAs are highly effective regardless of a patient's HIV co-infection status. However, potential DDI between HIV and HCV medications needs to considered. Contrary to lifelong antiretroviral therapy (ART), HCV infection is curable with short treatment. Therefore dose adjustment of a DAA in order to address DDI issues is acceptable, and scores more favourably than a requirement to switch or adjust a WHO-preferred ART.
	b) Can this DAA regimen be used in pregnant and breastfeeding women?	In general, most DAAs have not yet been clinically studied in this population. If there are no adequate human or animal data at the time of assessment, we will revisit this section as evidence becomes available. Ultimately, clinically established safety in this population score most favourably, whereas relevant results from animal studies may be acceptable in the interim.
	c) Can this DAA regimen be used in people with HCV younger than 18 years of age?	In general, most DAAs have not yet been clinically studied in patients younger than 18 years of age. If there are no data in this population at the time of assessment, we will revisit this section as evidence becomes available.
	d) Other specific populations	Regimens that meet need gaps in other special populations may be considered for a small bonus score. For instance, safety and efficacy in people with HCV with severe renal impairment (creatinine clearance ⩽ 30 mL/min) or end stage renal disease without having to adjust DAA dosage could be a plus.
Acute hepatitis C	Is this DAA regimen also effective for treating acute hepatitis C infection?	Clinically proven efficacy for acute hepatitis C with reasonable treatment duration is a plus.
Future improvement	Does this DAA regimen offer an opportunity for improving options for treating HCV in RLS?	This section serves to capture innovations that offer an opportunity for improving options for treating HCV in resource-limited settings. This could be, for instance, a novel mechanism of action, or a paradigm-shifting strategy that could improve or simplify HCV care, such as future long-acting formulations of combination regimens that may enable "single-visit cure" suitable for use in resource-limited settings.

4.2 Intellectual Property Criteria

SUB-CRITERIA	KEY QUESTION	COMMENTS
Time to expiry of patents blocking the DAA regimen	When do patent(s) on the molecule and/or main formulation(s) expire?	Products that have longer time to patent expiry score higher. This criterion focuses on patents on the molecules themselves or those that could block the development of generic versions of the DAA regimen.
Additional years of exclusivity provided by (i) Secondary patents that block some formulations only or (ii) patents that may be blocking main formulations but may potentially be invented around ("quasi blocking patents")	When do secondary patent(s) on specific formulations or "quasi blocking patents" expire?	As above, products that have longer time to patent expiry score higher. This criterion focuses on additional years of exclusivity provided by patents on specific formulations (e.g. a fixed-dose combination), or by other secondary patents that may potentially block the development of generics (e.g. certain process patents or patents on polymorphs).
Geographical coverage of patents blocking all or main formulations containing the DAA regimen	How widely has the patent(s) been filed/granted?	Products for which patents have been filed or granted in countries that are home to a higher percentage of people with HCV score higher. Given India's role as the likely manufacturing base for most DAA regimens that meet international quality requirements, products that are patented in India are given high priority.
Geographical coverage of secondary patents	What is the geographical coverage of the patent(s) on the secondary formulations?	As above, products for which patents have been filed or granted in countries that are home to a higher percentage of people with HCV score higher.

4.3 Licensing Criteria

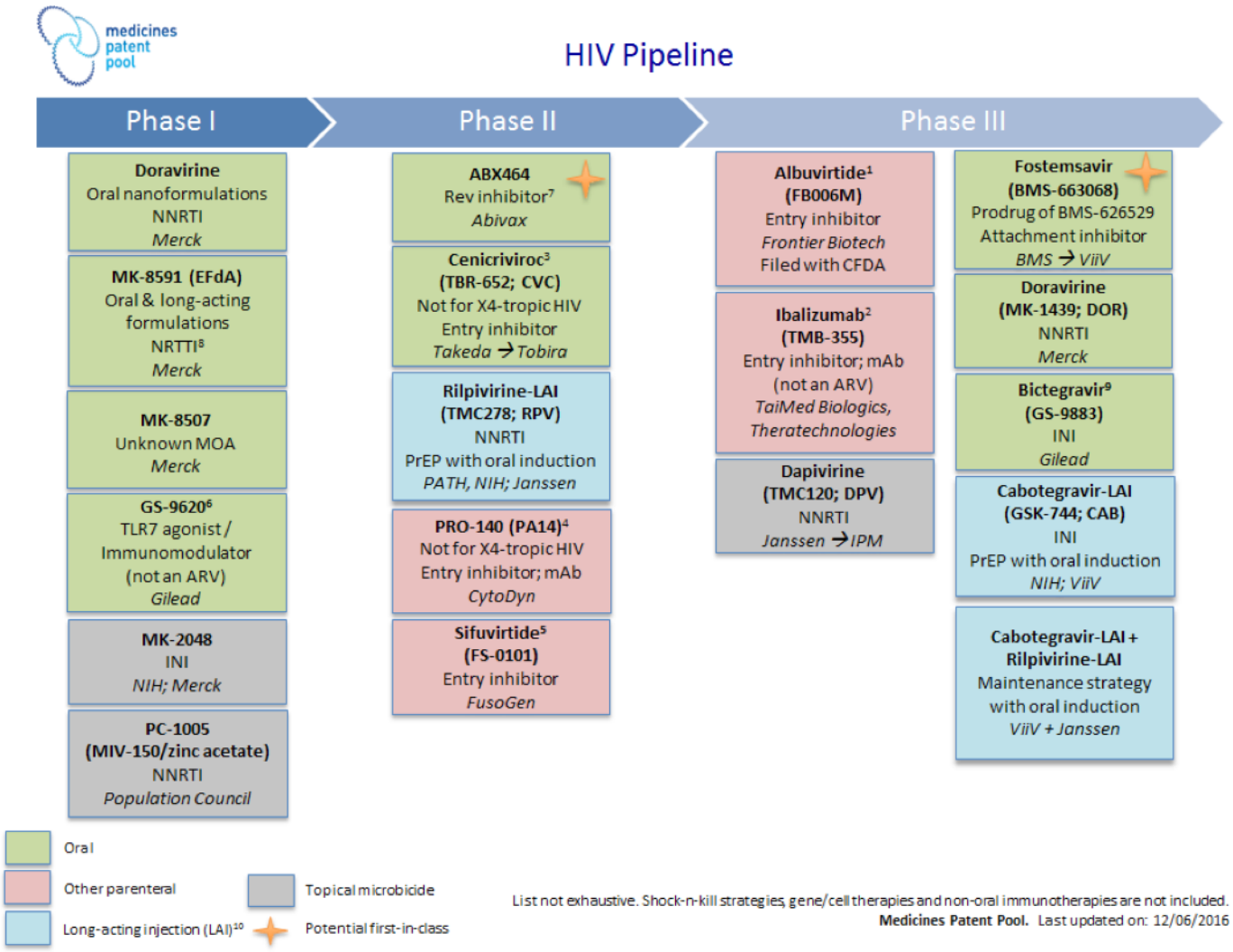
SUB-CRITERIA	KEY QUESTION	COMMENTS
Licensing status	Has the medicine been licensed to generic manufacturers for manufacture and sale in developing countries? How many companies have licences to make the DAA regimen and is this likely to be sufficient in light of forecasted needs?	DAA regimens for which there are no licensees or only a limited number of licensees score higher. The assessment takes into account licences and commitments to licence.
Geographical coverage of licences	What is the geographical scope of current licences (or licensing policy of the patent holder) and is there significant scope for expansion under an MPP licence?	Geographical scope is one of the key features in access-oriented voluntary licences. DAA regimens licensed with a limited geographical scope are considered higher priority as there may be greater room for improvements by the MPP. This criterion takes into consideration countries explicitly included in the licence as well as additional countries that may be able to benefit in light of specific provisions in the licence.

SUB-CRITERIA	KEY QUESTION	COMMENTS
Transparency of licences	Has the licence been made publicly available in full form?	This criterion takes into consideration the importance of transparency in licensing terms and conditions, as this is another area in which the MPP has been able to improve on existing licences.
Restrictions in licence	Are there any important restrictions in the licence that could be improved by the MPP if it were to seek a licence?	In addition to geographical scope, there are many other terms and conditions in a licence that can impact on access to medicines. This would include, for example, provisions that provide maximum flexibility to licensees; provisions that ensure complementary with other access strategies; clauses relating to anti-diversion; clauses enabling development of adapted formulations. Where detailed terms and conditions of the licence are not available, the assumption is that there are several restrictions in the licence.

4.4 Market Criteria

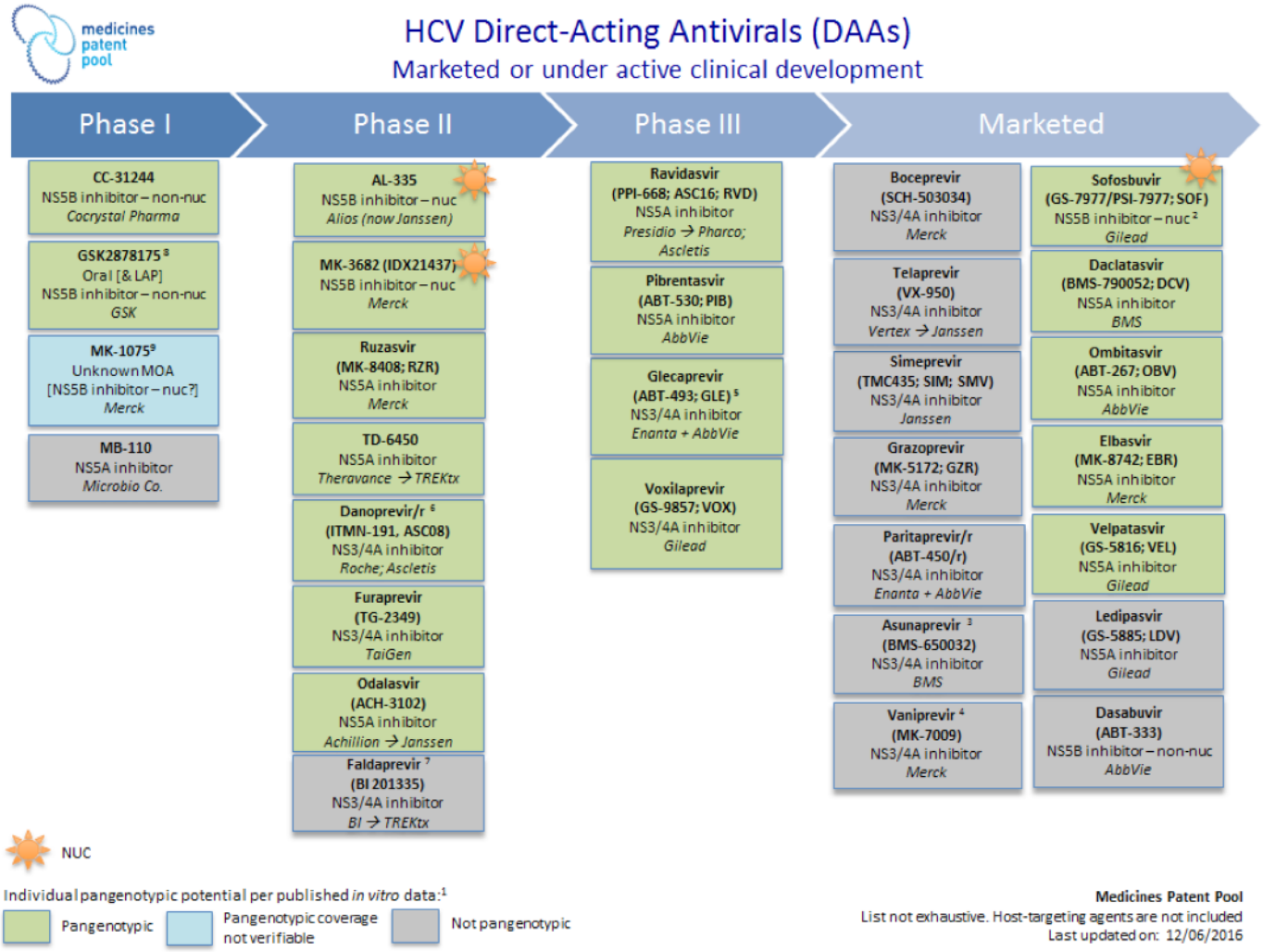
SUB-CRITERIA	KEY QUESTION	COMMENTS
Size of market	How large is the market for this regimen or for formulations containing this regimen?	Given the lack of clear market forecasts for HCV, the potential size of the market has been estimated depending on the number of genotypes for which the product has approval or has potential. The highest priority is for pan-genotypic products or pipeline regimens with pan-genotypic potential.
Market trend (for marketed products)	What is the trend in market demand for this regimen over the coming five years or more?	This takes into consideration the likely evolution in demand for this regimen over the coming years. Is demand rising, stable or decreasing?
Price differential between originator and generic (for marketed products)	What is the current price differential between the originator product in LMICs in which it is patented and the generic version in countries in which it is available?	This criterion is used only for DAA regimens that are already on the market. It prioritzes products that have a higher price differential between the originator product and generics and where an MPP licence enabling generic market entry could have a major impact.
Potential for low price as compared to standard of care (for pipeline products)	Does the DAA regimen have the potential for being made available at low(er) prices?	This criterion is used for pipeline DAA regimens only. A DAA regimen may have the potential for lower price than the standard of care due to lower dosage; less frequent dosing; no need for booster; smaller or shorter regimens; simple(r) manufacturing processes.

5. ANNEX 3 – HIV PIPELINE

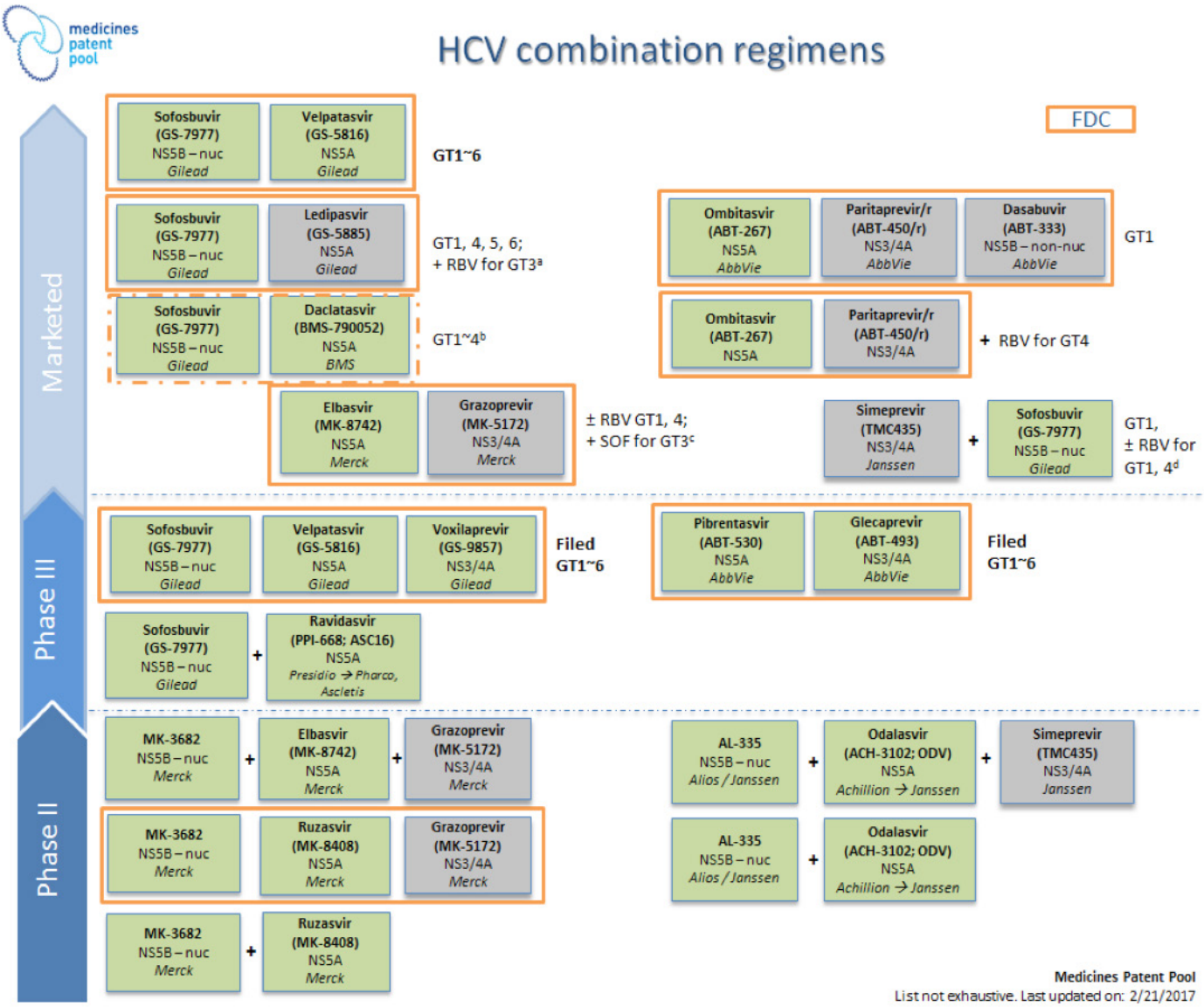


Sources: clinicaltrials.gov; WHO ICTRP; and relevant conference presentations and publications in peer-reviewed journals.

6. ANNEX 4 – HCV PIPELINE



Sources: clinicaltrials.gov; WHO ICTRP; and relevant conference presentations and publications in peer-reviewed journals.



Sources: clinicaltrials.gov, and relevant prescribing information.

7. ACRONYMS

ARV	Antiretroviral (drug)
BIC	Bictegravir
CAB-LAI	Cabotegravir long-acting injectable
CADO	Conference on antiretroviral drug optimization
DAA	Direct-acting antiviral
FTC	Emtricitabine
HCV	Hepatitis C virus
HIV	Human immunodefficiency virus
INSTI	Integrase strand transfer inhibtor
IP	Intellectual property
LMICs	Low- and middle-income countries
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NS5A	Non-structural protein 5A (of HCV)
NS3/4A	Non-structural protein 3/4A
PMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
RAV	Resistance-associated variant
RLS	Resource limited settings
RPV	Rilpivirine
SOC	Standard of care
SOF	Sofosbuvir
TAF	Tenofovir alafenamide
WHO	World Health Organization

8. BIBLIOGRAPHY

8.1 General references

1. MedsPaL - the Medicines Patents and Licences Database. Available at: www.medspal.org
2. World Health Organization, Global Price Reporting Mechanism (GPRM). Available at: http://www.who.int/hiv/amds/gprm/en/
3. World Health Organization, Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, 2016, Geneva.
4. World Health Organization, Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection, 2016, Geneva.

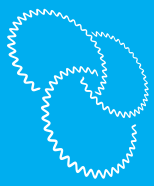
8.2 Key References – HIV

1. Abraham, BK and Gulick, R. Next-generation oral preexposure prophylaxis: beyond tenofovir. Curr Opin HIV AIDS. Nov, 2012;7(6): 600-6
2. AIDS*info*, a service of the U.S. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/
3. Anderson, MS et al. A 2-Way Steady State Pharmacokinetic Interaction Study of Doravirine (MK-1439) and Dolutegravir. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy: May 26-28, 2015; Washington, DC.
4. Andrews, CD et al. Long-Acting Integrase Inhibitor Protects Macaques from Intrarectal Simian/Human Immunodeficiency Virus. Science. March 2014. 343 (6175): 1151–1154.
5. Clinicaltrials.gov, a service of the U.S. National Institutes of Health. Available at https://clinicaltrials.gov/
6. Dejesus, E et al. Attachment Inhibitor Prodrug BMS-663068 in ARV-Experienced Subjects: Week 96 Analysis. Abstract 472, CROI: Feb 22-25, 2016; Boston.
7. Feng M et al. In vitro Resistance Selection with Doravirine (MK-1439), a Novel Nonnucleoside Reverse Rranscriptase Inhibitor with Distinct Mutation Development Pathways. Antimicrob Agents Chemother. 2015 Jan;59(1):590-8
8. Gatell, JM et al. Doravirine 100mg QD vs Efavirenz +TDF/FTC in ART-Naive HIV+ Patients: Week 48 Results. Abstract 470, CROI: Feb 22-25, 2016; Boston.
9. Gupta, A. et al, Projected Uptake of New Antiretroviral (ARV) Medicines in Adults in Low- and Middle-Income Countries: A Forecast Analysis 2015-2025, PLOS One, October 2016
10. HIV Drug Interaction Checker, University of Liverpool. Avaialble at http://www.hiv-druginteractions.org/
11. Jones G et al. GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile. American Society for Microbiology (ASM) Microbe; June 16-20, 2016; Boston.
12. Lai MT et al. In vitro Characterization of MK-1439, a Novel HIV-1 Nonnucleoside Reverse Transcriptase Inhibitor. Antimicrob Agents Chemother. 2014 Mar;58(3):1652-63
13. Landry IS et al. HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with DRV/r and/or ETR. Abstract 523, CROI: Feb 23-26, 2015; Seattle.
14. Margolis DA et al. Cabotegravir+Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results. Abstract 31LB, CROI: Feb 22-25, 2016; Boston.
15. Margolis, A et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis. July 2015. 15: 1145-55.
16. Molina J et al. Doravirine Is Non-Inferior To Darunavir/R In Phase 3 Treatment-Naïve Trial At Week 48. Abstract 45LB, CROI: Feb 13-16, 2017; Seattle.
17. Sax, PE et al. Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy. Abstract 41, CROI: Feb 13-16, 2017; Seattle.

18. Spreen, B. Cabotegravir Long-Acting (LA) Injectable Nanosuspension. 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; June 8-10, 2016; Washington DC.
19. The World Health Organization International Clinical Trials Registry Platform. Available at http://apps.who.int/trialsearch/Default.aspx
20. Thompson, M et al. Attachment Inhibitor Prodrug BMS–663068 in ARV-Experienced Subjects: Week 48 Analysis. Abstract 545, CROI: Feb 23-26, 2015; Seattle.
21. White K et al. Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates with INSTI-Resistance. American Society for Microbiology (ASM) Microbe; June 16-20, 2016; Boston.
22. Williams, P. Current Status of Clinical Development of LA-Rilpivirine? Long-Acting/Extended Release (LA/ER) Antiretroviral Drugs Workshop: Current Status and Future Prospects. Feb 21, 2016; Boston.
23. Zhang, H et al. Clinical Pharmacology Of The Hiv Integrase Strand Transfer Inhibitor Bictegravir. Abstract 40, CROI: Feb 13-16, 2017; Seattle.

8.3 Key References – HCV

1. Asselah, T et al. ENDURANCE-4: Efficacy and Safety of Glecaprevir/Pibrentasvir (Formerly ABT-493/ABT-530) Treatment in Patients with Chronic HCV Genotype 4, 5, or 6 Infection. AASLD: Nov 11-15, 2016; Boston.
2. Clinicaltrials.gov, a service of the U.S. National Institutes of Health. Available at https://clinicaltrials.gov/
3. Colonno, RJ et al. Characterization and identification of PPI-437, PPI-668 and PPI-833 as potent and selective HCV NS5A inhibitors with activity against all HCV genotypes. International Liver Congress: March 30 – April 3, 2011; Berlin.
4. Esmat, G et al. High Virologic Response Rate in Egyptian HCV-Genotype 4 Patients Treated with Ravidasvir (PPI-668) and Sofosbuvir: Results of a Large Multicenter Phase 3 Registrational Trial. AASLD: Nov 13-17, 2015; San Francisco.
5. Esmat, G et al. FINAL RESULTS OF THE PYRAMID 1 STUDY, A PHASE 3 REGISTRATIONAL TRIAL OF RAVIDASVIR (PPI-668) AND SOFOSBUVIR IN HCV GENOTYPE-4 PATIENTS: HIGH RATES OF SUSTAINED VIRAL CLEARANCE IN CIRRHOTIC AND NON-CIRRHOTIC PATIENTS. International Liver Congress: April 13-17, 2016; Barcelona.
6. Gane, E et al. EXPEDITION-4: EFFICACY AND SAFETY OF GLECAPREVIR/PIBRENTASVIR (ABT-493/ABT-530) IN PATIENTS WITH RENAL IMPAIRMENT AND CHRONIC HEPATITIS C VIRUS GENOTYPE 1 – 6 INFECTION. AASLD: Nov 11-15, 2016; Boston.
7. Hassanein, T et al. SURVEYOR-II, Part 4: Glecaprevir/Pibrentasvir Demonstrates High SVR Rates in Patients With HCV Genotype 2, 4, 5, or 6 Infection Without Cirrhosis Following an 8-Week Treatment Duration. AASLD: Nov 11-15, 2016; Boston.
8. HEP Drug Interaction Checker, University of Liverpool. Available at http://www.hep-druginteractions.org/
9. Kosloski, MP et al. ABT-493 and ABT-530 combination demonstrated minimal potential for CYP-mediated drug-drug interactions. Abstract THU-229, International Liver Congress: April 13-17, 2016; Barcelona.
10. Kowdley, KV et al. ENDURANCE-2: Safety and Efficacy of Glecaprevir/Pibrentasvir in Hepatitis C Virus Genotype 2-infected Patients without Cirrhosis: a Randomized, Double-Blind, Placebo-Controlled Study. AASLD: Nov 11-15, 2016; Boston.
11. Ng, T et al. ABT-493, a Potent HCV NS3/4A Protease Inhibitor With Broad Genotype Coverage. Abstracct 636, CROI: March 3-6, 2014; Boston.
12. Ng, T et al. A next generation HCV DAA combination: potent, pangenotypic inhibitors ABT-493 and ABT-530 with high barriers to resistance. AASLD, Nov 7-11, 2014; Boston.
13. Zeuzem, S et al. ENDURANCE-1: A Phase 3 Evaluation of the Efficacy and Safety of 8- versus 12-week Treatment with Glecaprevir/Pibrentasvir (formerly ABT-493/ABT-530) in HCV Genotype 1 Infected Patients with or without HIV-1 Co-infection and without Cirrhosis. AASLD: Nov 11-15, 2016; Boston.



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